tal impairments, when properly controlled by medication, therapy and other treatment, did not result in limitations that were of a "marked" or "extreme" nature. For the reasons previously discussed, we consider the ALJ's findings to be well supported by the record.

IV. CONCLUSION

Based upon the foregoing reasons, the Plaintiff's motion for summary judgment will be denied and the Commissioner's motion will be granted. An appropriate order follows.

ORDER

AND NOW, this 6th day of December, 2002, for the reasons set forth in the accompanying Memorandum Opinion,

IT IS HEREBY ORDERED THAT Plaintiff's Motion [Doc. No. 6] for Summary Judgment is DENIED and Defendant's Motion [Doc. No. 9] for Summary Judgment is GRANTED.

JUDGMENT is hereby entered in favor of Defendant Jo Anne B. Barnhart, Commissioner of Social Security, and against Plaintiff Ann Marie Sheriff.

Lisa A. SOLDO, Plaintiff,

v.

SANDOZ PHARMACEUTICALS CORPORATION, Defendant.

No. CIV.A.98–1712.

United States District Court, W.D. Pennsylvania.

Jan. 13, 2003.

Mother brought product liability action in the United States District Court for the District of New Jersey, alleging that manufacturer's drug for control of postpartum lactation caused her to have a stroke. After action was transferred to the Western District of Pennsylvania, manufacturer moved for summary judgment. The District Court, Lee, J., held that plaintiff's expert failed to render scientifically-reliable opinions that would assist trier of fact in resolving whether lactation-inhibiting drug could cause postpartum stroke and whether it did so in mother's case.

Summary judgment granted.

1. Products Liability ⚿15

Absent a causal relationship between defendant's product and plaintiff's injury, defendant cannot be held liable on a theory of negligence, strict product liability, or misrepresentation.

2. Products Liability ⚿46.2

In a products liability action alleging that she was injured by a drug manufacturer's product, a plaintiff, to meet her causation burden, must first establish general causation, that the drug is capable of causing such injury as she suffered, and then must establish specific causation, that, in her particular case, the drug did in fact cause her injury.

3. Products Liability ⚿46.2, 83

In a products liability action alleging that she was injured by a drug manufacturer's product, if plaintiff has not demonstrated sufficiently reliable evidence of general causation, her claims fail and there is no need to consider specific causation.

4. Products Liability ⚿83

In a products liability action alleging that she was injured by a drug manufac-

turer's product, plaintiff must prove medical causation to a reasonable degree of medical certainty.

5. Evidence ⚿601(1)

Negligence ⚿1675

In a case involving complex issues of causation not readily apparent to the finder of fact, plaintiff must present admissible expert testimony to carry her burden.

6. Evidence ⚿547.5

In a products liability action alleging that plaintiff was injured by a drug manufacturer's product, opinions of plaintiff's experts must be expressed to a reasonable degree of medical certainty; opinions merely expressing possibilities do not suffice to support the admissibility of expert testimony.

7. Evidence ⚿527, 545, 555.2

In a products liability action, a plaintiff bears burden of demonstrating that each of her proffered experts is qualified to render an expert opinion, that the opinion is reliable, and that the opinion would assist trier of fact in resolving a disputed issue of material fact, such as causation. Fed.Rules Evid.Rule 702, 28 U.S.C.A.

8. Evidence ⚿555.2, 555.4(2)

In *Daubert* analysis of admissibility of proffered expert testimony on scientific issues, such testimony must be reliable; testimony must be scientific, meaning grounded in the methods and procedures of science, and must constitute knowledge, meaning something more than subjective belief or unsupported speculation. Fed. Rules Evid.Rule 702, 28 U.S.C.A.

9. Evidence ⚿555.2

In assessing reliability of proffered expert testimony, court considers, but is not limited to, whether expert's methodology has been tested or is capable of being tested, whether the technique has been subjected to peer review and publication, the known and potential error rate of the methodology, whether technique has been generally accepted in the proper scientific community, existence and maintenance of standards controlling methodology's operation, relationship of technique to methods established to be reliable, experts' qualifications, and nonjudicial uses to which method has been put. Fed.Rules Evid. Rule 702, 28 U.S.C.A.

10. Evidence ⚿508

In assessment of reliability of proffered expert testimony, *Daubert* requires an appropriate fit with respect to the offered opinion and the facts of the case, such that proffered expert testimony must assist the trier of fact; scientific testimony does not assist the trier of fact unless the testimony has a valid scientific connection to the pertinent inquiry. Fed.Rules Evid. Rule 702, 28 U.S.C.A.

11. Evidence ⚿570

Expert opinions generated as the result of litigation have less credibility than opinions generated as the result of academic research or other forms of pure research. Fed.Rules Evid.Rule 702, 28 U.S.C.A.

12. Evidence ⚿555.2

It is appropriate for a Court to conduct an evidentiary hearing to determine whether plaintiff's experts' reasoning or methodology is admissible under the standards of *Daubert*.

13. Evidence ⚿555.10

In a products liability action, a failure to establish a valid and strong temporal relationship between the alleged toxic exposure and the adverse event in question constitutes sufficient reason to exclude a plaintiff's expert testimony on specific causation.

14. Evidence ⚿555.10, 557

In products liability action alleging that lactation-inhibiting drug caused mother's stroke, hypothesis of mother's experts as to medical causation was not scientifically reliable, and therefore was inadmissible; hypothesis was not based on statistically-significant epidemiologic studies showing that use of the drug increased the risk of postpartum intracerebral hemorrhage (ICH) or postpartum stroke of any kind. Fed.Rules Evid.Rule 702, 28 U.S.C.A.

15. Evidence ⚿146, 557

In products liability action alleging that manufacturer's lactation-inhibiting drug caused mother's stroke, probative value of epidemiologic study purportedly relied on by mother's experts was substantially outweighed by its unfair prejudicial effect, tendency to confuse and mislead the jury, and waste of judicial time, even if evidence could be reliable and relevant; study showed no statistically-significant association between drug and postpartum stroke. Fed.Rules Evid.Rule 403, 28 U.S.C.A.

16. Evidence ⚿555.10

Testimony proffered by mother's experts, which relied on adverse drug experience (ADE) reports and anecdotal case reports to support their causation opinions, was not admissible in products liability action alleging that manufacturer's lactation-inhibiting drug caused mother's stroke; reliance on such reports did not provide scientific knowledge and did not assist trier of fact, and data was not of a type normally relied on by experts in the field. Fed.Rules Evid.Rule 702, 28 U.S.C.A.

17. Evidence ⚿555.10, 556

Testimony proffered by mother's experts, which relied on medical treatises to support their causation opinions, was not admissible in products liability action alleging that manufacturer's lactation-inhibiting drug caused mother's stroke; treatises were not reliable inasmuch as they were merely second-hand statements that recited anecdotal information from case reports, and thus did not provide scientific knowledge and did not assist trier of fact, and data was not of a type normally relied on by experts in the field. Fed.Rules Evid.Rule 702, 28 U.S.C.A.

18. Evidence ⚿555.10

Testimony proffered by mother's experts, which relied on Food and Drug Administration (FDA) actions with respect to lactation-inhibiting drug to support their causation opinions, was not admissible in products liability action alleging that drug caused mother's stroke; FDA postmarketing surveillance and regulations regarding reports of adverse events did not reliably establish causation. Fed.Rules Evid.Rule 702, 28 U.S.C.A.

19. Evidence ⚿555.10

Testimony proffered by mother's experts, relying on methodology allegedly endorsed by Drug Monitoring Centre (DMC) of lactation-inhibiting drug manufacturer's foreign affiliate to support experts' causation opinions, was not admissible in products liability action alleging that drug caused mother's stroke; DMC methodology was adopted for foreign regulatory purposes and did not meet any *Daubert* criteria or show any other indicia of reliability. Fed.Rules Evid.Rule 702, 28 U.S.C.A.

20. Evidence ⚿555.10

Testimony proffered by mother's experts, relying on phrases plucked from corporate documents of manufacturer of lactation-inhibiting drug to support their causation opinions, did not provide scientific evidence of causation and therefore was

not admissible in products liability action alleging that drug caused mother's stroke; statements did not constitute admission that drug could cause an intracerebral hemorrhage (ICH). Fed.Rules Evid.Rule 702, 28 U.S.C.A.

21. Evidence ⚿555.10

Testimony proffered by mother's experts, relying on causality assessments, allegedly made by drug manufacturer's foreign affiliate, to support experts' causation opinions, was not admissible in products liability action alleging that lactation-inhibiting drug caused mother's stroke, even if methodology was reliable; alleged attribution of digital vasospasm to drug was not relevant in that it did not fit issue of causation of intracerebral hemorrhage (ICH). Fed.Rules Evid.Rule 401, 28 U.S.C.A.

22. Evidence ⚿555.10

Testimony proffered by mother's experts, relying on causality assessments, allegedly made by drug manufacturer's foreign affiliate, to support experts' causation opinions, was not admissible in products liability action alleging that lactation-inhibiting drug caused mother's stroke; likelihood that alleged causality assessments, prepared for entirely different purposes than the scientific determination of causation in controlled settings, would mislead finder of fact greatly outweighed any probative value. Fed.Rules Evid.Rule 403, 28 U.S.C.A.

23. Evidence ⚿557

To ensure that an expert's conclusion based on animal studies is reliable, for purposes of a products liability action alleging injury to a human being, there must be a scientifically valid link—such as supporting human data—between the sources or studies consulted and the conclusion reached.

24. Evidence ⚿557

In products liability action alleging that manufacturer's lactation-inhibiting drug caused mother's stroke, mother's experts' causation opinions, to extent they were based on studies involving animals treated with drug, were not scientifically reliable, and therefore were inadmissible; dosage used on animals was not correlated to doses taken by mother, dogs and rats used in studies were not sufficiently similar to humans, and observed effects of tail necrosis and ear tip necrosis were not sufficiently similar to cerebral vasoconstriction alleged to have caused mother's stroke. Fed.Rules Evid.Rule 702, 28 U.S.C.A.

25. Evidence ⚿555.10

In products liability action alleging that manufacturer's lactation-inhibiting drug caused mother's stroke, testimony proffered by mother's experts, relying on evidence that chemically-related drugs caused vasoconstriction, was unreliable and irrelevant, and therefore was inadmissible; testimony was based on unproven assumptions that drug mother took must have modes of action pharmacologically identical to those of related drugs and that mother's stroke was result of such vasoconstriction. Fed.Rules Evid.Rules 401, 402, 403, 702, 28 U.S.C.A.

26. Evidence ⚿141

In a products liability action, that evidence of other injuries allegedly involves the same product is not enough to make the evidence relevant and thus admissible. Fed.Rules Evid.Rule 401, 28 U.S.C.A.

27. Evidence ⚿141, 555.10

In products liability action alleging that manufacturer's lactation-inhibiting drug caused vasoconstriction which resulted in mother's intracerebral hemorrhage (ICH), testimony proffered by mother's experts, relying on alleged evidence that

drug caused other injuries, was irrelevant and therefore inadmissible, where experts failed to articulate a mechanism by which drug caused cerebral vasoconstriction; evidence failed to show that prior injuries had also been caused by cerebral vasoconstriction. Fed.Rules Evid.Rule 401, 28 U.S.C.A.

28. Evidence ⚿141, 146

In products liability action alleging that manufacturer's lactation-inhibiting drug caused vasoconstriction which resulted in mother's intracerebral hemorrhage (ICH), probative value of testimony proffered by mother's experts, as to alleged evidence of other injuries caused by drug, was outweighed by likelihood of jury misdecision based on inflamed passions or confusion of issues, and was therefore inadmissible; proffered evidence that drug caused other injuries was irrelevant. Fed. Rules Evid.Rule 403, 28 U.S.C.A.

29. Evidence ⚿555.5

In a products liability action, the mere statement by an expert that he or she applied differential diagnosis in determining causation does not ipso facto make that application scientifically reliable or admissible.

30. Evidence ⚿555.10

In products liability action alleging that manufacturer's lactation-inhibiting drug caused mother's stroke, differential diagnosis methodology used by mother's experts was not scientifically reliable and therefore was inadmissible; methodology did not demonstrate sufficient diagnostic techniques to rule out plausible alternative causes for stroke, such as risk of the postpartum period, background risk of stroke occurring independently of drug use, over-the-counter sympathomimetic drugs, and endogenous vasoconstrictive substances. Fed.Rules Evid.Rule 702, 28 U.S.C.A.

31. Evidence ⚿555.10

In products liability action alleging that manufacturer's lactation-inhibiting drug caused mother's stroke, differential diagnosis methodology used by mother's experts was not scientifically reliable and therefore was inadmissible; methodology was not based on a valid and strong temporal relationship inasmuch as evidence as to timing of mother's last dose of the drug was uncertain and evidence as to effect of drug's half-life on levels of the drug in mother's blood was uncertain. Fed.Rules Evid.Rule 702, 28 U.S.C.A.

32. Evidence ⚿555.10

In products liability action alleging that manufacturer's lactation-inhibiting drug caused mother's stroke, differential diagnosis methodology used by mother's experts was not scientifically reliable and therefore evidence based on such methodology was inadmissible; experts failed to demonstrate adequate evidence that mother's intracerebral hemorrhage (ICH) was caused by vasospasm or vasoconstriction. Fed.Rules Evid.Rule 702, 28 U.S.C.A.

33. Evidence ⚿571(9)

In products liability action alleging that manufacturer's lactation-inhibiting drug caused mother's stroke, even if testimony of mother's experts on medical causation for her stroke were admissible, evidence was not sufficient to allow a reasonable jury to find that mother's intracerebral hemorrhage (ICH) was caused by the drug; testimony provided only a scintilla of support for mother's position. Fed.Rules Evid.Rules 401, 402, 403, 702, 703, 28 U.S.C.A.

34. Evidence ⚿555.10

In products liability action alleging that manufacturer's lactation-inhibiting drug caused mother's stroke, methodology used by mother's experts failed to demonstrate general causation, and thus experts'

testimony was inadmissible; existing data regarding drug and stroke were insufficient to reliably support the testimony, and experts' opinions that drug could cause stroke were unreliable inasmuch as experts failed to apply their own scientific standards and could not explain the biological and/or pathological mechanism by which drug allegedly caused stroke. Fed. Rules Evid.Rule 702, 28 U.S.C.A.

35. Evidence ⚿555.2

An scientific expert's testimony should be excluded if testing his methodology does not generate consistent results.

36. Evidence ⚿555.4(1)

Expert testimony based on false assumptions and fictional or random data is inadmissible.

37. Evidence ⚿528(1)

In products liability action alleging that manufacturer's lactation-inhibiting drug caused vasoconstriction which resulted in mother's intracerebral hemorrhage (ICH), testimony proffered by mother's experts, that drug acted as a cerebral vasoconstrictor, did not fit the facts of the case and did not assist trier of fact in evaluating the evidence, and was thus inadmissible; purported evidence that drug could cause peripheral vasoconstriction or digital vasospasm did not demonstrate that drug caused constriction of the cerebral arteries. Fed.Rules Evid.Rule 702, 28 U.S.C.A.

38. Evidence ⚿528(1)

In products liability action alleging that manufacturer's lactation-inhibiting drug caused mother's intracerebral hemorrhage (ICH), testimony proffered by mother's experts, that drug caused other kinds of strokes, did not fit the facts of the case and did not assist trier of fact in evaluating the evidence, and was thus inadmissible; no reliable evidence established a valid connection between contention that drug caused other strokes and conclusion that it also caused ICH. Fed.Rules Evid.Rule 702, 28 U.S.C.A.

39. Evidence ⚿555.10

In products liability action alleging that manufacturer's lactation-inhibiting drug caused mother's intracerebral hemorrhage (ICH), testimony proffered by mother's experts, that drug caused vasoconstriction resulting in ICH because it was one of family of drugs of which some were known to cause vasoconstriction, was too great a leap and thus was inadmissible, particularly in light of evidence that lactation-inhibiting drug caused vasodilation; no reliable evidence established that all drugs in drug family acted alike in producing vasoconstriction, much less ICH, or that any drug in family produced both vasoconstriction and vasodilation. Fed.Rules Evid.Rule 702, 28 U.S.C.A.

40. Evidence ⚿557

In products liability action, testimony proffered by mother's experts, that studies using animals supported opinion that lactation-inhibiting drug caused vasoconstriction resulting in mother's intracerebral hemorrhage (ICH), did not fit facts of the case and was thus inadmissible; study used significantly higher doses of drug, animals' nervous systems had been destroyed and they were not in postpartum period, drug was injected into arteries that had been removed from animals, and animal body parts may have had different receptors than cerebral arteries of same animal or human cerebral arteries. Fed.Rules Evid. Rule 702, 28 U.S.C.A.

41. Evidence ⚿557

In products liability action, testimony proffered by mother's experts, that studies using human hand veins supported opinion that lactation-inhibiting drug caused vasoconstriction resulting in mother's intracer-

ebral hemorrhage (ICH), did not fit facts of the case and was thus inadmissible; study used significantly higher doses of drug, drug was directly injected rather than orally ingested, hand veins were used rather than cerebral arteries, and veins were removed from body's blood system. Fed.Rules Evid.Rule 702, 28 U.S.C.A.

42. Evidence ⚿555.10

Proffered testimony of mother's experts in products liability action, that manufacturer's lactation-inhibiting drug caused vasoconstriction resulting in mother's intracerebral hemorrhage (ICH), failed to establish specific causation, and was therefore inadmissible; experts failed to use differential diagnosis methodology in a scientifically reliable manner, in that they did not reliably rule out alternative possible causes of mother's ICH and did not identify any reliable evidence from mother's medical records indicative of drug-induced ICH. Fed.Rules Evid.Rule 702, 28 U.S.C.A.

43. Evidence ⚿544, 555.10, 557

Expert's testimony was not scientifically reliable and thus was inadmissible in products liability action alleging that manufacturer's lactation-inhibiting drug caused mother's intracerebral hemorrhage (ICH); expert was not qualified in fields of epidemiology, statistics, neurology, neuropathology, or obstetrics/gynecology, his opinion that drug could and did cause ICH did not satisfy *Daubert* factors, he was unable to explain mechanism by which drug allegedly caused ICH, his reliance on animal studies and effects of similar drugs did not fit facts of case, and he failed to exclude possible alternative causes of mother's ICH. Fed.Rules Evid.Rule 702, 28 U.S.C.A.

44. Evidence ⚿555.10

Expert's testimony was inadmissible in products liability action alleging that manufacturer's lactation-inhibiting drug caused mother's intracerebral hemorrhage (ICH); facts and data upon which expert relied to support his opinions were not the kind of information reasonably relied upon by experts forming medical causation opinions in the applicable medical and/or scientific fields of epidemiology, pharmacology, neurology, neuropathology, statistics, or obstetrics/gynecology. Fed.Rules Evid. Rule 703, 28 U.S.C.A.

45. Estoppel ⚿68(2)

Proper application of judicial estoppel requires (1) party to be estopped must have taken two positions that are irreconcilably inconsistent, (2) judicial estoppel is unwarranted unless the party changed his or her position in bad faith-i.e., with intent to play fast and loose with the court, and (3) a district court may not employ judicial estoppel unless it is tailored to address the harm identified and no lesser sanction would adequately remedy the damage done by the litigant's misconduct.

46. Estoppel ⚿68(2)

In products liability action alleging that manufacturer's lactation-inhibiting drug caused mother's stroke, manufacturer's arguments in previous cases, that amphetamine-type drugs could not cause stroke, did not warrant invocation of judicial estoppel to estop manufacturer from arguing that such drugs might have played a role in mother's stroke or were not properly ruled out by her experts; issue was medical rather than legal, and manufacturer's assertion was not made in bad faith and did not assault dignity or authority of Court.

Damon J. Faldowski, Kathleen Smith–Delach, Phillips, Faldowski & McCloskey,

Washington, PA, Jeffrey A. Lutsky, Stradley, Ronon, Stevens & Young, Philadelphia, PA, Catherine T. Heacox, Ellen Relkin, Denise M. Dunleavy, Weitz & Luxenberg, New York, NY, Jerry M. Kristal, Weitz & Luxenberg, Cherry Hill, NJ, for Lisa A. Soldo, plaintiff.

Mark D. Shepard, Babst, Calland, Clements & Zomnir, Pittsburgh, PA, Joe H. Hollingsworth, Bruce J. Berger, Conrad J. Jacoby, Neil S. Bromberg, William J. Cople, III, Spriggs & Hollingsworth, Washington, DC, for Sandoz Pharmaceuticals Corporation, defendant.

FINDINGS OF FACT AND CONCLUSIONS OF LAW

LEE, District Judge.

Introduction

This pharmaceutical products liability action was originally filed by the plaintiff, Lisa A. Soldo, in the United States District Court for the District of New Jersey which transferred the action to this Court because the plaintiff is a resident of Pennsylvania and also because Pennsylvania is the situs where she allegedly suffered an intracerebral hemorrhage as a result of her ingestion of Parlodel®, a drug manufactured and marketed by the defendant and also where she received most of her medical treatment.

The Court has jurisdiction based on diversity of citizenship and the amount in controversy pursuant to 28 U.S.C. § 1332.[1]

The plaintiff is a citizen of the Commonwealth of Pennsylvania, residing at 101 West Lake Road, Transfer, Pennsylvania 16154.

The defendant, Sandoz Pharmaceuticals Corporation, now Novartis Pharmaceutical Corporation ("NPC"), is organized and existing under the laws of the State of Delaware, with its principal place of business located at 59 Route 10, East Hanover, New Jersey 07936.

Procedural Background

Before the Court for disposition is the defendant's **Motion for Summary Judgment on Issues of Medical Causation** (Document No. 77), to which plaintiff responded in **Plaintiff's Memorandum of Law in Opposition to Defendant's Motion for Summary Judgment on Issues of Medical Causation** (Document No. 84).

NPC moves the Court to enter judgment in its favor as a matter of law on the basis that plaintiff's evidence of general and specific causation fails to meet the test of scientific reliability set out in *Daubert v. Merrell Dow Pharmaceuticals,* 509 U.S. 579, 113 S.Ct. 2786, 125 L.Ed.2d 469 (1993) and followed by the Court of Appeals for the Third Circuit in *In re Paoli Railroad Yard PCB Litig.,* 35 F.3d 717 (3d Cir.1994) and *Heller v. Shaw Indus., Inc.,* 167 F.3d 146 (3d Cir.1999).

Pursuant to NPC's **Motion for Evidentiary Hearing Regarding NPC's Motion for Summary Judgment on Issues of Medical Causation** (Document No. 63), the Court conducted a *Daubert* hearing during which medical expert witnesses testified on behalf of the parties and exhibits were introduced into the record. At various other times, on motions of the parties, other extensive exhibits, including medical treatises, were also introduced into the record.

Following the *Daubert* hearing, with the assistance of the Duke University School

1. Plaintiff's complaint was filed on May 11, 1995, at which time the jurisdictional threshold was $50,000.

of Law Registry of Independent Scientific and Technical Advisors, the Court appointed three medical experts who were directed to opine as to whether the methodology or technique employed by the plaintiff's medical experts in opining that Parlodel ® can cause stroke and did cause plaintiff's intracerebral hemorrhage is scientifically reliable.

Those three experts are:

(i) David A. Savitz, Ph.D.—Epidemiology

(ii) William J. Powers, M.D.—Neurology/Radiology

(iii) David A. Flockhart, M.D., Ph.D.—Pharmacology

Additionally, both before and after the *Daubert* hearing, the parties submitted proposed findings of fact and conclusions of law, and, after receipt of the reports of the court-appointed experts, the parties were invited to file and did file supplemental proposed findings of fact and conclusions of law.

Based on the record before it, the Court enters the following Findings of Fact and Conclusions of Law.[2]

Findings of Fact

A. Findings of Fact Regarding the History of Parlodel ®

1. Parlodel ® is a prescription drug formulated and sold by Novartis Pharmaceutical Corporation f/k/a Sandoz Pharmaceuticals Corporation ("NPC") since 1978. The active ingredient of Parlodel ® is bromocriptine mesylate ("bromocriptine").

2. In November 1976, NPC submitted a New Drug Application ("NDA") for Parlodel ® for treatment of amenorrhea/galactorrhea. [Summary for Basis of Approval: Amenorrhea/Galactorrhea] (Att.61).

3. Parlodel ® has been approved by the Food and Drug Administration ("FDA") since 1977 for treatment of amenorrhea/galactorrhea associated with hyperprolactinemia. [Summary for Basis of Approval: Amenorrhea/Galactorrhea] (Att.61).

4. In 1980, after reviewing extensive submissions from NPC's predecessor Sandoz Pharmaceuticals Corporation ("SPC"), the FDA approved Parlodel ® for the indication prevention of physiological lactation ("PPL"). Parlodel ® was found to be "both effective and safe" for the prevention of lactation. [Summary for Basis for Approval of Parlodel ®: Prevention of Physiological Lactation, at 9] (Att.62).

5. The FDA approved the use of Parlodel ® to treat individuals with Parkinson's Disease and also to treat infertility associated with hyperprolactinemia in 1981. [Summary for Basis for Approval of Parlodel ®: Parkinson's Disease] (Att.63); [Summary for Basis for Approval of Parlodel ®: Agromegaly] (Att.64).

6. The FDA approved Parlodel ® for the treatment of acromegaly in 1984. [Summary for Basis for Approval of Parlodel ®: Female Infertility] (Att.65).

7. The FDA approved Parlodel ® for the treatment of Prolactin–Secreting Adenomas. [Summary Basis of Approval of Parlodel ®: Prolactin–Secreting Adenomas] (Att.66).

2. The Court has adopted almost verbatim most of the proposed findings of fact and conclusions of law submitted by the defendant for the reason those proposed findings of fact and conclusions of law correctly reflect the facts in the record as well as relevant law. *Cf. Lansford–Coaldale Joint Water Auth. v. Tonolli Corp.,* 4 F.3d 1209 (3d Cir.1993). (The district court's findings were not deficient, even though they were a verbatim adoption of many of the defendant's proposed findings and did not contravene the purposes of Fed. R.Civ.P. 52(a)).

8. In 1990, an approved indication for Parlodel ® was the PPL.1990 PDR, (Att.68).

9. At all times relevant to this case, Parlodel ® was FDA-approved for the indication PPL. [Summary for Basis for Approval of Parlodel ®: Prevention of Physiological Lactation] (Att.63).

10. In its 1984 *FDA Drug Bulletin*, FDA noted that though the labeling of Parlodel ® was being revised to reflect reports of adverse reactions, "[a] cause and effect relationship has not been established." *FDA Drug Bulletin*, April, 1984 (Ex. 19). The 1984 Drug Bulletin expressly referenced dechallenge and rechallenge data.

11. The 1988 FDA Advisory Committee concluded that there was insufficient "evidence to indicate a causal relationship between the use of Parlodel ® and postpartum stroke/seizure." *See 1988 Summary Minutes* (Ex. 20).

12. The 1989 FDA Advisory Committee concluded that there was no "need" for pharmaceutical treatment of postpartum breast engorgement, but did not present or review any new data on safety, did not review any new data on efficacy, and did not vote on the safety and efficacy of Parlodel ® for the PPL. *See 1989 Summary Minutes* (Ex. 21).

13. Subsequent to the 1989 Advisory Committee meeting, Dr. Solomon Sobel prepared an internal memorandum to the Commissioner of the FDA concerning the Advisory Committee's recommendation that notes, *inter alia*, that "Ms. Ann Witt in the General Counsel's office reports that we have a case for a NOOH [Notice of Opportunity for a Hearing] based on updated *perceptions* of efficacy and safety, 'but it won't be easy' since we can raise *doubts* about safety but *we cannot prove that risks exist.*" *See* Memorandum from Solomon Sobel to The Commissioner, June 27, 1989 at 4 (Ex. 22) (emphasis added.)

14. SPC voluntarily withdrew the Parlodel ® indication for PPL on August 18, 1994. [Letter from Thomas Koestler to Solomon Sobel, 8/18/94] (Att.89).

15. FDA's August 1994 Notice of Opportunity for Hearing ("NOOH")—which was a proposal to withdraw the indication PPA—did *not* conclude that there was a causal connection between Parlodel ® and stroke in general, or ICH in particular. *See* 59 *Fed.Reg.* 43347 (August 23, 1994).

16. FDA's August 1994 NOOH states only that the information on adverse events raises safety *questions*, and seeks consideration of those issues. *See* 59 *Fed. Reg.* 43347, 43351 (August 23, 1994).

17. The FDA Notice of Opportunity for Hearing was based on FDA's receipt of reports of adverse experiences, and the Notice articulated the FDA's *perception* that no pharmaceutical intervention was needed, though it confirmed that FDA could not *prove* that Parlodel ® was not both "effective and safe," as it had determined in 1980. The Notice, in this regard, also confirmed the FDA's internal assessment in 1989 (when the FDA requested voluntary withdrawal of all lactation prevention drugs) that FDA could "raise doubts about safety but [FDA] cannot prove that risks exist." Memorandum from Solomon Sobel to The Commissioner, June 27, 1989, at 4 (Att.90).

18. SPC's voluntary withdrawal of the indication PPL from Parlodel ® mooted the administrative hearing process, and thus no hearing or formal proceeding was held.

19. Notwithstanding SPC's withdrawal of the indication PPL from Parlodel ®, on January 17, 1995, the FDA formally withdrew the indication PPL from Parlodel ®. 60 Fed.Reg. 3404–03 (January 17, 1995), (Att.94).

20. At least 10,000,000 (ten million) women in the United States are estimated to have used Parlodel ® for PPL between 1980 and 1994. Iffy/*Revels* Dep. at 58 (Att.1C); Iffy Dep. at 137 (Att.1A).[3]

21. Parlodel ® remains FDA approved today for the treatment of Parkinson's Disease, amenorrhea and galactorrhea, and pituitary and Prolactin disorders, such as acromegaly.

B. Use of FDA Proceedings in Assessing the Effects of Parlodel ® Use in Postpartum Women

22. The current FDA-approved labeling for Parlodel ® states that **"a causal relationship between Parlodel ® (bromocriptine mesylate) administration and hypertension, seizures, strokes, and myocardial infarction in postpartum women has not been established."** Physicians' Desk Reference, Aug. 1, 1998 (bold emphasis in original), Ex. RB.

23. The WARNINGS section of the current package labeling for Parlodel ® states that a causal relationship between Parlodel ® and the adverse events of stroke, seizure, and hypertension *has not been established:*

> Symptomatic hypotension can occur in patients treated with Parlodel ® (bromocriptine mesylate) for any indication. In postpartum studies with Parlodel ® (bromocriptine mesylate), decreases in supine systolic and diastolic pressures of greater than 20 mm and 10 mm Hg, respectively, have been observed in almost 30% of patients receiving Parlodel ® (bromocriptine mesylate). On occasion, the drop in supine systolic pressure was as much as 50–59 mm of Hg. **While hypotension during the start of therapy with Parlodel ® (bromocriptine mesylate) occurs in some patients, in postmarketing experience in the U.S. in postpartum patients 89 cases of hypertension have been reported, sometimes at the initiation of therapy, but often developing in the second week of therapy; seizures have been reported in 72 cases (including 4 cases of status epilepticus), both with and without the prior development of hypertension; 30 cases of stroke have been reported mostly in postpartum patients whose prenatal and obstetric courses had been uncomplicated. Many of these patients experiencing seizures and/or strokes reported developing a constant and often progressively severe headache hours to days prior to the acute event. Some cases of strokes and seizures were also preceded by visual disturbances (blurred vision, and transient cortical blindness). Nine cases of acute myocardial infarction have been reported.**
>
> **Although a causal relationship between Parlodel ® (bromocriptine mesylate) administration and hypertension, seizures, strokes, and myocardial infarction in postpartum women has not been established, use of the drug for prevention of physiological lactation, or in patients with uncontrolled hypertension is not recommended.**

Physicians' Desk Reference, Aug. 1, 1998 (bold emphasis in original), Ex. RB.

3. An expert's deposition in this case is cited as "[expert] Dep." Their depositions in other cases are cited as "[expert] [case name] Dep. Citation to any expert's deposition in the Alabama cases of *Brasher/Globetti/Quinn* may be abbreviated as "*B/G/Q.*" " Thus, "Kulig/*Rider* Dep. 209" refers to page 209 of Dr. Kulig's deposition in the case of *Rider v. Sandoz Pharmaceuticals Corporation.* Dr. Kulig has also testified at trials or hearings involving Parlodel ®; testimony from these proceedings is cited, *e.g.,* as "Kulig/[case name] Trial Transcript."

24. In the sub-section entitled "Adverse Events Observed in Other Conditions, *Postpartum Patients*" of the ADVERSE REACTIONS section, the current package labeling further states:

> In postmarketing experience in the U.S. serious adverse reactions reported include 72 cases of seizures (including 4 cases of status epilepticus), 30 cases of stroke, and 9 cases of myocardial infarction among postpartum patients. Seizure cases were not necessarily accompanied by the development of hypertension. An unremitting and often progressively severe headache, sometimes accompanied by visual disturbance, often preceded by hours to days many cases of seizure and/or stroke. Most patients had shown no evidence of any of the hypertensive disorders of pregnancy including eclampsia, preeclampsia or pregnancy induced hypertension.... **The relationship of these adverse reactions to Parlodel® (bromocriptine mesylate) administration has not been established.**

Physicians' Desk Reference, Aug. 1, 1998, Ex. RB (emphasis added).

25. This language appeared on the Parlodel® label in March 1995, just two months after FDA published in the *Federal Register* its notice of the withdrawal of the prevention of PPL. *See* Ex. RP

26. At the *Daubert* hearing in *Railey v. Sandoz Pharmaceuticals Corporation,* Dr. Kenneth William Kulig agreed with Judge McDade that FDA, being a prudent agency, would err on the side of caution if there were even a possibility that an adverse effect outweighed the benefit of a drug. 11/9 Tr. at 124–25; *see also* Ex. SR (Kulig/*Railey* Tr. at 118).

27. In his testimony at the *Daubert* hearing in *Railey v. Sandoz Pharmaceuticals Corp.,* Dr. Kulig admitted that the December 1994 FDA *Federal Register* notice regarding Parlodel® was not proof that Parlodel® causes strokes. Ex. SR (Kulig/*Railey* Tr. at 119).

C. Findings of Fact Regarding the Pharmacology of Parlodel®

28. Like dozens of other drugs, bromocriptine is derived from ergot, a naturally-occurring substance. The drugs deriving from ergot are known as "ergot alkaloids." Berde and Strumer, "Introduction to the Pharmacology of Ergot Alkaloids and Related Compounds as a Bases of Their Therapeutic Application," *Ergot Alkaloids and Related Compounds* (hereinafter "Berde"), (Att.23).

29. Bromocriptine differs physically from the other ergot alkaloids in several respects, the most notable of which is that a bromine atom has been added. Clark, *et al,* "Actions on the Heart and Circulation," *Ergot Alkaloids and Related Compounds* 321 (1978), (Att.67).

30. Slight differences in molecular structure can cause seemingly similar compounds to have radically different biological effects. Berde p. 2, (Att.23).

31. For example, bromocriptine inhibits uterotonic activity, whereas methlyergotamine has potent uterotonic activity in the rabbit. Berde p. 4, (Att.23).

32. Bromocriptine acts on dopamine receptors in the brain and elsewhere to produce its clinically useful effects. "*Parlodel®*," Physicians' Desk Reference, (Medical Economics Data 1990) (hereinafter "1990 PDR"), (Att.68). Most of these effects occur due to the drug's action on dopamine receptors in the pituitary gland, a midbrain structure that controls many hormonal functions. *Id.* Bromocriptine blocks the secretion of the hormone Prolactin, which acts on the breasts to induce secretion of milk. Bromocriptine thus prevents lactation from occurring by blocking

the hormone that causes it. *Id.* Because it prevents the secretion of Prolactin, bromocriptine has traditionally been used (and is still used today) for a number of disorders characterized by hyperprolactinemia, or excess prolactin secretion: amenorrhea, galactorrhea, some types of female infertility, hypogonadism, and Prolactin-secreting adenoma.[4] *Id.* In addition, bromocriptine is used for acromegaly and Parkinson's disease.[5]

33. For PPL, Parlodel ® is typically taken for 14 days, but hyperprolactinemia, acromegaly, and Parkinson's patients may take the drug every day for years. *Id.*

D. Findings of Fact Regarding the Medical History Giving Rise to This Lawsuit

34. Plaintiff was admitted to the hospital and delivered her second child on December 26, 1990. 12/26/90, Labor and Delivery Summary, Sentara Norfolk General Hospital, (Att.69).

35. Plaintiff was normotensive (that is, did not have elevated blood pressure) before or during her pregnancy or during or immediately after her delivery. 8/3/89 and 4/5/90, Office Notes, Dr. Shawne R. Bryant, (Att.70); 6/4/90 to 12/26/90, Prenatal Flow Sheet, Dr. Gad E. Brosch, (Att.71); 12/26/90, Labor Record, Sentara Norfolk General Hospital, (Att.72); 12/26/90, Anesthesia Record, Sentara Norfolk General Hospital, (Att.73); 12/26/90, Recovery Room Record, Sentara Norfolk General Hospital, (Att.74); 12/26/90 to 12/27/90, Postpartum Nurses' Records, (Att.75).

36. Plaintiff elected not to breast feed. 12/26/90, Assessment Screening Room Form, Sentara Norfolk General Hospital, (Att.76).

37. On December 26, 1990, plaintiff's treating OB–GYN, Dr. Gad E. Brosch, dictated a 15–day order for Parlodel ®, 5 mg/day, to be taken in two 2.5 mg doses per day. 12/26/90, Physician's Post Partum Orders Form, Sentara Norfolk General Hospital, (Att.77).

38. The hospital medication administration records reflect Parlodel ® was not administered while plaintiff was in the hospital. 12/26/90, Medication Administration Record, Sentara Norfolk General Hospital, (Att.78).

39. Plaintiff was discharged from the hospital on December 27, 1990. 12/27/90, Physician's Order Form, Sentara Norfolk General Hospital, (Att.79).

40. There are no records of any prescription for Parlodel ® being filled after plaintiff left the hospital on December 27, 1990.

41. Plaintiff does not recall when she started taking Parlodel ®. Deposition of Lisa Soldo ("Soldo Dep."), p. 121, (Att.8).

42. Plaintiff does not remember how often she took Parlodel ®. Soldo Dep. p. 121–22, (Att.8).

4. Amenorrhea is the absence of menses; galactorrhea is the abnormal production of milk at a time other than after pregnancy; hypogonadism is a condition characterized by low levels of sexual hormones; and a prolactin-secreting adenoma is a type of pituitary-gland tumor. Each condition benefits from the blocking of prolactin secretion.

5. Acromegaly is a condition caused by excess secretion from the pituitary gland of human growth hormone ("HGH"); bromocriptine has no effect on HGH secretion in people with normal levels of the hormone but reduces secretion in acromegalics. Parkinson's disease is primarily a disease of the dopamine receptors in the central nervous system. By a mechanism thought to involve its dopamine-receptor action, bromocriptine helps to reverse the effects of the disease.

43. Plaintiff does not remember how many pills of Parlodel ® per day she took. Soldo Dep. p. 121–22, (Att.8).

44. Plaintiff testified that she took Parlodel ® while she was visiting her parents in Transfer, Pennsylvania. Soldo Dep. p. 129, (Att.8).

45. Plaintiff recalls that she discarded her empty Parlodel ® bottle "about one or two days" before her stroke. Soldo Dep. p. 128, (Att.8).

46. Plaintiff's experts credit plaintiff's deposition testimony that she did not follow her prescription and instead completed her Parlodel ® regimen "one or two days" before her intracerebral hemorrhage ("ICH"). (11/8 Tr. at 73); 11/15 Tr. at 38, 57.

47. Plaintiff's experts cannot state, given plaintiff's deposition testimony, when plaintiff took her last dose of Parlodel ®. 11/15 Tr. at 57.

48. There is no evidence other than plaintiff's deposition testimony regarding the frequency and duration of plaintiff's Parlodel ® usage.

49. There is no scientific method to determine when plaintiff took her last dose of Parlodel ®. 11/15 Tr. at 62.

50. A 15–day prescription for Parlodel ®, started on December 27, 1990, would have been completed on or around January 9, 1991.

51. On January 18, 1991, 23 days after her discharge, while still in Pennsylvania, plaintiff complained of a very severe headache, and laid down in a room at her mother's house. Soldo Dep., pp. 132–33, (Att.8).

52. When awakened several hours later, plaintiff was unresponsive.

53. Plaintiff was taken to Sharon General Hospital, where a CT-scan of the brain revealed an ICH. 1/18/91, Head CT-scan Report, Sharon General Hospital, (Att.80).

54. Plaintiff's Emergency Room admission form, completed with information provided by her family, lists possible aspirin use, but not Parlodel ®. 1/18/91, Emergency Room Record, Sharon General Hospital, (Att.52).

55. Shortly after admission to Sharon General Hospital, at 11:12 p.m., a urine sample was collected for a toxicology screen. The drug screen results indicated the presence of salicylate (aspirin) and "large amount present" of amphetamines. 1/18/91, Laboratory Report, Sharon General Hospital, (Att.81).

56. On January 19, 1991, plaintiff was transferred to Saint Elizabeth Hospital Medical Center for further treatment. While there, she was given a four-vessel cerebral arteriogram to help diagnose her condition. 1/19/91, Arteriogram Report, Saint Elizabeth Hospital Medical Center, (Att.82). Plaintiff also underwent a craniotomy to evacuate a large hematoma that had built up as the result of her cerebral bleed. 1/20/91 Operation Report, Saint Elizabeth Hospital Medical Center (incorrectly dated 1/21/91), (Att.83). Fragments of the hematoma were examined and found consistent with an acute hemorrhage. 1/20/91, Pathology Report, Saint Elizabeth Hospital Medical Center, (Att.84).

57. Plaintiff's highest recorded blood pressure in the Sharon General emergency room was 130/70. 1/18/91, Emergency Room Record, Sharon General Hospital, (Att.52); 1/18/91—1/19/91, frequent Vital Signs Form, Sharon General Hospital, (Att.91). Plaintiff's highest recorded blood pressure at Saint Elizabeth Hospital Medical Center, prior to her craniotomy was a single reading of 150/90. Most readings at Saint Elizabeth Hospital Medical Center averaged in the 110/80 range. 1/19/91, Crit-

ical Care 24 Hour Flowsheet, Saint Elizabeth Hospital Medical Center, (Att.85).

58. On January 20, 1991, plaintiff was again screened for substances in her blood. The results were negative for most substances, including salicylates, acetaminophen, and amphetamine. The test also found "substance present consistent with sympathomimetic amine." 1/20/91, Laboratory Report, Saint Elizabeth Hospital Medical Center, (Att.86).

59. There were no objective measurements made of the amount of Parlodel ®, if any, in plaintiff's blood or tissue at the time of plaintiff's ICH. 11/8 Tr. at 91–92.

60. Plaintiff's experts testified that the half-life of Parlodel ® in the blood may be as short as three hours and may be a high as 100 hours. 11/15 Tr. at 58.

61. Plaintiff's experts assume that plaintiff had "a substantial amount" of Parlodel ® in her system at the time of her ICH. 11/15 Tr. at 20.

62. If plaintiff took her last dose of Parlodel ® only one day (24 hours) before her ICH, based on a three-hour serum half life the Parlodel ® in plaintiff's system would have gone through eight half-lives prior to the event. After eight half-lives, only 1/256th of the amount of Parlodel ® initially in plaintiff's blood stream would be present. 11/15 Tr. at 60–61.

63. If plaintiff took her last dose of Parlodel ® only two days (48 hours) before her ICH, based on a three-hour serum half life only 1/65,000th of the amount of Parlodel ® initially in plaintiff's blood stream would have been present at the time of the event. 11/15 Tr. at 61.

64. If plaintiff last took Parlodel ® as much as 60 hours prior to her stroke, a possibility recognized by plaintiff's experts (11/15 Tr. at 57), based on a three-hour serum half-life her blood levels of bromocriptine would be reduced by a factor of 2 20 from their initial, therapeutic level, *i.e.*, would be less than one two-millionth of their starting levels at the time of her event.

65. If plaintiff took her last dose of Parlodel ® only one day (24 hours) before her stroke, a possibility recognized by plaintiff's experts (11/15 Tr. at 58), based on a 100–hour half-life, her blood levels at the time of the stroke would be only barely lower than they were when last at therapeutic levels.

66. Given the uncertainties in the timing of plaintiff's last dose and uncertainties with respect to the half-life of bromocriptine articulated by plaintiff's experts, it is unknown whether the level of bromocriptine in plaintiff's blood stood at the therapeutic level at one extreme or 1/2,000,000 of the therapeutic level at the other extreme or somewhere in between.

67. Plaintiff has not demonstrated a scientifically valid basis to conclude that she was taking Parlodel ® one or two days before her ICH.

68. Plaintiff has not demonstrated that she had a substantial amount of Parlodel ® in her system at the time of her ICH.

69. Plaintiff has not demonstrated that she had an amount of Parlodel ® in her system at the time of her ICH sufficient to cause any biological effect.

70. At the time of her stroke, plaintiff smoked between half a pack and a pack of cigarettes per day. 1/19/91, History and Physical, Saint Elizabeth Hospital Medical Center, (Att.52).

71. At her deposition, plaintiff could not remember the date of her stroke. Soldo Dep. p. 129, (Att.8).

72. Plaintiff has testified that her stroke keeps her from remembering facts about her Parlodel ® usage. Soldo Dep. p. 122, (Att.8).

E. Findings of Fact Regarding Epidemiology

73. Stroke is a relatively common and widespread disease in the United States; there are 700,000 new stroke cases a year in the United States, and it is the third leading cause of death in the United States. 11/16 Tr. at 69.

74. A background risk for stroke exists in all age groups. 11/17 Tr. at 56.

75. Dr. Kulig conceded that he does not know the annual incidence of stroke in the United States. 11/8 Tr. at 169.

76. Dr. Kulig conceded that he does not know whether stroke is more common than breast cancer in the United States. 11/8 Tr. at 171.

77. Dr. Kulig conceded that he does not know whether stroke is the third leading cause of death in the United States after diseases of the heart and all cancers combined. 11/8 Tr. at 170–71.

78. Dr. Kulig conceded that he does not know what percentage of stroke victims in the United States is persons under age 65. 11/8 Tr. at 170.

79. Differential diagnosis alone cannot establish causation to a degree of medical certainty in a case involving a disease as common as stroke. 11/16 Tr. at 99; *see also* Ex. SQ (*In re New York State Silicone Breast Implant Litigation, Brusch v. Cooper Companies,* No. 128115/93, Tr. (9/29/97)) at 859 ("a cause and effect relationship" cannot be shown with a disease as common as breast cancer in humans "*by a process of differential diagnosis*") (discussed in 11/8 Tr. at 179–80).

80. Roughly one-third of all strokes, despite careful evaluation, go undiagnosed as to their cause. 11/15 Tr. at 174.

81. Strokes exist for which a particular cause cannot be ascertained, even after extensive investigation. 11/10 Tr. at 212.

82. There are strokes in persons of any age for which we do not have a mechanism to explain their causality. 11/10 Tr. at 214.

83. "In the absence of an understanding of the biological and pathological mechanisms by which disease develops, epidemiological evidence is the most valid type of scientific evidence of toxic causation." Federal Judiciary Center, *Reference Manual on Scientific Evidence* ("Ref. Man. Sci. Evid.") at 126.

84. Regardless of whether the mechanism is known, given the existence of a background risk of stroke, the scientific way to determine whether bromocriptine increases the risk of stroke in humans is through a proper controlled clinical or epidemiologic study. 11/15 Tr. at 181–82; 11/17 Tr. at 56; Ex. SQ at 859 (Dr. Kulig agrees controlled study is required to establish a cause and effect relationship between a substance and a disease as common as breast cancer).

85. For example, because of the background risk of birth defects, it was necessary to conduct epidemiologic studies to determine whether Bendectin use raises the risk of developing birth defects. Ultimately, epidemiology demonstrated that there was a negative association between Bendictin and an increased risk of birth defects, or, put another way, Bendectin use did not raise the odds of having a child with a birth defect. 11/17 Tr. at 57–58.

86. A particular epidemiologic study's measurement of relative risk has no meaning by itself but must be interpreted in conjunction with its statistical degree of confidence. Ref. Man. Sci. Evid. at 152–55. Relative risk is always expressed with "confidence intervals" that indicate a range of relative risk values in which the "true" relative risk is very likely to fall. *Id.* at 154–55. A confidence interval that includes 1.0 means that the relative risk estimate in

a particular study is not statistically significant. *Id.* at 154–55. *See generally* Ref. Man. Sci. Evid. at 147–49, 154–55. Relative risk is the ratio of the incidence of disease in exposed individuals to the incidence in unexposed individuals. A relative risk of 1.0 means that the incidence in each group is the same, *i.e.,* the exposure has no association with the disease. A relative risk significantly below 1.0 means that the exposure is associated with the absence of the disease, whereas a relative risk significantly above 1.0 means that exposure is associated with an increased risk of the disease.

87. During the postpartum period, women are at an increased risk of many types of cerebrovascular accidents, including cerebral infarction, ICH, and subarachnoid hemorrhage. *See* The Kittner Study; *see also* 11/15 Tr. at 168–71.

88. Indeed, postpartum stroke is a common serious complication of pregnancy. 11/15 Tr. at 168; 11/16 Tr. at 24; *see also* Kulig/*Roberts* Tr. at 44–45 (pregnancy and delivery are risk factors for stroke; probably increased incidence of postpartum stroke;) *see generally* Lanska and Kryscio, *Peripartum Stroke and Intracranial Venous Thrombosis in the National Hospital Discharge Survey,* 89 Obstetrics & Gynecology 412 (1997), Ex. GT; *see also* 11/16 Tr. at 73–74.

89. "There are a number of physiological changes that occur in the transformation from pregnancy back to the non-pregnant state. These take place in what's known as the postpartum period, which is defined as the first six weeks post-delivery. During that time there's a major decrease in blood volume; there are hormonal changes, as the woman shifts from the hormonal state of pregnancy to non-pregnancy; there are changes in coagulation of the blood that are thought to create a hypercoagulable state, that is a state in which blood clots more easily in some women in this period. Those are some of the mechanisms that have been put forth to account for the rise in stroke in the postpartum period." 11/15 Tr. at 170.

90. Data on pregnancy and the postpartum period gathered for the past five decades reflect that postpartum stroke is a common serious complication of pregnancy. Douglas J. Lanska, M.D., M.S., M.P.H., and Richard J. Kryscio, Ph.D., "Stroke and intracranial venous thrombosis during pregnancy and puerperium," 51 *Neurology* 1622, 1627 (1998) (table 3 citing epidemiologic studies of stroke), Ex. GU; *see also* 11/15 Tr. at 168–70.

91. Plaintiff concedes that no epidemiology exists that demonstrates that a woman taking Parlodel ® postpartum is more than twice as likely to have a stroke than a woman who has not taken Parlodel ®, *i.e.,* statistically-significant epidemiology demonstrating a relative risk greater than 2.0. 11/8 Tr. at 9, 10.

92. Plaintiff cannot present any statistically significant study demonstrating an association between *any* ergot alkaloid and stroke in human beings. 11/9 Tr. at 132.

93. Plaintiff cannot cite any study showing that the rate of postpartum stroke increased significantly starting in 1980 when Parlodel ® was introduced for the prevention of postpartum lactation in the United States. 11/15 Tr. at 70.

94. Plaintiff cannot cite any article that indicates that the risk of postpartum stroke significantly decreased after 1994 when the Parlodel ® PPL indication was withdrawn in the United States. 11/15 Tr. at 71.

95. There is no prospective, double-blind, randomized, placebo-controlled study—published or unpublished—that shows that bromocriptine causes stroke. 11/10 Tr. at 187.

96. Epidemiology has methods and standards and, as such, is by its very nature "testable." Epidemiologists express study results in terms of a relative risk.

97. Plaintiff's experts, Drs. Kenneth Kulig and Dennis Petro, disregard the *express* conclusion of the studies that eclampsia is not a sufficient explanation for the increased risk of postpartum stroke. *E.g., id.;* Kulig/*Hollander* Dep. 117 (Att.2A); Petro Dep. 225, 227 (Att.3E); Petro/*Rider* Dep. 242–43 (Att.3A).

98. Drs. Kulig and Petro both concede that there is no statistically-significant epidemiologic study showing that Parlodel ® increases the risk of stroke. *See* Petro/*B/G/Q* Dep. 290 (Att.3C); Iffy/*NJC* Dep. 46–52, 143 (Att.1A); Kulig/*Hollander* Dep. 108–09 (Att.2A).

99. At his deposition in *Brasher v. Sandoz Pharmaceuticals Corporation,* 160 F.Supp.2d 1291 (N.D.Ala. 2001) Dr. Petro, plaintiff's expert, acknowledged that the postpartum period itself is a risk factor for stroke. Petro/*Brasher* Dep. at 322.

100. Notwithstanding the existence of compelling evidence of an elevated risk of stroke in the postpartum period, Dr. Petro offered no basis to rule out the postpartum period in performing his differential diagnosis for plaintiff's stroke. *E.g.,* 11/10 Tr. at 105 ("there's no reason to believe that just having a child three weeks prior will in fact make that person susceptible to stroke").

101. Plaintiff designated, but declined to call to testify, Dr. George Macones, an expert epidemiologist.

102. Dr. Macones rejects Dr. Kulig's hypothesis. Dr. Macones previously testified that the epidemiology clearly showed an increased risk of stroke in the postpartum period, even excluding preeclampsia and eclampsia. In an unrelated Parlodel ® case, Dr. Macones testified regarding the Kittner Study:

> Q. So postpartum stroke can clearly occur in women who up to that point have had normal pregnancies and are deemed healthy. Correct?
>
> A. Yes.
>
> Q. Now, focusing on figures one and two, if we excluded all strokes associated with preeclampsia and eclampsia, we could apply the formula that we discussed earlier to make a relative risk estimation for the postpartum period compared to the balance of pregnancy. Correct?
>
> A. Yes, we could use your formula.
>
> . . .
>
> Q. And that would yield a relative risk estimate of 11.9, roughly?
>
> A. 11.9, good job.
>
> Q. So using that estimate that would indicate that if one excludes preeclampsia and eclampsia, there still seems to be substantial increased risk of stroke in the postpartum period compared to the balance of pregnancy. Correct?
>
> A. . . . [A]gain, using person weeks is one way of doing it. And if you look at it in terms of weeks like that and weeks at risk, then your 11 relative risk is right. I think another legitimate way to look at it is just to look at pregnancy and postpartum and not count the number of weeks. . . . [T]he relative risk would be whatever, 1.8, 1.9, something like that.
>
> Q. . . . [E]ven if we did it your way, . . . one still finds roughly twice as many postpartum strokes as strokes during pregnancy. Correct?
>
> A. Yeah, that's absolutely what they found.
>
> Q. Even if you exclude preeclampsia and eclampsia?
>
> A. Yeah, that's correct.

Macones/*B/G/Q* Dep. 94–95 (Att.4A). Thus, Dr. Macones testified that he had no basis to disagree with the conclusion of Kittner that "[a] causal role for preeclampsia and eclampsia does not fully explain the much stronger associations in stroke found for the postpartum state than for pregnancy itself."

Macones/*B/G/Q* Dep. 101 (citing Kittner) (Att.4A).

103. Dr. Macones admits that the epidemiologic data do not support the conclusion that Parlodel ® increases the risk for postpartum stroke: "Based on the epidemiological data that I have reviewed, not having reviewed anything else, the answer would be that I can't say either way." Macones/*NJC* Dep. 41–42 (Att.43).

104. Dr. Macones has testified that it is unknown whether there is a positive or a negative association between Parlodel ® and stroke. Macones/*Hernandez* Dep. 65–66 (Att.9).

105. Plaintiff's experts are similarly unable to point to any clinical trial for any indication of Parlodel ® in which there was a statistically-significant increased risk of stroke. Petro/*B/G/Q* Dep. 311 (Att.3C). Nor can plaintiff's experts point to any treatises or textbooks stating that bromocriptine causes stroke. Petro/*B/G/Q* Dep. 337 (Att.3C); Iffy/*NJC* Dep. 181–83 (Att.1A).

106. Plaintiff's experts do not rely on any clinical trial that demonstrated stroke associated with any use of Parlodel ®. 11/9 Tr. at 74.

(i) Study 60

107. Dr. Kulig testified that the Sandoz Study 60 shows that "at least one case of hypertension was caused by the drug [Parlodel ®] using the drug company's own causation assessment." 11/9 Tr. at 78.

108. The investigators/authors of Sandoz Study 60 do not state anywhere in the report that hypertension was demonstrated in any participant in the study. Ex. LG (Study 60).

109. Indeed, the authors of Sandoz Study 60 stated that "Parlodel ® was safe and relatively well tolerated, although a blood pressure *lowering* effect was noted." Ex. LG at 6.

110. Dr. Kulig does not recall whether he reviewed the actual blood pressure data from any of the patients in Sandoz Study 60 to see whether the data supported his assertion that at least one case of hypertension during the clinical trial was caused by Parlodel ®. 11/9 Tr. at 83.

111. In Sandoz Study 60, one trial participant-Patient 62—exhibited a single diastolic hypertensive blood pressure reading during a second 24–week phase of a three-phase clinical trial. 11/16 Tr. at 165–66.

112. As plaintiff's expert Dr. Petro testified, a single reading of elevated blood pressure is insufficient to support a finding of hypertension. 11/10 Tr. at 195–97.

113. In any event, Patient 62 in the Sandoz Study 60 was hypertensive *prior to* participating in the Parlodel ® clinical trial. 11/16 Tr. at 171.

114. After her 72–week involvement in the Sandoz Study 60, Patient 62's measured blood pressure was significantly lower than it had been before her participation in Study 60. 11/16 Tr. at 171–72.

115. The Sandoz Study 60 did not demonstrate that Parlodel ® treatment causes hypertension or elevated blood pressure.

116. There is no evidence that the Sandoz Study 60 raw data was "sanitized" in any way, at any time. 11/17 Tr. at 14–15.

117. Plaintiff presented no factual evidence that Sandoz Study 60 was terminated prematurely or "sanitized" in any way.

118. Plaintiff has not demonstrated that the Sandoz Study 60 supports her hypothesis that Parlodel ® taken in therapeutic doses causes cerebral vasoconstriction or vasospasm.

119. Plaintiff has not demonstrated that the Sandoz Study 60 raw data supports her hypothesis that Parlodel ® taken in therapeutic doses causes cerebral vasoconstriction or vasospasm.

120. Plaintiff has not demonstrated that the Sandoz Study 60 or its raw data supports her hypothesis that Parlodel ® taken in therapeutic doses causes ICH.

(ii) Hand Vein Study

121. Dr. Kulig testified that the Sandoz "hand vein study" demonstrates that "Parlodel ®, like the other ergot alkaloids, is a vasoconstrictor, and in this case the blood vessel that was examined was the hand veins [sic] of human beings." 11/8 Tr. at 145–46.

122. At his deposition in *Siharath v. Sandoz Pharmaceuticals Corp.,* Dr. Kulig stated that he does not know whether the hand vein study results can be extrapolated to cerebral veins. 11/9 Tr. at 114; *see also* Kulig/*Siharath* Dep. at 199 (Att.10).

123. Dr. Kulig conceded that he also does not know whether the results of the hand vein study can be extrapolated to cerebral *arteries.* 11/9 Tr. at 114–19.

124. Dr. Kulig did not attempt to compare the doses and blood levels of bromocriptine in Sandoz' experiment against those seen in women receiving oral doses of Parlodel ®. 11/9 Tr. at 119.

125. A woman would have to take 5,000 Parlodel ® 2.5 mg tablets in a single dose to place the same amount of bromocriptine in her bloodstream as was used in the "hand vein study." 11/16 Tr. at 154–55.

126. The hand vein study is a dose response study in which no effect was noted except at the highest of the test infusion doses, which was many times the dose and blood level of bromocriptine ingested under prescription for the Parlodel ® PPL indication.

127. The hand vein study does not demonstrate that any person taking Parlodel ® at therapeutic doses would develop any of the outcomes which Dr. Kulig asserts based on his interpretation of the hand vein study.

128. The hand vein study does not demonstrate that any person taking Parlodel ® at therapeutic doses would develop cerebral vasoconstriction.

129. Extrapolation from the massive Parlodel ® doses given in the hand vein study to postpartum women taking Parlodel ® does not comport with the fundamental principle of dose response. *Cf.* 11/17 Tr. at 42–43.

130. Plaintiff's experts, Drs. Kulig and Petro, do not use a scientifically valid methodology in relying on the results of the hand vein study as support for their opinion that Parlodel ® can cause ICH in postpartum women when taken at therapeutic doses.

(iii) Epidemiological Studies re: Parlodel ® and Stroke

131. Among the epidemiologic studies concerning Parlodel ® and stroke are the ERI Study, the HCIA Study, the Kittner Study and the Witlin–Sibai Study. In the first study, investigators reviewed hospital databases with information about 280,096 women delivering babies. Kenneth Rothman, *An Epidemiologic Evaluation of the Possible Relation Between Bromocriptine, Puerperal Seizures and Strokes,* (Sept. 30,

1988) ("ERI Study") (Att.14). (The case-control model of epidemiologic studies is explained in detail in the Ref. Man. Sci. Evid. at 136–38.) Out of a total of 10 postpartum strokes in this population, only *one* occurred in a woman who had taken Parlodel ®. The resulting relative risk calculation (8.4) was not statistically-significant, and the study was deemed "not informative." ERI Study (Att.14) at 2.

132. Dr. Rothman found that, at the 90% confidence level, the lower confidence interval for the risk of stroke due to Parlodel ® use was only 0.40, consistent with a negative association. *Id.*

133. Plaintiff's experts state that this single occurrence of a stroke among more than 280,000 women is evidence of general causation, though they nonetheless agree that it lacks statistical significance. Petro/*B/G/Q* Dep. 409 ("the sample size was inadequate to appropriately address the question [whether Parlodel ® causes stroke]") (Att.3C); Iffy/*NJC* Dep. 48 (ERI study did not reach statistical significance) (Att.1A); Kulig/*NJC* Dep. 83 ("I don't believe it's a very reliable study. . . .") (Att.2B); Kulig/*Daubert* Hearing Transcript in *Nussel (Railey v. Novartis Pharms. Corp.,* Case No. 94–1440 (C.D. Ill., Peoria Div.)), Apr. 6, 1999, Vol. I, at 79–80 ("I'm not claiming that [the ERI] study shows that the drug Parlodel ® causes stroke") (Att.2C); Kulig/*O'Connor* Dep. 35–39 (admission that he is bound by investigator's statement that study is inconclusive) (Att. 2D).

134. Dr. Kulig testified that the ERI study is the only epidemiologic study on which he relies as support for his opinion that Parlodel ® causes ICH in the postpartum period. 11/8 Tr. at 206; *see* Ex. KW.

135. Dr. Kulig concedes that the confidence interval for the stroke data in the ERI study crossed the number one and therefore could not exclude the possibility that the calculated relative risk of stroke in women using Parlodel ® was due to chance. 11/8 Tr. at 207, 212–13.

136. The results of the ERI study concerning stroke are negative in terms of the hypothesis that Parlodel ® causes stroke. 11/15 Tr. at 183.

137. In his deposition in *O'Connor v. Sandoz Pharmaceuticals Corp.,* Dr. Kulig testified: "[The ERI study] doesn't prove anything basically if you want to use proof in a very scientific sense of the word, it doesn't prove that Parlodel ® causes strokes or seizures, it's suggested that it does, but it doesn't prove it, and I think we need to prove it one way or the other in order to call this drug safe or effective." Kulig/O'Connor *Dep. at 38 (Att.7).*

138. In an affidavit submitted in the case *Railey v. Sandoz Pharmaceuticals Corporation,* Dr. Kulig wrote, "This [ERI] study is inherently unreliable and is not relied upon. . . ." 11/8 Tr. 191; *see also* Ex. SP (*Railey* Affidavit).

139. Dr. Kulig concedes that the basis for his opinion in *Railey v. Sandoz Pharmaceuticals Corporation* is the same as the basis for his opinion in this case. 11/8 Tr. at 209.

140. Dr. Kulig testified that he relies on the ERI study as support for his opinion that Parlodel ® causes ergotism. 11/9 Tr. at 8–9.

141. As Dr. Kulig concedes, the ERI study nowhere concludes or states that Parlodel ® causes ergotism. 11/9 Tr. at 10.

142. Indeed, the ERI study does not make findings about a link between Parlodel ® and ergotism. 11/15 Tr. at 184.

143. Dr. Petro testified that he is not relying on the ERI study for any portions of his opinion. 11/10 Tr. at 99.

144. Dr. Petro nevertheless cites the ERI study as evidence that Parlodel ® used in the postpartum period was a significant risk factor for stroke. 11/15 Tr. at 71.

145. Dr. Macones admits that the ERI study on Parlodel ® and postpartum stroke, upon which plaintiff's other experts rely, is "uninformative" on that issue and does not even begin to address the question. Macones/*Hernandez* Dep. at 65 (Att.9).

146. Dr. Macones admits that, if additional stroke cases had been found in the ERI study, it is entirely speculative as to whether such stroke cases would have been women who used Parlodel ® or women who did not. Macones/*B/G/Q* Dep. at 78–80 (Att.42). Similarly, Dr. Macones admits that, if additional stroke cases had been found, additional controls would have been selected and it is entirely speculative as to whether such controls would have been women who used Parlodel ® or women who did not. *Id.*

147. The ERI study stroke results are not statistically significant and may not be used in a scientifically valid manner to support an expert's opinion that bromocriptine causes stroke.

148. The Witlin–Sibai study, "Postpartum Stroke: A Twenty–Year Experience," examined the incidence of stroke in postpartum women. Ex. OE.

149. When the underlying study data were examined for the possible role of Parlodel ® use in postpartum stroke, the Witlin–Sibai study results supported the hypothesis that bromocriptine use in the postpartum period was protective of stroke, or, to put it another way, the study showed that women taking bromocriptine were eight times less likely than women not taking bromocriptine to develop stroke in the postpartum period (Odds Ratio 0.12). This result is statistically significant. 11/17 Tr. at 67–68.

150. Dr. Sibai reliably obtained the 40,000 Parlodel ® user figure used in the Witlin–Sibai study by asking Roberta Rogers, a Pharm.D., to review the hospital pharmacy records to determine how many Parlodel ® prescriptions were written over a two-year period. This figure was then extrapolated and applied over the entire period when Parlodel ® was used for postpartum lactation at Dr. Sibai's hospital. 11/17 Tr. at 77–78.

151. Even if the number of bromocriptine users in the Witlin–Sibai study were overstated by 33% (of which there is no evidence), the results of the study would not fundamentally change; the study results would still reflect that women taking bromocriptine were five times less likely than women not taking bromocriptine to develop stroke. This result would still be statistically significant. 11/17 Tr. at 70.

152. The Witlin–Sibai study was peer-reviewed and initially accepted for publication. 11/17 Tr. at 73.

153. After plaintiff's counsel contacted the journal editor by telephone and in writing, the journal editor "knuckled under" and declined to publish the study. 11/17 Tr. at 73.

154. Dr. Laura Carolyn Green relied upon Dr. Sibai's affidavit regarding the Witlin–Sibai study, an affidavit with a higher degree of reliability than the kinds of explanatory information she would normally have access to in assessing the scientific validity of a study. 11/17 Tr. at 65.

155. Although Dr. Kulig characterizes the Witlin–Sibai study as "litigation science," Dr. Witlin was not an expert witness for NPC when the manuscript was written and Dr. Sibai was not an expert witness for NPC when the data on which

the manuscript is based was collected. 11/9 Tr. at 21.

156. A third epidemiologic study analyzed 533,816 delivery records from 128 hospitals and tracked postpartum complications, correlating these complications with Parlodel ® use. HCIA, *Postpartum Complications and Parlodel* ® (October 1995), Ex. DZ. This study estimated a relative risk for stroke associated with bromocriptine use of 1.088 with a confidence interval ("CI") from 0.448 to 2.643. Because the CI included 1, this result was not statistically-significant. *Id.; see also* 11/9 Tr. at 14–15 (dismissing results from HCIA study); Kulig/*NJC* Dep. 78 (" . . . overall I think the [HCIA] study is not reliable in answering the questions that need to be answered.") (Att.8); Macones/*Hernandez* Dep. 76–77 ("the confidence intervals are extremely wide which suggest . . . huge amounts of uncertainty in the data.") (Att.9).

157. The HCIA study does not support plaintiff's hypothesis that bromocriptine use increases the risk of stroke in postpartum women.

158. The Kittner study determined that the risk of ICH during the postpartum period is 28.3 times higher than in similarly aged women who are not postpartum. 11/15 Tr. at 173.

159. Plaintiff's ICH falls in the postpartum time frame identified by the Kittner study as a period of significantly increased risk for stroke. 11/15 Tr. at 176–77.

160. The results of the Kittner study are consistent with the long-standing literature and studies that support the hypothesis that the postpartum period is a risk factor for stroke. 11/17 Tr. at 137–38; 11/16 Tr. at 73–76.

161. Because of the different baseline risk for stroke between European and African–American women, and the differing baseline risks of stroke depending on age, the Kittner study was age and race adjusted to minimize these possible biases in the study data. 11/16 Tr. at 16.

162. Although the Kittner study population included both European and African–American women, there is no reason to believe that the elevated *relative* risk for stroke in the postpartum period is different for white women and black women, even though white women and black women have different baseline risks for stroke. 11/16 Tr. at 15, 18.

163. Plaintiff's experts suggest that Parlodel ® perhaps accounted for the significant increased risk documented in the Kittner study. The suggestion is based on at least two critical assumptions for which no evidence was presented:

— that Parlodel ® was in fact in regular use at the hospitals involved in the Kittner study during the two years of that study;

— that some or all of the women identified in the Kittner study with postpartum stroke had been (a) bottle-feeding, and (b) using a drug to suppress lactation.

164. In Dr. Kulig's own hospital, Parlodel ® was taken off of the preprinted standing orders in the mid–1980's, *i.e.,* before the time frame of the Kittner study. 11/8 Tr. at 32.

165. After the Kittner study was published, Dr. Kittner engaged in a case-control study examining the potential risk factors for ischemic stroke in the same geographic area. 11/15 Tr. at 179–80; Ex. GB. The case-control study *did* seek information concerning drug use within one month of an incident stroke, and none of the seven postpartum women who had a stroke in that study indicated usage of Parlodel ®. These facts were set forth in

a letter from Dr. Kittner published in the New England Journal of Medicine. 11/15 Tr. at 178–80; Ex. GB.

166. The facts support an inference that Parlodel ® may not have been available in the hospitals covered by the Kittner study. In any event, there was no evidence whatsoever presented to support plaintiff's experts supposition that Parlodel ® may have played a role in the Kittner study.

167. Parlodel ® is not a scientifically probable confounder for the increased risk of stroke in postpartum women reported in the Kittner study. 11/15 Tr. at 180–81.

168. The Kittner Study specifically evaluates the role of eclampsia and concludes that eclampsia does *not* account for the findings of significant increased risk of stroke (for example, the 28–times increased risk of ICH). Ex. GA at 773.

169. In still another epidemiologic study, investigators compared hospital admissions and drug use to identify women who experienced ischemic heart disease, hypertension, or cerebrovascular events (such as stroke) before, during, and after Parlodel ® for PPL. *No* women were admitted to hospitals for these conditions during the presumed exposure period or in the two months following. Herings and Stricker, *Bromocriptine and Suppression of Postpartum Lactation,* 17 *Pharmacy World & Sci.,* 133–37 (1995), Ex. EA.

170. The Herings and Stricker study does not support plaintiff's hypothesis that bromocriptine use increases the risk of stroke in postpartum women.

171. The only two patients documented in the Herings and Stricker study to have had cerebrovascular disease, which includes stroke, were not users of Parlodel ®. Macones/*Colangelo* at 66–67.

F. Scientific Method

172. The definition of science is being able to test a hypothesis in a manner which is valid—that is, controlled, unbiased, blinded whenever possible, significant in its conclusions by statistically valid techniques, and where the conclusions are supported by the data. 11/8 Tr. at 182; *see also* 11/10 Tr. at 182.

173. The scientific method is the naming of a hypothesis, the careful testing of that hypothesis, and the use of scientific judgment to evaluate the results of those tests. 11/17 Tr. at 35.

174. The hallmark of the scientific method is the generation of testable hypotheses which are then subjected to the real world crucible of experimentation, validation, and replication. *Daubert v. Merrell Dow Pharm.,* 509 U.S. 579, 593, 113 S.Ct. 2786, 125 L.Ed.2d 469 (1993) (citing K. Popper, *Conjectures and Refutations: The Growth of Scientific Knowledge,* at 37 (5th ed.1989) ("the criterion of the scientific status of a theory is its . . . testability")). The *Daubert* Court went on to note that " 'scientific methodology is based on generating hypotheses and testing them to see if they can be falsified; indeed, this methodology is what distinguishes science from other fields of human inquiry.' " *Id.* (citations omitted).

175. To "falsify" a hypothesis in this context means to prove that the "null hypothesis"—that Parlodel ® has no effect on the risk of postpartum stroke—is false, *i.e.,* that Parlodel ® in fact significantly increases the risk of postpartum stroke. The failure of plaintiff's experts to show any study proving that the null hypothesis has been falsified demonstrates that their causal hypothesis has not been tested or verified by the means of science.

176. Plaintiff's experts acknowledge that epidemiologic studies are the best evi-

dence of medical causation. *See* Kulig/*Nussel* Hearing Transcript, Apr. 6, 1999, Vol. II, at 168–70 (Att.2C) (well performed epidemiologic study generally strongest evidence of causation); Iffy/*Globetti* Dep. 89–90 (case reports are "much less suitable" than epidemiology for proving medical causation) (Att.1B).

177. In the following dialogue, which occurred between Dr. Kulig and Chief Judge McDade in an evidentiary *Daubert* hearing, Dr. Kulig conceded that epidemiologic studies are the best evidence of causation:

> THE COURT: If you had a choice between that type of study [epidemiologic study] and adverse event reporting sheet, which would you choose?
>
> THE WITNESS: Well, if it was the only choice?
>
> THE COURT: Yes, if that was the only choice.
>
> THE WITNESS: And the epidemiologic study was a good one. I would obviously choose that.
>
> THE COURT: You would choose it in every case when it's matched against something else, wouldn't you?
>
> THE WITNESS: If it was well performed.
>
> THE COURT: Yes.
>
> THE WITNESS: Yes.

Kulig/*Nussel* Hearing Transcript, Apr. 6, 1999, Vol. II at 170 (Att.2C).

178. Dr. Kulig testified that he uses "exactly the same" scientific methodology in assessing whether a substance causes a potential adverse event in both his Parlodel ® litigation work on behalf of plaintiffs and his breast implant litigation work on behalf of defendants. 11/8 Tr. at 36–37 (Kulig). He testified to his scientific methodology in the breast implant litigation as follows:

> Q. 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 first showing an association through a controlled study?*
>
> A. *No.*
>
> Q. Can it be shown with case reports?
>
> A. No.
>
> Q. Can it be shown with case series, multiple case reports?
>
> A. No.
>
> Q. Can it be shown by a process of differential diagnosis?
>
> A. No.

Ex. SQ (*In re New York State Silicone Breast Implant Litigation, Brusca v. Cooper Companies,* No. 128115/93, Tr. (9/29/97)) at 859 (discussed at 11/8 Tr. at 172–81) (emphasis added).

179. In assessing medical causation, the scientific method requires valid scientific proof first that a drug can cause the effect in question and then valid scientific proof that the drug did cause the effect in a particular individual. For example:

> Dr. Kulig agrees that he would not offer an expert opinion as to causation in a specific case with one patient unless he thought as a matter of science that both general causation and specific causation had been established in a scientifically reliable way. 11/9 Tr. at 140.
>
> Dr. Petro testified that he must know whether bromocriptine can cause ICH before being able to state that a particular individual suffered an ICH caused by bromocriptine. 11/10 Tr. at 181–82; Petro/*Brasher* Dep. at 107 (Att.2).

G. Toxicologic Principles of Dose Response and Threshold

180. The principle of dose response is fundamental to the scientific method, the

toxicological method, and the medical method. 11/17 Tr. at 42; 11/10 Tr. at 158.

181. The principle of dose response states that the possibility of an effect increases as the amount of substance to which a living being is exposed is increased. 11/10 Tr. at 158.

182. The principle of threshold is fundamental to toxicology. 11/10 Tr. at 158.

183. The principle of threshold states that no effects are seen in a living being until they are exposed to a certain—*i.e.*, threshold—level of a substance. 11/10 Tr. at 158–59.

184. Bromocriptine, the parent compound, does not accumulate in the human body even after multiple doses. 11/15 Tr. at 133.

185. In this Court's judgment, plaintiff's experts abandon the scientific method—as they themselves define it—in this case. For example, Dr. Petro acknowledged that the scientific method requires the formulation and testing of hypotheses. Petro/*B/G/Q* Dep. 348 (Att.3C). To test the hypothesis that a particular drug causes a particular adverse event, Dr. Petro admitted that the scientific method would require one to (1) conduct a prospective, double-blind, randomized, placebo-controlled study, *id.* at 351; (2) utilize a single patient trial design, *id.* at 356–57; or (3) establish through epidemiology that an overwhelming number of people experience the adverse event when given the drug compared to those who experience the event in its absence, *id.* at 368–69. However, when asked whether such studies had ever been conducted showing that bromocriptine causes stroke, Dr. Petro admitted that they had not. *Id.* at 351–52 (no prospective, double-blind, randomized, placebo-controlled study); *id.* at 360 (no single patient trial design); *id.* at 369 (no epidemiology).

186. Dr. Petro admitted that one could not show general causation using scientific methodology in the absence of such studies:

> Q. In the absence of such studies, is there a particular methodology that tests the hypothesis that substance A causes effect B?
>
> A. Well, again, the observation of the effect in an uncontrolled manner does not meet the standard you are raising.
>
> Q. And when you use the term, sir, weight of evidence, that is not a scientific methodology, is it?
>
> A. Well, in certain situations, you can't do any of these other tests, so you make a judgment. Again, it's more subjective than scientific methodology.
>
> Q. All right.
>
> A. But again, I would suggest that that has a certain merit in scientific research in the absence of the other type of study designs, but it's not conclusive, et cetera. I mean I—it does not rise to the standard you are suggesting.

Id. at 369–70. Thus, plaintiff's experts' methodology in this case is subjective—in the words of her own expert—as opposed to scientific.

187. Similarly, Dr. Leslie Iffy described the scientific method as requiring "controlled studies [that] ... show ... significant evidence for [a] certain effect...". Iffy/*Revels* Dep. 75–76 (Att.1C); *see also* Iffy/*Globetti* Dep. 58 (causation established through epidemiology or "[s]etting up controlled and blinded investigations in order to test a certain premise") (Att.1B). Nevertheless, he abandons these scientific requirements in litigation generally:

> Q. It's your understanding of the law that the causation opinion in the context of litigation does not need to be as strong or rigorous as a causation opinion

offered in a publication in the medical or scientific literature?

A. Correct.

Iffy/*Kuhn* Dep. 121 (Att. 1D). Accordingly, Dr. Iffy opined that Parlodel ® can cause stroke, even though he conceded that the necessary studies have not been conducted. *See, e.g.,* Iffy/*NJC* Dep. 46–52, 143 (Att.1A). Dr. Iffy testified that there are no objective requirements necessary to satisfy the scientific method and that "we have to satisfy ourselves with less than ideal scientific approaches." Iffy/*Globetti* Dep. 274 (Att.1B).

188. Dr. Kulig likewise discards the scientific method. Upon questioning by Chief Judge McDade at an evidentiary *Daubert* hearing, Dr. Kulig agreed that the scientific method can be described as follows:

> Scientists employ an approach to gathering information known as the scientific method. Although this approach is as varied as scientists themselves, there are still certain processes that can be identified as typical of these scientific methods: First, accumulate scientific data used to formulate the hypothesis, observations, and experiments; test the hypothesis; the new data allows researchers to come to a general conclusion about the phenomenon being studied; and then you may repeat that process again and again as you get more information, as you get closer to perhaps a true relationship.

Kulig/*Nussel* Hearing Transcript, Apr. 6, 1999, Vol. II, at 173–74 (Att.2C). Dr. Kulig has admitted that the testing of hypotheses has not been conducted with respect to bromocriptine and stroke. *See, e.g.,* Kulig/*Hollander* Dep. 108–09 (Att.2A).

189. In prior deposition testimony, Dr. Kulig testified that pregnancy and delivery are risk factors for the development of stroke. Kulig/*Roberts* Dep. at 44–45 (Att.5).

190. In his deposition testimony, Dr. Macones agreed that the postpartum period, by itself, is a risk factor for stroke. Dr. Macones testified that he had no basis to disagree with the conclusion of the Kittner study that "[a] causal role for preeclampsia and eclampsia does not fully explain the much stronger associations in stroke found for the postpartum state than for pregnancy itself." Macones/*B/G/Q* Dep. 101 (citing Kittner) (Att.42).

191. Plaintiff's experts do not rely on any epidemiologic studies regarding Parlodel ® when used for any indication other than postpartum lactation. 11/9 Tr. at 24.

192. Although Dr. Kulig testified at the hearing that the postpartum period is *not* a high risk period for stroke if eclampsia is excluded, 11/9 Tr. at 157, his testimony is not based on affirmative evidence but instead is based upon criticisms of the epidemiologic studies showing the increased risk. *Id.* at 157–58.

193. Dr. Kulig is not an expert in epidemiology. Kulig/*Warren* Dep. 54 (does not consider himself an expert in epidemiology) (Att.15).

194. The existing epidemiology regarding postpartum stroke and Parlodel ® does not support plaintiff's experts' hypothesis that Parlodel ® can cause ICH.

195. There is no scientifically reliable evidence that bromocriptine, taken in therapeutic doses in humans, causes either generalized or cerebral vasoconstriction or vasospasm. *E.g.,* 11/16 Tr. at 32, 33.

196. There is no scientifically reliable evidence that bromocriptine caused plaintiff to suffer either generalized or cerebral vasoconstriction or vasospasm.

197. There is no scientifically reliable evidence that bromocriptine, taken in ther-

apeutic doses in humans, causes ICH. *E.g.,* 11/16 tr. at 41–42.

198. There is no scientifically reliable evidence that bromocriptine caused plaintiff's ICH

199. Dr. Kulig testified that he relied on the Bradford Hill criteria in making causality assessments. 11/8 Tr. at 57.

200. However, application of the Bradford Hill criteria depends first upon an association by epidemiology between a disease and an exposure to an agent. The association must rule out chance. Ex. EB; *see also* 11/8 Tr. at 188–89 (discussing Bradford Hill criteria).

201. There is no epidemiology that rules out chance and supports a link between ICH and exposure to Parlodel®.

202. Dr. Kulig is not aware of any peer reviewed published papers in which the Bradford–Hill criteria have been applied to the question of whether Parlodel® causes vasoconstriction of cerebral arteries, ICH, or stroke. 11/8 Tr. at 199–200.

203. Dr. Kulig improperly used the Bradford–Hill criteria to attempt to support his opinion that Parlodel® can cause ICH.

204. Dr. Kulig did not demonstrate that any statistically-significant epidemiology exists that supports the hypothesis that the use of Parlodel® can cause ICH.

H. Parlodel® Pharmacology and the Alleged Mechanism by Which Parlodel® Can Cause ICH

205. Plaintiff's experts hypothesize that plaintiff's therapeutic use of Parlodel® caused cerebral vasoconstriction or vasospasm that led to ICH. 11/8 Tr. at 103; 11/15 Tr. at 5.

206. Plaintiff's experts cannot identify to a reasonable degree of medical certainty the specific mechanism by which Parlodel® allegedly causes cerebral vasoconstriction in humans. 11/9 Tr. at 88–89; *see also* 11/16 Tr. at 103 (no proven mechanism).

207. Plaintiff introduced no evidence of published peer-reviewed studies that state as a matter of scientific knowledge that bromocriptine causes cerebral vasoconstriction or cerebral vasospasm.

208. Bromocriptine causes a *reduction* in blood pressure via peripheral dilation of blood vessels in intact, normotensive animal models. 11/17 Tr. at 50.

209. Bromocriptine has either no effect or causes a reduction in blood pressure in spontaneously hypertensive rats. 11/17 Tr. at 50.

210. Bromocriptine also causes reductions in blood pressure via vasodilation in intact anesthetized cats. 11/17 Tr. at 50.

211. Bromocriptine in very small doses has been demonstrated to inhibit the known vasoconstrictive effects of much larger doses of serotonin, which is naturally produced by the human body. 11/16 Tr. at 157.

212. The human body itself naturally produces vasoconstrictive substances, such as hormones, norepinephrine, epinephrine, and serotonin. 11/16 Tr. at 146–47; 11/15 Tr. at 24.

213. These endogenous (naturally produced) vasoconstrictors are far more potent than bromocriptine at causing peripheral vasoconstrictive events. 11/16 Tr. at 150; *see also* Ex. G.

214. The most recent edition of Ellenhorn's Medical Toxicology, which plaintiff herself introduced into evidence as plaintiff's exhibit 1406, lists the vasoconstrictive properties of bromocriptine as *zero.* Ex. CI at Table 41–37; 11/9 Tr. at 136–39.

215. Plaintiff has characterized Ellenhorn's Medical Toxicology as a "well recog-

nized authoritative toxicology textbook." 11/8 Tr. at 44.

216. Other than a theory of individual "sensitivities" for which he offered no basis, 11/10 Tr. at 49, Dr. Petro did not offer any methodology or mechanism for explaining how or why a patient taking Parlodel ® will develop vasoconstriction or vasospasm rather than the expected vasodilation.

217. Dr. Petro states that studies of active metabolites of bromocriptine have not been done to test whether any metabolites have any vasoconstrictive effects. 11/10 Tr. at 177–78.

218. Plaintiff has not demonstrated that metabolites of bromocriptine have vasoconstrictive effects.

219. Plaintiff has not demonstrated that the pharmacology of bromocriptine supports the hypothesis that Parlodel ® in therapeutic doses causes vasoconstriction or vasospasm.

220. Plaintiff has not demonstrated the mechanism by which Parlodel ® in therapeutic doses allegedly causes vasoconstriction or vasospasm.

221. Where a vasospasm has been shown to cause stroke, *i.e.,* vasospasm secondary to a subarachnoid hemorrhage causing stroke, the strokes caused are ischemic strokes rather than hemorrhagic strokes. 11/16 Tr. at 39.

222. Plaintiff has not demonstrated that the pharmacology of bromocriptine supports the hypothesis that bromocriptine causes ICH.

223. Plaintiff has not demonstrated the mechanism by which Parlodel ® in therapeutic doses causes ICH.

224. The causal hypothesis of plaintiff's experts that bromocriptine causes stroke has never been borne out by statistically-valid testing or otherwise shown by scientifically reliable means. Plaintiff's epidemiologist, Dr. Macones, opines that there is *no* evidence that Parlodel ® increases the risk of postpartum stroke. Macones/*Hernandez* Dep. 86 (Att.4C). Accordingly, plaintiff's experts' hypotheses cannot pass muster under the first, and most important, *Daubert* factor, testability.

I. Findings of Fact Regarding Case Reports and Adverse Drug Experience Reports ("ADEs")

225. Case reports, which may or may not be published in the scientific or medical literature, describe isolated and uncorroborated instances of medical events occurring coincident with the use of a prescription drug. They tend to be brief recitals of events which do not consider potential alternate causes or attempt to investigate or to explain methods of causation.

226. Case reports do not use control groups, are not susceptible to statistical analysis of risk, and are not verifiable through meaningful peer review. 11/10 Tr. at 205–06.

227. Case reports often fail to address the individual's prior medical history, risk factors, use of other medications or drugs, family medical history, and other individual factors necessary to assess a cause-and-effect relationship between the use of the drug and the reported adverse effect. *See, e.g.,* Kulig/*B/G/Q* Dep. 431–35, 532 (Att.11); Kulig/*Siharath* Dep. 142–43 (Att.10); Petro/*Rider* Dep. 181–82 (Att.12); Petro/*B/G/Q* Dep. 428–29 (Att.2).

228. Case reports are not controlled studies. 11/10 Tr. at 206; Petro/*Brasher* Dep. at 428.

229. Standing alone, a case report does not establish causation. 11/9 Tr. at 36–37.

230. For any given case report, no scientifically probable conclusion can be

drawn that the suspect drug caused the reaction. 11/9 Tr. at 38.

231. The event reported in a case report may have been related to an underlying disease for which the drug was given. 11/9 Tr. at 38.

232. The event reported in a case report may have occurred by chance at the same time that the suspected drug was taken. 11/9 Tr. at 39.

233. One can have a temporal relationship between the use of a drug and an effect without there being a causal relationship. 11/10 Tr. at 204.

234. Case reports cannot be used to determine relative risk. 11/10 Tr. at 205.

235. According to Dr. Kulig, when one addresses "people studies," one should "tak[e] it from the most important to the least important, epidemiology studies being the most important, case series, case reports being the least important." Kulig/*Oregon Breast Implant* Tr. at 705 (Att.28); 11/8 Tr. at 186; 11/9 Tr. at 26–27.

236. As Dr. Kulig has written, "case reports are traditionally viewed as the least vigorous form of proof of a hypothesis or validation of a therapy." 11/9 Tr. at 27; *see also* Brent, Kulig and Rumack, "Analysis of the Types of Papers Presented at the Annual Toxicology Meetings," 32 *Vet. Hum. Toxicol.* (April 1990) (Att.44).

237. In a *Daubert* hearing in *Railey v. Sandoz Pharmaceuticals Corporation*, Dr. Kulig testified that dechallenge and rechallenge case reports are "hardly proof that the drug caused the effect." 11/9 Tr. at 48; Ex SR (Kulig/*Railey* hearing at 149).

238. The Larrazet "re-challenge" relied upon by plaintiff's experts is a case report. 11/16 Tr. at 195.

239. The Larrazet case report did not address cerebral arteries. 11/16 Tr. at 196.

240. In Larrazet, a patient with previous coronary vasospasm was instructed to stop taking antispasm medications 36 hours prior to the so-called "re-challenge." 11/16 Tr. at 196.

241. The Larrazet case report did not involve any controls, *i.e.,* catheterizing to visualize coronary artery prior to the so-called "re-challenge." 11/16 Tr. at 197.

242. The Larrazet case report did not show that Parlodel ® caused vasoconstriction because, *inter alia*, it did not demonstrate lack of vasoconstriction prior to the co-called "re-challenge," *i.e.,* it was uncontrolled. 11/17 Tr. at 17.

243. ADRs are a form of case report compiled by drug manufacturers which are submitted to the FDA and describe "any adverse event associated with the use of a drug in humans, whether or not considered drug related." 21 C.F.R. § 314.80(a) (Att.37).

244. "[B]ecause of incomplete data and the uncertainty caused by the underlying illness, indication, or other drug exposures, adverse experience reports may be attributed to a drug or biological product even though it may not necessarily have caused the adverse experience." Final Rule, Department of Health and Human Services, Food and Drug Administration, "Postmarketing Expedited Adverse Experience Reporting for Human Drug and Licensed Biological Products; Increased Frequency Reports," 62 Fed.Reg. 34166, 34167 (1997) (to be codified at 21 C.F.R. Chapters 310, 314, and 600) (Att.46).

245. Over a decade ago, FDA's Surveillance and Data Processing Branch of the Division of Epidemiology and Surveillance published a "Brief Description [of Adverse Reaction Reporting System ("ARRS")] with Caveats of [the] System." According to FDA, "[t]he primary purpose of maintaining the [ARRS] data base is to serve

as an early warning or signaling system. . . ." Brief Description with Caveats of System, Surveillance and Data Processing Branch of the Division of Epidemiology and Surveillance, Division of Epidemiology & Surveillance, Dec. 1988, at p. 1 ("FDA Caveats"), Ex. RN; *see also* Nov. 1991 FDA Caveats, at p. 1 (Att.25).

246. These FDA Caveats further state that:

> "for any given case report, *there is no certainty that the suspect drug caused the reaction.* This is because physicians are encouraged to report all suspected drug events, not just those that are known to have been caused by the drug. The event reported in a case report may have been related to an underlying disease for which the drug was given, to other drugs being taken concurrently, or may have occurred by chance at the same time the suspected drug was taken."

Dec.1988 FDA Caveats, at p. 1 ¶ 1, Ex. RN; *see also* Nov. 1991 FDA Caveats, at p. 1 ¶ 1 (Att.25). Thus, "[a]ccumulated case reports cannot be used to calculate incidence or estimates of drug risk. They must be carefully interpreted as reporting rates and not occurrence or incidence rates. Comparisons of drug safety cannot be made from these data." Dec.1988 FDA Caveats, at p. 2 ¶ 2, Ex RN; *see also* Nov. 1991 FDA Caveats, at p. 2 ¶ 2 (Att.25).

247. A reporting physician may report an alleged adverse effect which occurred while an individual was taking multiple prescription drugs. *See, e.g.* Kulig/*B/G/Q* Dep. 431–35, 532 (Att.11); Kulig/*Siharath* Dep. 142–43 (Att.10); Petro/*Rider* Dep. 181–82 (Att.12); Petro/*B/G/Q* Dep. 428–29 (Att.2).

248. The reports serve as a tracking system, and do not "reflect a conclusion by the applicant or the FDA that the report or information constitutes an admission that the drug caused or contributed to an adverse effect." 21 C.F.R. § 314.80(k) (Att.37).

249. Dr. Kulig testified that he relies upon third-party "causality assessments" as an example of the appropriate methodology for assessing causation. 11/9 Tr. at 105.

250. NPC did not perform these "causality assessments."

251. The "causality assessments" were prepared by the Drug Monitoring Centre ("DMC") (part of Sandoz Pharma AG ("Pharma"), a Swiss corporation that is not a party to this case). 11/8 Tr. at 12 (opening statement of plaintiff's counsel Kristal); 11/8 Tr. at 111–12; *see also* Ex. PR, Complaint (naming only Sandoz Pharmaceuticals Corporation as defendant).

252. Dr. Kulig has conceded that such "causality assessments" could not be published in a peer-reviewed publication because the methodology for making "causality assessments" is not adequately described therein. Kulig/*Hollander* Dep. 115–16 (Att.3).

253. Dr. Kulig does not know if the DMC's "methodology," whatever it was, was created and applied for regulatory purposes rather than scientific ones. *E.g.*, Kulig/*Hollander* Dep. 114 (Att.3)

254. In filling out "causality assessments," DMC employees evaluated an ADR or case report and checked off "yes" or "no" as responses to a pre-set list of questions. *See, e.g.*, 11/8 Tr. at 115–16 (discussing box-checking on form).

255. Plaintiff has referred to "causality assessments" showing that the DMC attributed "probable causation" in certain case reports of digital vasospasm to Parlodel®. No such "causality assessments" showed the DMC attributing "probable causation" in a case of ICH to Parlodel®.

See 11/15 Tr. at 51 (concession by Dr. Petro that digital vasospasm is not the same as ICH); 11/17 Tr. at 47–48 (unchallenged testimony of Dr. Green that "it is well-known in medicine and science that the body has different vascular beds[;] [and that] [t]here are different sorts of receptors, populations of receptors on the peripheral vasculature that serves our fingers and toes than there are for major vessels, such as coronary arteries or cerebral arteries").

256. As with any other ADR or case report, the data are not controlled or subject to statistical evaluation and the "assessment" is necessarily based on the self-selected and limited information provided. 11/9 Tr. at 67.

257. European authorities require "causality assessments" for regulatory purposes. Krupp/*NJC* Dep. at 185 (Att.19). FDA has no comparable requirement. *Id.*

258. Dr. Maurice Nelson Graham Dukes, who styles himself as the world's foremost "adverse drug reaction scientist," states that causality assessments are subjective and unreliable:

> An outcome grading employing such terms as 'not possible,' 'unlikely,' 'possible' and 'probable' is currently used in some adverse reaction monitoring agencies, primarily to determine which reports of suspected adverse 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. . . .

M.N.G. DUKES, RESPONSIBILITY FOR DRUG–INDUCED INJURY: A REFERENCE BOOK FOR LAWYERS, THE HEALTH PROFESSIONS AND MANUFACTURERS, 46 (2d ed. Dec. 1998) (emphasis added) (Att.21); *cf.* 11/9 Tr. at 63–65.

259. Plaintiff has not shown that DMC "causality assessments" are based on the comprehensive or otherwise scientific review of all facts giving rise to the reported adverse event. 11/9 Tr. at 66 (admission by Dr. Kulig that he did not know how "causality assessments" were done at DMC and, in particular, whether DMC had "received everything" at the time DMC made such assessments). Among other things, incomplete medical records would preclude DMC from adequately considering whether there were confounding factors in the patients addressed by the "causality assessments," *e.g.,* concomitant use of other drugs. *Id.* at 67 ("causality assessments" may not take into account confounding factors.).

260. Plaintiff has not shown that DMC "causality assessments" are based on objectively reliable data or are otherwise testable.

261. Plaintiff has not shown, or even argued, that the regulatory "causality assessment" methodology is one that is generally accepted in medical or scientific fields for purposes of reliably establishing medical causation.

262. Plaintiff has not shown an acceptable error rate (or any error rate) for this methodology.

263. DMC causality assessments have not been demonstrated to form part of a scientifically reliable methodology for testing the hypothesis that Parlodel® causes cerebral vasoconstriction or ICH.

J. Animal Evidence Re: Effects of Parlodel ®

264. The use of animal studies to prove causation in human beings has "two significant disadvantages," which "are almost always fraught with considerable, and currently unresolvable, uncertainty." Federal Judicial Center, Reference Manual on Scientific Evidence, at 130 (1994). First, extrapolating from animals to humans is difficult because "differences in absorption, metabolism, and other factors may result in interspecies variation in responses." *Id.* A second difficulty is that "the high *doses* customarily used in animal studies requires consideration of the *dose-response relationship* and whether a threshold no-effect dose exists." *Id.*

265. Dr. Kulig has previously testified that in the absence of evidence of an association between an exposure in humans and a common human disease, causation cannot be established using animal studies:

> Q. . . . I want to jump down to the experimental category, the experimental criteria, and ask you whether, in the absence of evidence of an association between an exposure in humans and a common human cancer such as breast cancer, whether causation can be established by studies in rodents?
>
> A. No, it cannot.
>
> Q. Why not?
>
> A. There are many problems with animal experimentation in trying to apply that data to the human situation, particularly in rodents, and I think I have prepared a list of those problems.
>
> * * * * * *
>
> There is significant interspecies and gender variation in animals. For example, a chemical may cause cancer in rats but not mice. It may cause it in guinea pigs but not monkeys. Risk assessors frequently assume that, if it's caused in any species, it's a positive test, even if other animals do not demonstrate the same effect. Likewise, some chemicals cause cancer in males and not females, or vice-versa. Some risk assessors generally assume any positive is a positive test even if there are many more negative experiments on the same subject.
>
> Other species, especially rodents, may not be relevant for humans because they absorb, distribute, metabolize and excrete chemicals quite differently than we do. They may not be able to activate a chemical in the same way.
>
> Animals used in experiments are deliberately inbred for generic susceptibility to cancer, and that frequently results in a pretty high baseline rate of cancers, even when they are not exposed to the test chemicals.
>
> MTDs are the maximum tolerated doses used in risk assessment of animal experimentation where the highest dose possible without making the animals clinically sick is used, and frequently these doses are very, very high and they are usually not relevant to humans. Humans are not exposed to the same chemicals in doses that ever approach doses used in these experiments. At these high doses, the chemicals may cause cellular damage, and that results in neoplasms because there is an increased cell turnover in an attempt to repair the damage. You would not see the same affect (sic) at lower doses where there is no tissue damage.

Ex. SQ, Kulig/*Brusca* 9/29/97 *Daubert* hearing Tr. at 862–63; 863–65 (referenced at 11/9 Tr. at 122–23).

266. Dr. Laura Carolyn Green, NPC's expert in toxicology has reviewed hundreds of human and animal studies, both

published and unpublished, all of which support her scientific conclusion that Parlodel ® taken at therapeutic doses did not cause cerebral vasoconstriction or vasospasm. 11/17 Tr. at 43–47.

267. Plaintiff's experts do not rely on any animal studies where an animal was given Parlodel ® and suffered a stroke. 11/10 Tr. at 83.

268. Toxicologic methods to assist with the testing and affirming or refuting the hypothesis of whether a substance causes cerebral vasoconstriction have been available since at least 1950, if not the 1930s. 11/17 Tr. at 39.

269. An abundance of animal models exist to assist with testing the hypothesis that a foreign substance can induce cerebrovascular accidents. 11/17 Tr. at 52–53.

270. For example, the combination of PPA and caffeine has been reproducibly shown to cause stroke in animal models. 11/17 Tr. at 54.

271. As of November 17, 1999, the Medline research database, a recognized source of scientific literature, has classified 115 articles as pertaining to the topic of chemically-induced ICH in animal models. 11/17 Tr. at 53; *see also* Ex. TO.

272. Dr. Petro, without alluding to these data and articles, testified that there are no good animal models for inducing stroke with a drug. 11/10 Tr. at 85.

(i) The hind limb study

273. Plaintiff's experts rely on the "hind limb" study as support for their opinion that Parlodel ® has "amphoteric" properties, meaning that the drug is both a vasodilator and a vasoconstrictor, not dependent on dose, and that these properties are classic properties of ergot alkaloids. 11/8 Tr. at 142–43; 11/10 Tr. at 90–91.

274. The hind limb study is the only Parlodel ® study that plaintiff's experts say shows such an "amphoteric action" in bromocriptine. 11/10 Tr. at 169.

275. The hind limb study was a dose response study that measured effects of Parlodel ® infused in an isolated animal extremity in three doses: 1 microgram/kilogram; 5 micrograms/kilogram; and 25 micrograms/kilogram. 11/16 Tr. at 177, 187.

276. The methodology used in the hind limb study was designed to eliminate any effects of bromocriptine on the nervous system of the dog. 11/10 Tr. at 178. Systemic or oral administration of Parlodel ® would lead to both local effects as studied in the hind limb study and central nervous system effects of bromocriptine, and it is not known what effects would have been observed in the hind limb study if the drug had been administered systemically instead of injected locally. 11/10 Tr. at 178–79.

277. The control animals presented with up to seven percent constriction, according to the methodology protocol—as documented in a German article reviewed (in English translation) only by defense expert Karl Engelman. 11/16 Tr. at 185–87.

278. In the hind limb study, when vehicle controls were taken into account, Parlodel ® had no effect in the isolated animal extremity at the two lower doses; it showed an effect only at the 25 microgram/kilogram dose. 11/16 Tr. at 187. Thus, the hind limb study demonstrates that Parlodel ® exhibits a threshold below which it does not cause vasoconstriction even in the isolated limb. 11/16 Tr. at 187.

279. Only about five percent of an oral dose of Parlodel ® actually enters the bloodstream, compared with 100 percent of the drug when it was injected directly into the hind limb of the dogs in the hind limb

study. 11/10 Tr. at 175–76. Thus, a woman taking standard 2.5 mg Parlodel ® tablets would need to take 1,250 tablets at a time to place the same amount of Parlodel ® in her bloodstream as was used in the 25 microgram/kilogram assay of the hind limb study. 11/16 Tr. at 187–88.

280. None of the animals in the hind limb study developed ICH. *Cf.* 11/10 Tr. at 83.

281. In his deposition in the case *Brasher v. Sandoz Pharmaceuticals Corporation*, Dr. Kulig testified that he did not know whether the hind limb methodology had been compared with outcomes in animal studies to determine if they are predictive of whole animal toxicity. Kulig/*Brasher* Dep. at 49 (Att.11).

282. Dr. Kulig does not know how the dog artery resistance measured in the hind limb study compares to human artery resistance. 11/9 Tr. at 111–12.

283. For example, when questioned about the "perfused hind limb of the dog" study, Dr. Kulig testified:

> Q. Have you attempted to compare what the concentration of bromocriptine is after a 2.5 milligram dose for PPL with the concentration of bromocriptine that would have resulted in this hind limb test?
>
> A. No, that's really not necessary.
>
> . . .
>
> Q. You have not attempted to do any such correlation, correct?
>
> A. It's not necessary. It would not be productive to make that correlation.
>
> Q. Have you attempted to do such a correlation?
>
> A. Why would I attempt to do something that wouldn't be productive?
>
> Q. The answer is, no, you have not attempted to do a correlation, correct?
>
> A. That's correct.

Kulig/*B/G/Q* Dep. 80, 84 (Att.2H).

284. Dr. Petro concedes that comparing a mongrel ten kilogram dog, such as that used in the hind limb study, to a postpartum woman, "is a stretch." 11/10 Tr. at 175.

285. Dr. Petro has not even attempted to determine the vascular resistance in human beings to compare it to the vascular resistance of the dogs studied in the hind limb study. 11/10 Tr. at 169–70.

286. The hind limb study does not support plaintiff's hypothesis that a person taking therapeutic doses of Parlodel ® could develop vasoconstriction as observed in the hind limb study.

287. The hind limb study does not support plaintiff's hypothesis that a person taking Parlodel ® at therapeutic doses could develop cerebral vasoconstriction.

288. The hind limb study does not support plaintiff's hypothesis that a person taking Parlodel ® at therapeutic doses could develop ICH.

289. Extrapolating from the massive Parlodel ® doses given in the hind limb study to postpartum women taking Parlodel ® does not comport with the fundamental principle of dose response. *Cf.* 11/17 Tr. at 42–43.

290. With respect to the dog "hind limb" study in particular, plaintiff's experts do not have any experience in using this type of animal model in their own laboratory research. *E.g.,* Kulig/*Rider* Dep. 226 (Att.2J). They do not know whether this animal model in dogs has ever been validated in other laboratories. *E.g.,* Kulig/*B/G/Q* Dep. 48 (Att.2H). There is no federal or foreign regulatory body that has ever adopted the methodology or approved the methodology used in this study and the methodology of this dog hind limb study has never been compared to outcomes in

intact animals to show whether it predicts what happens in whole animals. Kulig/*B/G/Q* Dep. 49, 151 (Att.2H). Further, bromocriptine was administered in such a way that it had no systemic effects—it was not allowed to affect the brain, and it was not allowed to affect the nervous system, Kulig/*Siharath* Dep. 148–49 (Att.2I), but plaintiff's experts do not know whether the results would have been the same, similar, or different if systemic effects had been allowed. *E.g.,* Kulig *B/G/Q* Dep. 43 (Att.2H).

(ii) The 62–week oral toxicity study in dogs

291. Dr. Petro finds the 62–week oral toxicity study in dogs to be significant to his causation opinions because it resulted in ear necrosis in some tested animals, suggesting vasoconstriction. 11/10 Tr. at 82.

292. Neither of plaintiff's causation expert witnesses presented evidence that demonstrated a scientifically valid methodology for translating ear necrosis to cerebral vasospasm.

293. Neither Dr. Kulig nor Dr. Petro presented evidence that receptors in peripheral blood vessels such as those found in the ears are sufficiently similar to those found in cerebral blood vessels to support the hypothesis that reactions in peripheral blood will also occur similarly in cerebral blood vessels.

294. In the dog study, animals received bromocriptine for 62 weeks, whereas plaintiff took Parlodel ® for at most three weeks. 11/10 Tr. at 161.

295. In the dog study, the study animals, at the lowest dose (1 mg/kg/day), received roughly 14 times the daily dose of Parlodel ® prescribed to plaintiff for PPL. 11/10 Tr. at 160.

296. No ear necrosis was observed at the lowest dose level. 11/10 Tr. at 161.

297. Viewed over the full length of the study, the dogs ingesting Parlodel ® at the lowest study dose ingested more than 280 times the Parlodel ® that plaintiff ingested while she was taking Parlodel ®. 11/10 Tr. at 161.

298. The animals in the dog study being administered 280 times the amount of Parlodel ® that plaintiff ingested demonstrated no evidence of any vasoconstrictive effects. 11/10 Tr. at 161–62.

299. The dogs that were administered three milligrams/kilogram per day for 62 weeks ingested approximately 840 times more Parlodel ® than plaintiff ingested while she was taking Parlodel ® for PPL. 11/10 Tr. at 162.

300. The dogs that were administered ten milligrams/kilogram per day for 62 weeks ingested approximately 2,800 times more bromocriptine on a body weight basis than plaintiff ingested while she was taking Parlodel ® for PPL. 11/10 Tr. at 162.

301. None of the animals in the dog study developed ICH. 11/10 Tr. at 165.

302. The dog study does not support plaintiff's hypothesis that a person taking therapeutic doses of Parlodel ® could develop any vasoconstriction as observed in the ear necrosis study.

303. The dog study does not support plaintiff's hypothesis that a person taking Parlodel ® at therapeutic doses could develop cerebral vasoconstriction.

304. The dog study does not support plaintiff's hypothesis that a person taking Parlodel ® at therapeutic doses could develop ICH.

305. Extrapolating from the Parlodel ® doses given in the dog study to postpartum women taking Parlodel ® does not comport

with the fundamental principle of dose response. *Cf.* 11/17 Tr. at 42–43.

(iii) The 53–week oral toxicity study in rats

306. Dr. Petro finds a 53–week oral toxicity study in rats to be significant to his causation opinions because it resulted in ear necrosis in some tested animals, suggesting vasoconstriction. 11/10 Tr. at 82.

307. In the 53–week oral toxicity study, rats who received five milligrams of Parlodel ® per kilogram of body weight per day for 53 weeks demonstrated no vasoconstrictive effects. This daily dose is roughly 70 times the daily dose that plaintiff was prescribed for the prevention of postpartum lactation. 11/10 Tr. at 163–64.

308. In the 53–week oral toxicity study, rats demonstrated no vasoconstrictive effects in the tail tip until they ingested 20 milligrams of Parlodel ® per kilogram of body weight, or roughly 280 times the daily dose that plaintiff was taking for the prevention of postpartum lactation. 11/10 Tr. at 165.

309. Rats in the 53–week oral toxicity study that developed blue discoloration of the tail tip did not exhibit this effect until the 37th week of their ingestion of 280 times the daily dose plaintiff was taking for PPL. 11/10 Tr. at 165.

310. Plaintiff, at most, took Parlodel ® for three weeks.

311. Regardless of the dose, none of the rats in the 53–week oral toxicity study developed ICH. 11/10 Tr. at 165.

312. The 53–week oral toxicity study in rats does not demonstrate that a person taking therapeutic doses of Parlodel ® could develop vasoconstriction.

313. The 53–week oral toxicity study in rats does not demonstrate that a person taking Parlodel ® at therapeutic doses could develop cerebral vasoconstriction.

314. The 53–week oral toxicity study in rats does not demonstrate that a person taking Parlodel ® at therapeutic doses could develop ICH.

315. Extrapolating from the Parlodel ® doses given in the rat study to postpartum women taking Parlodel ® does not comport with the fundamental principle of dose response. *Cf.* 11/17 Tr. at 42–43.

K. Findings of Fact Regarding Other Ergot Alkaloids

316. Parlodel ®, or bromocriptine mesylate as it is known by its generic name, is a member of the ergot alkaloid group of compound—a group composed of many hundreds of chemicals. Ergot alkaloids are compounds which have molecular structures that include several carbon, hydrogen, and nitrogen atoms configured into interconnecting rings, with most of the rings being six-sided rings and at least one being a five-sided ring, and which can be obtained by extraction of different strains of the fungus claviceps which is grown on rye or cultivated in fermentation tanks.

317. Parlodel ® is a product that has been marketed for over 20 years in the United States. There is a vast body of pharmacologic, clinical, and other evidence about the drug. *See, e.g.,* B. Berde and E. Strumer, "Introduction to the Pharmacology of Ergot Alkaloids and Related Compounds as a Basis of Their Therapeutic Application" (Ch. 1), in B. Berde and H.O. Schild, *Ergot Alkaloids and Related Compounds,* 49 Handb. Exp. Pharmacol. (1978), at 1 (Att.23); Clark et al, "How Does Bromocriptine Work?," *Triangle* 17(1): 21–31 (1978) (Att.24); Lahlou & Demenge, "Contribution of Spinal Dopamine Receptors to the Hypotensive Action of Bromocriptine in Rats," *J. Cardiovasc. Pharmacol.* 18(3):317–25 (1991) (Att.25).

318. It is well settled in this and comparable peer-reviewed literature that the members of the ergot alkaloid group contain an extraordinarily diverse range of characteristics and effects. For example, in *Ergot Alkaloids and Related Compounds*, recognized as an authoritative publication on ergot alkaloids, the authors compare the characteristics of several members of the ergot alkaloid group. Based on numerous laboratory experiments, the authors state that "there are few chemical groups which comprise substances with such diversified actions." B. Berde and E. Sturmer, *supra*, at 2 (Att.23). Due to the diversity of characteristics and effects among the ergot alkaloids, the authors state that "ergot has been of the nature of a treasure chest to pharmacologists, ... and has become a treasure-house for drugs." *Id.* at 2 (internal quotations omitted). "The *wide field of therapeutic application* of ergot alkaloids and related compounds corresponds to their chemical and pharmacological diversity." *Id.* at 10. Thus, not only do ergot alkaloids have a wide diversity of characteristics and effects, but also so do the drugs derived from ergot alkaloids.

319. To illustrate the diversity of the ergot alkaloids, the *Ergot Alkaloids* authors provide a table which compares the effect of seven different ergot alkaloids in ten categories of biological activity. *Id.* 2, 4 (Bromocriptine mesylate is a derivative of bromocriptine.) In the table, the relative effects of the compounds are listed, with the effect of the most active compound in each category arbitrarily characterized with the value 1000. As the authors intended, a quick review of this table clearly reveals the disparate effects of ergot alkaloids. The table also demonstrates that the characteristics of bromocriptine vary widely from other ergot alkaloids. *Id.*

320. For example, in a comparison of the level of uterotonic activity—the characteristic of giving tone to the uterine muscle—produced in rabbits, four of the alkaloids produce various levels of uterotonic activity, whereas three of the alkaloids (including bromocriptine) actually inhibit this activity. *Id.*

321. Likewise, in a comparison of the effect on body temperature in rabbits, five alkaloids increase body temperature whereas two decrease it, and although lysergic acid diethylamide ("LSD") and bromocriptine both increased body temperatures, LSD's effect on body temperature was 400 times that of bromocriptine. *Id.*

322. Similarly, in a comparison of stereotypical dopaminergic effect—the effect on tissues and organs by dopamine, a compound produced within animals and people that causes heightened responsiveness of certain nerve endings, three alkaloids produce various levels of effect, which were all more than 300 times greater than the negligible effects of the other four alkaloids. *Id.*

323. Finally, for inhibiting fertility in rats, only bromocriptine produces a comparatively significant effect. *Id.*

324. There is no statistically-significant epidemiologic study showing that *any* ergot increases the risk of stroke. Even if for argument's sake another member of the ergot alkaloid group could be shown to contribute to strokes, a proposition which NPC does not concede, it would be irrelevant to whether bromocriptine contributes to strokes.

325. Bromocriptine differs from other ergot alkaloids. For example, it prevents coronary artery vasoconstriction by blocking alpha adrenergic receptors. By contrast, many other ergot alkaloids directly act on these alpha adrenergic receptors to

cause coronary artery vasoconstriction. 11/17 Tr. at 55.

326. Also by way of example, Parlodel ® pressor activity is 5000 times less potent than that of the ergot alkaloid ergotamine. 11/17 Tr. at 26. Pressor activity relates to a compound's ability to cause vasoconstriction. 11/17 Tr. at 26.

327. Dr. Kulig testified that he does not rely on the fact that other ergot alkaloids cause vasoconstriction as proof that Parlodel ® causes vasoconstriction. 11/9 Tr. at 130.

328. In contrast, Dr. Petro testified that because LSD and bromocriptine are both ergot alkaloids, it is significant to him that LSD can cause vasospasm and hallucinations. 11/10 Tr. at 75.

329. Dr. Petro also relies on a published case report by Senter and Lieberman regarding use of the drug ergotamine as support for the hypothesis that Parlodel ® causes vasoconstriction. *E.g.,* 11/10 Tr. at 46–48, 65, Exhibit 1404.

330. Plaintiff did not experience hallucinations or any symptom identified in the Senter case report. 11/15 Tr. at 39–41.

331. In contrast to his reliance on evidence from other ergots to support his hypothesis that Parlodel ® can cause ICH, when discussing sympathomimetic amines, Dr. Petro testified that it is improper to "lump together" all the drugs in the sympathomimetic class, because there is a "whole range of drugs" within that class. 11/15 Tr. at 17.

332. The Court finds in conclusion that given the documented diversity of this chemical group, any reliance on general rules or principles purportedly associated with ergot alkaloids as a group would be particularly inappropriate.

L. Findings of Fact Regarding Other Injuries Not Alleged by Plaintiff and Parlodel ® Use for Other Indications

333. Plaintiff's experts rely in part on evidence of injuries other than ICH that are allegedly related to Parlodel ® use.

334. Plaintiff's experts rely in part on evidence gathered from Parlodel's ® use for other indications for which it is FDA-approved.

335. Evidence of so-called "other injuries" includes allegations that Parlodel ® when used for the PPL indication caused myocardial infarction, seizures, or ischemic stroke.

336. Evidence of so-called "other indications" includes either clinical studies or anecdotal reports and other allegations regarding Parlodel ® when used for the PPL indication. Some other indications include acromegaly, amenorrhea, galactorrhea, pituitary tumors, and treatment of Parkinson's Disease.

337. The issue in this case is whether Parlodel ® caused plaintiff's ICH, a specific type of stroke involving bleeding into the brain. Other injuries allegedly associated with Parlodel ®, such as myocardial infarction, seizures, hypertension, headaches, and non-hemorrhagic strokes are each distinct kinds of injuries with a multitude of different causal mechanisms.

338. The Court finds that plaintiff has not demonstrated that other injuries allegedly associated with the use of Parlodel ® are similar in causal mechanism to plaintiff's ICH.

M. Findings of Fact Regarding Plaintiff's Expert Dr. Kenneth Kulig

(i) Dr. Kulig's Qualifications

339. Dr. Kulig has never prescribed Parlodel ® for any indication. Kulig Dep. 80 (Att.2K).

(ii) Scientific Knowledge

340. Dr. Kulig opines that plaintiff "had an ergot-induced vasospasm of a cerebral artery that subsequently ruptured, resulting in a large intracerebral hemorrhage in her brain." Kulig Dep. 48 (Att.2K).

341. Dr. Kulig is not an epidemiologist, or a neurologist, or an ob/gyn. Kulig/*NJC* Dep. at 63 (not an epidemiologist) (Att.8); 11/8 Tr. at 169 (not board certified in neurology); Kulig/*Brasher* Dep. at 456 (not an ob/gyn) (Att.11).

342. Dr. Kulig's essential opinion is that bromocriptine (Parlodel ®) is an ergot derivative and that ergots are known to cause stroke by inducing vasospasm, *i.e.,* a constriction of arteries. Kulig Expert Report (Att.2M); *cf.* Kulig/*Rider* Dep. 209 (Att.2J).

343. Dr. Kulig knows of no epidemiologic or other study showing that Parlodel ® significantly increases the risk of either vasospasm or stroke. Kulig/*Railey* Dep. 42 (Att.2E); Kulig/*Simonson* Dep. 129 (Att.2Q).

344. Dr. Kulig cannot testify to a reasonable degree of medical certainty how Parlodel ® allegedly causes vasospasm. Kulig/*B /G /Q* Dep. 202 (Att.2H).

(iii) The Testing or Testability of Dr. Kulig's Opinions

(a) Epidemiology

345. Dr. Kulig concedes that, to test the hypothesis that bromocriptine or Parlodel ® can cause a particular adverse effect in a human being, one needs some type of experimental method. Kulig/*B /G /Q* Dep. 262–63 (Att.2H).

346. Dr. Kulig admits that such experiments or testing of hypotheses have *not* been conducted with respect to bromocriptine and stroke. *See, e.g.,* Kulig/*Hollander* Dep. 108–09 (Att.2A); *see* Kulig *Siharath* Dep. 105–06 (does not recall if he relies on any studies that state bromocriptine causes vasospasm in humans) (Att.2I).

347. Dr. Kulig concedes that no epidemiologic study in the peer-reviewed medical literature shows a statistically-significant association between Parlodel ® and stroke. Kulig/*Warren* Dep. 243 (Att.2G). Therefore, he agrees that there is no statistically-significant epidemiologic study showing that Parlodel ® increases the risk of stroke. *See* Kulig/*Hollander* Dep. 108–09 (Att.2A)

348. Dr. Kulig admits that the only way to calculate a relative risk is through an epidemiologic study of some type. Kulig/*Hernandez* Dep. 55 (Att.2R).

349. Dr. Kulig opines, however, that epidemiologic calculations of relative risk can be used to support a causation opinion without regard to statistical significance. *See, e.g.,* Kulig/*Railey* Dep. 42 (ERI study not statistically significant but is nevertheless a "strong piece of evidence") (Att.2E).

350. Dr. Kulig attempts to rely on the single occurrence of a stroke in the ERI Study among more than 280,000 women as evidence of general causation, notwithstanding the admitted lack of statistical significance. Kulig/*NJC* Dep. 83 ("I don't believe it's a very reliable study. . . .") (Att.2B); Kulig/*Nussel* Hearing Transcript, April 6, 1999, Vol. I, at 79–80 ("I'm not claiming that [the ERI] study shows that the drug Parlodel ® causes stroke") (Att.2C); Kulig/*O'Conner* Dep. 35–39 (admission that he is bound by investigator's statement that study is inconclusive) (Att. 2D).

(b) The Bradford Hill Criteria

351. In Dr. Kulig's opinion, the only epidemiologic study of Parlodel ® and stroke was the ERI study. Kulig/*Hol-*

lander Dep. 108 ("A. Okay. In my opinion, there's only one epidemiology study on Parlodel ® use in the postpartum period, and that's the ERI study. The ERI study, in my opinion, is . . . a red flag, if you will, for stroke development.") (Att.2A)

352. However, in his affidavit filed in the *Nussel* case, Dr. Kulig stated that the ERI study "is inherently unreliable and is not relied upon for [his] opinions." Kulig/*Nussel* Aff. p. 9 ¶ 7(i) (Oct. 20, 1998) (Att.2N).

353. Nevertheless, Dr. Kulig relies on the ERI study as evidence that Parlodel ® causes stroke. *E.g.,* Kulig/*Nussel* Aff., p. 11 ¶ 10(a) (using ERI to satisfy first Hill criterion, "strength") (Att.2N).

354. Regarding HCIA, another study failing to show a relationship between Parlodel ® and a risk of postpartum stroke, Dr. Kulig stated that, "overall I think the [HCIA] study is not reliable in answering the questions that need to be answered." Kulig/*NJC* Dep. 78 (Att.2B).

(c) Dr. Kulig's Reliance on Anecdotal Human Data

355. Dr. Kulig relies heavily on ADEs and anecdotal case reports.

356. Dr. Kulig admits, however, that case reports are traditionally the least rigorous form of proof of a hypothesis. Kulig/*Warren* Trial Transcript 187 (Att.2O).

357. Dr. Kulig acknowledges that case reports are not epidemiologic studies. Kulig/*Anderson* Dep. 232 (Att.2F); Kulig/*Warren* Dep. 104 (Att.2G). Dr. Kulig acknowledges that case reports are not blinded or controlled and that one cannot calculate a relative risk from case reports. Kulig/*B /G /Q* Dep. 271–72 (Att.2H); Kulig/*Siharath* Dep. 141 (Att.2I); Kulig/*Anderson* Dep. 232 (Att.2F). Further, Dr. Kulig admits that one cannot derive any confidence intervals for determining statistical significance from case reports. Kulig/*Anderson* Dep. 232 (Att.2F).

358. Dr. Kulig admits that one cannot scientifically attribute causation based on case reports. Kulig/*B /G /Q* Dep. 431–35, 532 (Att.2H); Kulig/*Siharath* Dep. 142–43 (Att.2I).

359. Dr. Kulig concedes that epidemiologic studies obviously trump case reports. Kulig/*Nussel* Hearing Transcript, Apr. 6, 1999, Vol. II, at 170 (Att.2C).

360. Dr. Kulig agrees that: "A claim by a physician that a particular product caused a plaintiff's injury based on the observation that the plaintiff developed a disease after exposure may amount to nothing more than a description of two events, exposure and disease, that are sequentially but not causally connected." Kulig/*B /G /Q* Dep. 272–73 (Att.2H).

361. Dr. Kulig concedes that a temporal relationship standing alone does not prove causation. Kulig/*Coleman* Dep. 64 (Att.2P).

(iv) Dr. Kulig's Opinion on Mechanism

362. Not only are vasoconstriction and hypertension absent in the women who take Parlodel ® for PPL, but also they are absent as well in the patients around the world who take Parlodel ®—in much higher doses and for longer periods of time—for other indications, such as Parkinson's disease. *See, e.g.,* Kulig/*Warren* Trial Transcript 127–28 (Att.2O).

363. Dr. Kulig does not describe the mechanism by which Parlodel ® supposedly causes vasoconstriction in some undefined, unpredictable, and unknowable tiny segment of the postpartum population, in the face of admitted evidence that the expected effect of Parlodel ® is exactly the opposite. For example, Dr. Kulig has no theory to explain the extreme rarity of the

vasoconstrictive phenomenon he hypothesizes. He offers only the speculation that unspecified "ergots" are unusual drugs that can sometimes, even in the same person, have different effects, Kulig/*NJC* Dep. 192 (Att.2B), but adds, "I don't know why that happens." *Id.* at 193.

364. Dr. Kulig does not endorse any mechanism by which Parlodel ® may cause vasoconstriction or stroke as a matter of reasonable medical certainty. Kulig/*B /G /Q* Dep. 202 (Att.2H); Kulig/*Siharath* Dep. 121–25, 136, 203 (Att.2I).

(v) Dr. Kulig's Methodology

365. Dr. Kulig has published case reports concerning Parlodel ®, but he has never set forth in those reports—or in any other published data susceptible of peer review—the definitive causation opinions he offers in court. Dr. Kulig's one published report presented two cases of headache. Kulig, *et al,* "Bromocriptine-associated headache: Possible life-threatening sympathomimetic interaction," *Obstet. Gynecol.* 78(5) Part 2:941–43 (1991) (Att.10).

366. The report states that Parlodel ® "has been postulated to be a vasoconstrictor," *id.* at 943, and concludes, "[a]lthough causation cannot be proven, the use of sympathomimetics to treat bromocriptine-induced headache may exacerbate the adverse effects of bromocriptine in some patients," *id.*

(vi) Rate of Error

367. Dr. Kulig's methodology reasons from anecdotal data, the error rate of which is impossible to know or establish. He admits that case reports are not controlled, blinded, capable of yielding statistical significance, or capable of ruling out other alternative causes of the events noted therein. *See, e.g.,* Kulig/*B /G /Q* Dep. 271–72 (Att.2H); Kulig/*Anderson* Dep. 232 (Att.2F).

368. The probable error rate accompanying any use of case reports is manifest where, as here, the epidemiology finds *no* statistically-significant association between Parlodel ® and stroke.

369. Dr. Kulig does not address the concept of the rate of error that is inherent in his methodology. *See, e.g.,* Kulig/*Anderson* Dep. 208–09 (does not know rate of error and does not agree that the concept has any significance to reliability of his opinions). (Att.2F); Kulig/*Hernandez* Dep. 220–21 (cannot quantify rate of error) (Att.2R); Kulig/*Rider* Dep. 226 (same) (Att.2J); Kulig/*Siharath* Dep. 187–88 (same) (Att.2I).

(vii) General Acceptance

370. The methodology of Dr. Kulig and his conclusions concerning bromocriptine has not attracted support in the scientific community. Kulig Dep. 107 (unable to cite any treatise in neurology stating that bromocriptine causes stroke) (Att.2K).

(viii) Dr. Kulig's Reliance on Animal and Other Studies

371. Dr. Kulig relies on animal studies in support of his causation opinion. Kulig Dep. 218 ("I've got a whole pile of animal studies behind me.") (Att.2K).

372. Dr. Kulig relies upon discrete parts of two or three animal studies in which the drug was not administered orally, as in plaintiff's case. *See, e.g.,* Kulig/*B /G /Q* Dep. 32–43, 80–88, 98–118, 121–22, 128–29, 175–91, 207–08 (Att.2C); Kulig/*Rider* Dep. 99–100 (Att.2J); Kulig/*Siharath* Dep. 99–102, 152–53 (Att.2I). Dr. Kulig acknowledges the weakness of such evidence. Kulig Dep. 196 ("If you give an intraperitoneal drug to a mouse, there's very little human corollary to that because we don't give drugs to people that way, for

instance.") (Att.2K); Kulig/*Nussel* Hearing Transcript, Apr. 6, 1999, Vol. II, at 129–34 (testifying that he was not "hanging his hat" on animal studies to prove that bromocriptine is a vasoconstrictor) (Att.2C).

373. Dr. Kulig cannot cite any animal study showing cerebral hypertension to have been caused by bromocriptine. Kulig/*Warren* Trial Transcript 64 (Att.2O).

374. Dr. Kulig cannot cite any animal experiments in intact animals in which bromocriptine has been shown to have a hypertensive effect. Kulig/*Warren* Dep. 431 (Att.2O).

375. In the animal studies relied upon by Dr. Kulig, doses of bromocriptine vastly in excess of those used for PPL were injected into animals whose nervous systems had first been destroyed to prevent compensating mechanisms, *see* Kulig/*B /G /Q* Dep. 118–19, 178 (Att.2H), or enormous doses of bromocriptine were injected into *in vitro* "preparations" involving not a live animal, but an isolated strip of an artery. Kulig/*B /G /Q* Dep. 193–94 (Att.2H).

376. The investigators in these studies on which Dr. Kulig relies studied parts of the animal that may have different receptors from the cerebral arteries of the same animal and may have been different receptors from the cerebral arteries of humans. *See* Kulig/*Siharath* Dep. 204 (Att.2I); Kulig/*Hollander* Dep. 89–91 (Att.2A).

377. These studies do not provide a scientifically valid link with the live, intact human being at issue in this case. *See. e.g.,* Kulig/*B /G /Q* Dep. 43, 56–57, 72, 74–75, 80–84, 174–75, 188–91, 223 (Att.2H); Kulig/*Rider* Dep. 99–101, 228–30 (bromocriptine is not administered to humans intra-arterially, as it was in study) (Att.2J); *id.* at 232–36 (does not know amount of bromocriptine that would have to be administered orally to a human to achieve a level comparable to 25 micrograms injected into a dog's femoral artery, as in this study); Kulig/*Siharath* Dep. 103–04, 209 (Att.2I); *id.* at 204 (limitations of using animal studies to predict effects in humans include different reactivity, pharmacokinetics, and pharmacodynamics among species; the fact that animals are often tested in overdose quantities; and differences between animals and humans in size, receptors, and receptor activity); Kulig/*Warren* Dep. 43, 149 (Att.2G).

378. No one has ever established a dose-response relationship with respect to bromocriptine and stroke. *See* Kulig/*B /G /Q* Dep. 116–17, 123 (failing to take dose-response into account in human studies) (Att.2H)

379. Dr. Kulig is not aware of any studies in intact animals showing that bromocriptine causes high blood pressure or stroke. Kulig/*B /G /Q* Dep. 207–08 (no studies showing high blood pressure or stroke) (Att.2H); *See* Kulig/*Siharath* Dep. 210 (Att.2I).

380. Dr. Kulig refers to an "inversion point" in the animal data, a point at which the vasodilatory effect of bromocriptine allegedly changes over to vasoconstriction in the "hind limb 'study,' " but he does not know either whether there is such an inversion point in human beings, or whether any experimental methodology shows the existence of inversion points in human beings. Kulig/*B /G /Q* Dep. 61 (Att.2H). Dr. Kulig admits that, if there *are* inversion points in humans, they may be at entirely different levels than for the dog. Kulig/*B /G /Q* Dep. 58 (Att.2H).

381. Dr. Kulig admits that the whole concept of an inversion point does not make any sense unless an artery is artificially isolated from the rest of the body. Kulig//*B /G /Q* Dep. 61–62 ("Q. Are you familiar with any experimental evidence showing that inversion points exist in an

animal model in which they do not attempt to isolate a particular limb? A. Well, the reason the question doesn't make sense is you can't collect data unless you isolate the limb. You are canulating specific arteries and doing tests on those specific arteries using the whole animal. The isolation is what allows one to collect data.") (Att.2H).

382. Dr. Kulig concedes that this is not how bromocriptine is administered in human beings. Kulig/*Rider* Dep. 230 (Att.2J).

383. When Parlodel® is used orally, the bromocriptine first has to be absorbed through the gastrointestinal ("GI") tract. Kulig/*B /G /Q* Dep. 85 (Att.2H). Only 28 percent of the bromocriptine is ever absorbed. Kulig/*Siharath* Dep. 157 (Att.2I). Once it gets into the GI tract, bromocriptine has to pass through the liver, where the vast majority of it is metabolized before it ever enters the blood stream. Kulig/*B /G /Q* Dep. 86 (Att.2H). Dr. Kulig admits he has no basis to dispute that approximately 96 percent of the bromocriptine that passes from the GI tract to the liver is metabolized and never enters the blood stream. Kulig/*B /G /Q* Dep. 86 (Att.2H). By comparison, in the dog "hind-limb 'study,' " Dr. Kulig admits that none of the bromocriptine is metabolized in the blood. Kulig/B/G/Q Dep. 158–59 (Att.2H).

(a) Carotid artery study

384. Dr. Kulig relies on a carotid artery study of dogs. The study, based on another animal model that has never been validated and has never been approved by a governmental or regulatory agency, shows that the blood pressures that three dogs in the study started out with were abnormally high. Kulig/*B /G /Q* Dep. 145–46 (Att.2H). Dr. Kulig does not know the reason for this, Kulig/*B /G /Q* Dep. 146 (Att.2H) and does not know what the results of this experiment would have been if the dogs had been normotensive. Kulig/*B /G /Q* Dep. 146 (Att.2H).

385. Dr. Kulig admits that "[i]t would be difficult if not a useless endeavor" to do any kind of statistical analysis on a sample of just three dogs. Kulig/*B /G /Q* Dep. 144 (Att.2H).

386. In the carotid artery study, blood pressure was measured in a dog after bromocriptine was injected intravenously; the blood pressure fell approximately 32 percent in a matter of just thirty minutes. Kulig/*B /G /Q* Dep. 143–45 (Att.2H).

387. Mammals have a homeostatis (or reflex) response to a sudden drop in blood pressure. Kulig//*b /G /Q* Dep. 151–52 (Att.2H).

388. "Homeostatic"—or reflex in this setting—means that there is some type of compensatory mechanism taking place to counteract an opposite effect. The net result of this compensatory response, admits Dr. Kulig, is that vital functions like blood pressure remain the same. Applying that term specifically to blood pressure, it means that the organism tries to maintain a range of blood pressures that allow its organs to continue to be perfused with blood. Kulig/*B /G /Q* Dep. 151–52 (Att.2H).

389. Dr. Kulig concedes that this is true in all mammals. Kulig/*B /G /Q* Dep. 151–52 (Att.2H).

390. Dr. Kulig admits that, if something causes a substantial reduction in blood pressure in a mammal, there are a variety of mechanisms by which the mammal will try to maintain blood pressure to keep its organs perfused with blood. Kulig/*B /G /Q* Dep. 151–52 (Att.2H).

391. According to Dr. Kulig, one of the means that a mammal has of maintaining

blood pressure in certain organs is vasoconstriction. Kulig/*B /G /Q* Dep. 153–55 (Att.2H).

392. Also according to Dr. Kulig, vasoconstriction is a homeostatic response to drug-induced hypotension. Kulig/*B /G /Q* Dep. 155–56 (Att.2H).

393. Dr. Kulig testified that, in the carotid artery study on the three dogs, after bromocriptine was infused, homeostatic or compensatory mechanisms were activated, *i.e.,* an increase in the heart rate was likely to be a homeostatic response as "compensation for the falling blood pressure." Kulig/*B /G /Q* Dep. 157 (Att.2H).

(b) Hand vein study

394. Dr. Kulig admits that evidence that a drug can cause vasoconstriction in some blood vessels in a *human* does not necessarily mean that it can cause vasospasm in the cerebral arteries sufficient to cause a stroke. *See, e.g.,* Kulig/*B /G /Q* Dep. 122–23 (cannot say that because bromocriptine allegedly causes constriction of hand veins it also causes spasm (constriction) of the cerebral or coronary arteries) (Att.2H); Kulig/*B /G /Q* Dep. 60 ("underlying vascular tone may be significantly different in one artery versus another") (Att.2H); Kulig/*Siharath* Dep. 199 (does not know if results can be extrapolated to cerebral veins) (Att.2I); *see also* Kulig/*Siharath* Dep. 187–88, 194–96, 200–02 (Att.2I).

395. The "hand vein" study excludes the systemic effects of bromocriptine. Kulig/*Siharath* Dep. 188 (particular model does not attempt to measure any systemic effects) (Att.2I).

396. To perform this study, the veins had to be artificially inflated, *i.e.,* congested and enlarged with blood. Kulig/*B/G/Q* Dep. 107–08 (Att.2H).

397. Dr. Kulig does not know what would happen in this experiment, if anything, if the veins were not first congested and enlarged with blood. Kulig/*B/G/Q* Dep. 108 (Att.2H).

398. Dr. Kulig does not know if the methodology employed in the "hand vein" study has ever been validated or approved by any government or regulatory agency. Kulig/*B/G/Q* Dep. 108–09 (Att.2H).

399. Dr. Kulig has not been able to cite any study that states that the effects in human hand veins can be correlated to effects in arteries. Kulig/*B/G/Q* Dep. 103 (Att.2H).

400. Dr. Kulig does not know whether the results of this study have ever been replicated. Kulig/*Siharath* Dep. 198 (Att.2I).

(ix) Dr. Kulig's Reliance on evidence of Drugs Other Than Bromocriptine

401. Although he concedes that bromocriptine causes vasodilation and hypotension, *see, e.g.,* Kulig/*NJC* Dep. 237 (Att.2B); Kulig/*Siharath* Dep. 154–55 (Att.2I), Dr. Kulig nevertheless argues that, in an otherwise unidentifiable subset of women that happens to include plaintiff, bromocriptine causes the opposite effect, vasoconstriction, because he claims, it is structurally similar to other ergot-derived drugs, some of which have vasoconstrictive properties. Kulig Dep. 196–97 (Att.2K); *see* Kulig/*Siharath* Dep. 177–78 (Att.2I).

402. Dr. Kulig concedes that "[t]he fact that bromocriptine is an ergot alkaloid in and of itself does not mean it does what other ergot alkaloids as a class do, and I have never made that claim." Kulig/*Nussel* Hearing Transcript, Apr. 6, 1999, Vol. I, at 52 (Att.2C).

403. Dr. Kulig admits that there is no statistically-significant epidemiologic study

showing that *any* ergot increases the risk of stroke. Kulig/*B/G/Q* Dep. 105–06 (Att.2H).

(x) Dr. Kulig's Opinions Regarding Specific Causation

(a) High Risk of Stroke in the Postpartum Period

404. Dr. Kulig has testified that "stroke may affect all sexes and all genders and all ages." Kulig/*B/G/Q* Dep. 257 (Att.2H).

405. Dr. Kulig has testified that "there are many patients who present with stroke where we don't know the cause." Kulig/*B/G/Q* Dep. 259 (Att.2H).

406. Dr. Kulig concedes that, in the postpartum period, there occur a variety of different kinds of stroke, including idiopathic strokes. Kulig/*Warren* Trial Transcript 158 (Att.2O).

407. Dr. Kulig has testified that the best way to answer the question whether the postpartum period itself is a risk factor for stroke is with a "well designed and performed epidemiologic study." Kulig/*Warren* Dep. 304 (Att.2G).

408. Dr. Kulig concedes that there are some studies that indicate there is an increased risk of stroke in the postpartum period. Kulig/*Warren* Dep. 304 (Att.22G).

409. Dr. Kulig believes that the postpartum period is *not* a high risk period for stroke if eclampsia is excluded. Kulig/*Hollander* Dep. 117 (Att.2A). Dr. Kulig does not cite evidence to support his view that the postpartum period is not a high risk period for stroke absent eclampsia, and instead challenges the studies showing the increased risk, even though he is not an expert in epidemiology. Kulig/*Warren* Dep. 54 (does not consider himself an expert in epidemiology) (Att.2G).

410. Dr. Kulig disregards the express conclusion of recent studies that eclampsia is not a sufficient explanation for the increased risk of postpartum stroke. *E.g.,* Kittner Study, at 768–74 (1996) (Att.7) (Kulig/*Hollander* Dep. 117) (Att.2A).

411. Plaintiff's epidemiologist Dr. Macones, however, testified that the epidemiology clearly showed an increased risk of stroke in the postpartum period, even excluding preeclampsia and eclampsia. Macones/*B/G/Q* Dep. 90–99 (Att.4A).

(b) Other Causal Factors

412. Dr. Kulig has no scientifically reliable means of excluding amphetamine, diet pills, or sympathomimetic amines as the cause of plaintiff's stroke. Dr. Kulig concedes that a January 19, 1991, drug screen performed after plaintiff presented with her stroke reflects the presence of aspirin and a "large amount present" of amphetamine. Kulig Dep. 120–121 (Att.2K).

413. Medical records noting a "large amount present" of amphetamine at the time of plaintiff's stroke, which Dr. Kulig did not review at the time he reached his causation opinion and drafted his expert report, do not change his opinion that Parlodel ® was the cause of plaintiff's ICH. Kulig Dep. 26 (Att.2K).

414. Dr. Kulig concedes the possibility that plaintiff was using diet pills at the time of her stroke. Kulig Expert Report, at 2 (noting the "question in her records of diet pill ingestion"). (Att.2M).

415. Dr. Kulig notes that diet pills contain sympathomimetic amines, such as phenylpropanolamine ("PPA"). Kulig Dep. 106–07 (Att.2K).

416. Amphetamine, methamphetamine, and PPA are all compounds known as sympathomimetic amines. Kulig Dep. 100, 106 (Att.2K).

417. Dr. Kulig agrees that amphetamine, methamphetamine, and PPA all cause vasoconstriction. 11/9 Tr. at 150.

418. Dr. Kulig concedes that amphetamine and methamphetamine, taken by themselves, can cause stroke. Kulig Dep. 134 (Att.2K).

419. Dr. Kulig concedes that PPA, taken in the absence of other drugs, can cause stroke. 11/9 Tr. at 152.

420. Dr. Kulig concedes that it is only "possible" that the sympathomimetic found in Contac resulted in a drug-drug interaction with Parlodel ®, and that he does not hold this opinion to a reasonable degree of medical certainty. Kulig Dep. 139 (Att.2K).

421. Dr. Kulig has no opinion regarding whether or when plaintiff started or stopped taking Contac. Kulig Dep. 108–09 (Att.2K).

(c) Plaintiff's Medical History

(1) Dr. Kulig's causation theory is not supported by plaintiff's medical history

422. Dr. Kulig states that an angiogram is necessary to determine whether or not vasospasm is taking place. Kulig Dep. 53 (Att.2K).

423. Dr. Kulig concedes that there are no medical records prior to plaintiff's stroke to document that vasospasm occurred. Kulig Dep. 62 (Att.2K).

(2) Dr. Kulig cannot demonstrate that plaintiff was taking Parlodel ® at or near the time of her ICH.

424. Plaintiff testified that she began taking Parlodel ® on or about December 27, 1990. Soldo Dep. 121–22 (Att.8).

425. A 15–day prescription of Parlodel ® started on or around December 27, 1990, would have been completed on or around January 10, 1991, eight days before plaintiff's stroke.

426. Dr. Kulig "just doesn't know" whether it is possible for bromocriptine to have a physiologic effect eight days after the time of last dose. Kulig Dep. 98 (Att.2K).

(xi) Dr. Kulig's Use of Differential Diagnosis

427. Plaintiff's experts both reached their specific causation opinion by using what they defined as a differential diagnosis methodology. 11/8 Tr. at 56; 11/10 Tr. at 63–64.

428. A differential diagnosis requires that plausible alternative causes to plaintiff's injury be ruled out.

429. Dr. Kulig testified "Parlodel ® caused vasospasm which resulted in an intracerebral hemorrhage in Lisa Soldo's brain." 11/8 Tr. at 103.

430. Dr. Kulig did not attempt to rule out an idiopathic stroke—that is, address the fact that stroke occurs in the general population with no known cause and in persons with no known risk factors. (11/9 Tr. at 147 (declining to categorize idiopathic as a cause of stroke).) In addition:

(a) Dr. Kulig did not offer an adequate basis to rule out the postpartum period as an alternative cause of plaintiff's ICH.

431. Plaintiff was squarely in the postpartum period when she suffered her ICH. 11/15 Tr. at 176.

432. Extensive epidemiology supports the fact that the postpartum period is a risk factor for stroke.

433. Dr. Kulig testified at the hearing in this case, contrary to earlier deposition testimony, that he did not believe that the postpartum period is a risk factor for

stroke. *See, e.g.,* 11/9 Tr. at 157. His hearing testimony is based on his belief that if the postpartum epidemiology studies had been controlled for eclampsia and Parlodel ® use, the study results may not have demonstrated the apparent significant increased risk of ICH postpartum. 11/9 Tr. at 157–58.

434. The Kittner study specifically evaluates the role of eclampsia and concludes that eclampsia does *not* account for the findings of significant increased risk of stroke (for example, does *not* account for the 28 times increased risk of ICH). Ex. GA at 773.

435. Dr. Kulig can only speculate that eclampsia accounts for the increased risk of stroke in the body of postpartum epidemiology. He offered no evidence—*i.e.,* published or unpublished studies—in support of the supposition that eclampsia accounts for the increased risk.

436. Dr. Kulig can only speculate that Parlodel ® played any role whatsoever in the Kittner study or any of the other postpartum stroke studies. He offered no evidence in support of the supposition that Parlodel ® was even prescribed to the study subjects, much less associated with any adverse events.

(b) Dr. Kulig did not provide any explanation for the possible role of sympathomimetic amines in plaintiff's ICH.

437. A routine drug screen conducted within hours of plaintiff's admission to the Sharon General Hospital emergency room returned a positive result for "large amount present" of "amphetamine." Exhibit 1503–F.

438. Dr. Kulig testified that this positive result was consistent with the use of an over-the-counter cold remedy, such as Contac. Such cold remedies contain one or more members of the sympathomimetic family of compounds as an active ingredient. 11/8 Tr. at 80.

439. Dr. Kulig testified that amphetamine, methamphetamine, PPA, pseudoephedrine, and ephedrine all would generate the same positive test result on such a drug screen. 11/8 Tr. at 80–81.

440. PPA and pseudoephedrine are found in many over-the-counter cold remedies. 11/15 Tr. at 18–19.

441. Both PPA and pseudoephedrine are sympathomimetic amines. 11/8 Tr. at 150–51.

442. Dr. Kulig testified that sympathomimetics as a class, which includes amphetamine, methamphetamine, PPA and pseudoephedrine, have been thought to cause vasoconstriction. 11/9 Tr. at 149–50.

443. Dr. Kulig did not offer any valid explanation as to how or why he "ruled out" PPA or other sympathomimetic use as a plausible alternative cause of plaintiff's ICH.

(c) Dr. Kulig did not validly rule out naturally-occurring endogenous vasoconstrictors generated by plaintiff's body as an alternative cause of plaintiff's ICH.

444. Dr. Kulig has testified that there can be massive releases of endogenous compounds for idiopathic reasons. Kittleson Dep. at 55–56 (Att.24).

445. Dr. Kulig has testified that endogenous vasoconstrictors like norepinephrine mimic the sympathomimetic drugs. Soldo Dep. at 100 (Att.29); *see also* Kerr Dep. at 277 (norepinephrine is endogenous vasoconstrictor) (Att.45).

446. Dr. Kulig has testified that serotonin is an endogenous "very potent" vasoconstrictor. Soldo Dep. at 210 (Att.29); *see also* Kerr Dep. at 280–81 (Att.45).

447. If ICH *could* be caused by vasoconstriction or vasospasm, vasoconstrictive substances naturally present in the human body are plausible potential causes. 11/16 Tr. at 149–150, 153–54.

448. Dr. Kulig has admitted he does not know any "sufficient diagnostic technique" for ruling out endogenous vasoconstrictors and that it is in fact impossible to do so. Kulig/*Globetti* Dep. at 135 (Att.11).

449. Dr. Kulig did not offer any valid explanation as to how or why he "ruled out" naturally-occurring endogenous vasoconstrictors as a plausible alternative cause of plaintiff's ICH.

(d) Dr. Kulig did not interpret certain medical records according to their plain meaning.

450. Dr. Kulig testified that "the evidence is overwhelming" that plaintiff had cerebral artery vasospasm that led to ICH. 11/9 Tr. at 51.

451. There is no mention of cerebral vasospasm in any of plaintiff's medical records surrounding her admission and treatment for her January 18, 1991 ICH. *E.g.,* Plaintiff's Ex. 1503 and 1504 (medical and hospitalization records).

452. There is no mention of cerebral vasospasm on plaintiff's arteriogram taken shortly after her admission for treatment of her ICH. Plaintiff's Ex. 1504C; *see also* 11/15 Tr. at 185–87.

453. There is no mention of vasospasm on the angiogram report. *Id.*

454. Dr. Kulig testified he interprets the radiographic report statement "The possibility of arthritis [arteritis] is not excluded" as a statement that the radiologist "could not exclude the possibility of vasospasm" from reading plaintiff's angiogram. 11/8 Tr. at 86.

455. The angiogram report in fact expressly notes a finding of ectasia or dilatation. *E.g.* 11/15 Tr. at 186.

456. There is no reliable scientific evidence that demonstrates that plaintiff had cerebral arterial vasospasm prior to or during her ICH. 11/16 Tr. at 104.

457. Dr. Kulig did not demonstrate that the results of any clinical trials and other studies conducted with humans support the hypothesis that the use of Parlodel ® can cause ICH.

458. Dr. Kulig did not demonstrate that the results of any animal studies support the hypothesis that the use of Parlodel ® can cause ICH.

459. Dr. Kulig did not identify any mechanism by which Parlodel ® can cause ICH or cerebral vasospasm.

460. Dr. Kulig did not demonstrate that his hypothesis that Parlodel ® can cause ICH has been tested by the scientific method.

461. Dr. Kulig did not present evidence that his methods were generally accepted.

462. Dr. Kulig has not presented evidence concerning the error rate of his causation methodology.

463. Dr. Kulig did not present evidence that his causation methodology has been tested by peer review; also, his case report publication does not make an assessment that Parlodel ® caused the adverse event.

464. Dr. Kulig did not reliably rule out the postpartum period as a plausible alternate cause of plaintiff's stroke.

465. Dr. Kulig did not reliably rule out a sympathomimetic compound as a plausible alternate cause of plaintiff's ICH.

466. Dr. Kulig did not attempt to rule out endogenous vasoconstrictive substances as a plausible alternate cause of plaintiff's ICH.

467. Dr. Kulig did not demonstrate use of any diagnostic techniques for ruling out plausible causes of plaintiff's stroke.

468. Dr. Kulig did not present any objective or corroborating evidence that supports any finding that plaintiff's stroke was caused by cerebral vasoconstriction or cerebral vasospasm.

469. Dr. Kulig did not present scientifically valid evidence to support a finding that plaintiff's ICH was caused by Parlodel ®.

N. Findings of Fact Regarding Plaintiff's Expert Dr. Denis Petro

(i) Dr. Petro's Qualifications

470. Dr. Petro is not an epidemiologist. Petro Dep. 21 at (Att.3E).

471. Dr. Petro is not a statistician. Petro Dep. at 2, 55, 56 (Att.3E).

472. Dr. Petro is not an obstetrician/gynecologist. Petro/*B/G/Q* Dep. at 81 (Att.3C).

(ii) Scientific Knowledge

473. Dr. Petro agrees that one must know whether or not bromocriptine can cause an ICH before reaching an opinion that a particular individual suffered an ICH due to bromocriptine ingestion. Petro Dep. at 107 (Att.3E).

474. Dr. Petro admitted that, to test the hypothesis that a particular drug causes a particular adverse event, the scientific method would require one to (1) conduct a prospective, double-blind, randomized, placebo-controlled study, Petro/*B/G/Q* Dep. at 351 (Att.3C); (2) utilize a single-patient trial design, *id.* at 356–57; Petro/*Rider* Dep. at 140 (Att.3A); or (3) establish through epidemiology that an overwhelming number of people experience the adverse event when given the drug compared to those who experience the event in its absence, Petro/*B/G/Q* Dep. at 368–69 (Att.3C). Dr. Petro admitted that one could not show general causation using scientific methodology in the absence of such studies. *Id.* at 369–70.

475. When he was asked whether studies showing that bromocriptine causes stroke have ever been conducted, Dr. Petro admitted that no such studies have been conducted. Petro/*B/G/Q* Dep. at 351–52 (Att.3C) (no prospective, double-blind, randomized, placebo-controlled study); *Id.* at 360 (no single patient trial design); *id.* at 369 (no epidemiology).

476. Dr. Petro cannot cite any epidemiologic or controlled clinical study showing a significantly increased risk of stroke or vasospasm associated with Parlodel ®. Petro/*B/G/Q* Dep. at 289–90 (Att.3C).

477. Dr. Petro cannot explain a mechanism for Parlodel ®-caused vascular toxicity. *Id.* at 191–95, 434, 492.

478. Dr. Petro has testified that he cannot testify to a reasonable degree of medical certainty that bromocriptine was the cause of plaintiff's stroke if the possibility that bromocriptine caused plaintiff's stroke is less than 50 percent. Petro Dep. at 115–16 (Att.3E).

(iii) The Testing or Testability of Dr. Petro's Opinions

(a) Epidemiology

479. Dr. Petro agrees epidemiology addresses whether an agent can cause a disease. Petro Dep. at 268–70 (Att.3E).

480. Dr. Petro concedes no epidemiologic study shows a statistically-significant association between Parlodel ® and stroke. He agrees there is no statistically-significant epidemiologic study showing that Parlodel ® increases the risk of stroke. *See* Petro/*B/G/Q* Dep. at 290 (Att.3C).

481. Dr. Petro is similarly unable to point to any clinical trial for any indication of Parlodel ® in which there was a statistically-significant increased risk of stroke. Petro/*B/G/Q* Dep. at 311 (Att.3C).

(b) Dr. Petro's Reliance on Anecdotal Human Data

482. Dr. Petro concedes that case reports are the only data he has in support of his opinion that an ICH could be caused by Parlodel ® taken eight days before the stroke. Petro Dep. at 180 (Att.3E).

483. Although case reports may be documented and published in the medical literature, Dr. Petro concedes that case reports *do not* establish causation: "Q. So would you agree that the mere fact that an ADE has been sent to FDA doesn't mean that there was a causal relationship? A. You're correct." Petro/*B/G/Q* Dep. at 428–29 (Att.3C); Petro/*Rider* Dep. at 181–82 (Att.3A).

484. Dr. Petro concedes that a temporal link between a medication and an observed event does not mean that causation has been established. Petro Dep. at 269 (Att.3E).

(iv) Dr. Petro's Opinion on Mechanism

485. Dr. Petro cannot describe the mechanism by which Parlodel ® supposedly causes vasoconstriction. For example, Dr. Petro has no theory to explain the extreme rarity of the vasoconstrictive phenomenon he hypothesizes. He offers only the speculation that unspecified "ergots" are unusual drugs that can sometimes, even in the same person, have different effects. Petro/*Siharath* Dep. 182 (Att.3B).

486. Dr. Petro has listed several possible candidates for a mechanism by which Parlodel ® supposedly causes vasoconstriction, but he endorses none as a matter of reasonable medical certainty. Petro/*B/G/Q* Dep. at 191–95, 434, 492 (Att.3C); Petro/*Rider* Dep. at 268 (Att.3A); Petro/*Siharath* Dep. at 182 (Att.3B).

(v) Dr. Petro's Methodology, Rate of Error, and General Acceptance

487. Dr. Petro has not exposed his opinions and methodology to his peers and does not rely on any peer-reviewed literature by third parties that makes the statement that bromocriptine causes stroke. Petro/*B/G/Q* Dep. at 335 (Att.3C).

488. Dr. Petro's methodology reasons from anecdotal data, the error rate of which is impossible to know or establish. He admits that case reports are not controlled, blinded, capable of yielding statistical significance, or capable of ruling out other alternative causes of the events noted therein. *See, e.g.,* Petro/*B/G/Q* Dep. at 426–28 (Att.3C).

489. Dr. Petro's methodology and conclusions concerning bromocriptine have not attracted support in the scientific community. Petro/*B/G/Q* Dep. at 335 (unable to cite any treatise in neurology stating that bromocriptine causes stroke) (Att.3C).

(vi) Dr. Petro's prior testimony and actions as an FDA medical reviewer of Parlodel ®.

490. Dr. Petro two decades ago was a medical reviewer for the FDA and recommended FDA approval of Parlodel ® as safe and effective for the Parkinson's Disease indication. Petro/*Rider* Dep. at 80, 127, 160–61 (Att.3A); Petro/*Siharath* Dep. 105 (Att.3B).

491. Dr. Petro testified at the 1980 Peripheral and Central Nervous System Drugs Advisory Committee hearing that Parlodel ® "may *or may not* be related" to two cardiovascular deaths. Petro/*Rider* Dep. at 128–29, 188 (Att.3A); Petro/*Sihar-*

ath Dep. 130–32, 148–52 (Att.3B). In his testimony in Parlodel®-related litigation, however, Dr. Petro has stated that Parlodel® "contributed significantly" to the myocardial infarction deaths.

492. In Dr. Petro's remarks made to the FDA in 1980 as a reviewer of the Parlodel® NDA for the Parkinsonism indication, Dr. Petro referred to literature that uniformly showed bromocriptine to have a hypotensive, or vasodilatory effect. 11/10 Tr. at 146–47.

493. Dr. Petro admits that there was no evidence of hypertension or vasoconstriction in the studies submitted to the FDA in support of the Parlodel® Parkinsonism indication. 11/10 Tr. at 148.

494. Dr. Petro testified that he had concerns that three vascular deaths were related to "Parlodel®-induced ergotism." 11/10 Tr. at 30.

495. The chief investigators who reported the three deaths concluded that those deaths were unrelated to Parlodel® therapy. 11/10 Tr. at 143–46.

496. One of these deaths occurred in a patient who had stopped Parlodel® therapy and who was pushing his car in July when he suffered an acute myocardial infarction. 11/10 Tr. at 144–45; *see also* Ex. TW at 708. This patient had ceased Parlodel® therapy four days prior to his myocardial infarction. 11/16 Tr. at 194–95; Ex. TW at 708.

497. The second of these deaths occurred because of an event of torsion around adhesion in the bowel, 11/10 Tr. at 145, and Dr. Petro did not offer any evidence of how adhesion in the bowel could be caused by Parlodel® use. NPC presented uncontested evidence that no one has ever suggested that bromocriptine could cause torsion of the bowel. 11/16 Tr. at 191–94; *see also* Ex. TW at 206.

498. The third of these deaths occurred in a 64–year old gentleman who died in his sleep. 11/10 Tr. at 146. In the opinion of this man's treating physician, this death was not related to medication. 11/16 Tr. at 194; Ex. TW at 708.

499. The three deaths reported during the Parkinsonism clinical trials provide no scientifically reliable evidence of "Parlodel®-induced ergotism."

500. Nowhere in the FDA Summary for Basis for Approval, his own medical review of the clinical trials, or his advisory committee hearing testimony did he make mention of his alleged concerns of hypertension or other cardiovascular effects. Petro/*Rider* Dep. at 115, 128–29 (Att.3A); Petro/*Siharath* Dep. at 127–32 (Att.3B). In the context of his involvement in Parlodel®-related litigation, however, he testified that Parlodel® "contributed significantly" to other adverse "cardiovascular effects," including hypertension. Petro/*Rider* Dep. at 115 (Att.3A).

501. Dr. Petro does not know whether hypertension actually occurred in the clinical trials. Petro/*Rider* Dep. at 157 (Att.3A).

(vii) Dr. Petro's Reliance on Animal and Other Studies

502. In the animal studies relied upon by Dr. Petro, doses of bromocriptine vastly in excess of those used for PPL were injected into animals whose nervous systems had first been destroyed to prevent compensating mechanisms, *see* Petro/*B/G/Q* Dep. at 172–74 (Att.3C); enormous doses of bromocriptine were injected into *in vitro* "preparations" involving, not a live animal, but an isolated strip of an artery, or the investigators studied parts of the animal that may have different receptors from the cerebral arteries of the same animal, not to mention different receptors from the cerebral arteries of hu-

mans. *See* Petro/*B/G/Q* Dep. at 191–95, 434, 492 (Att.3C).

503. Dr. Petro purports to rely upon discrete parts of two or three animal studies in which a drug was not administered orally as in plaintiff's case. *See, e.g.,* Petro/*B/G/Q* Dep. at 95–96 (Att.3C); Petro/*Siharath* Dep. at 183–86 (Att.3B). Dr. Petro acknowledges the weakness of such evidence. Petro/*Siharath* Dep. at 192–93 (Att.3B).

504. The Court finds that these studies do not provide a "scientifically valid link" with the live, intact human being at issue in this case. *See* Petro/*Siharath* Dep. at 192–93 ("Q. . . . [D]o you have an opinion to a reasonable degree of medical certainty based on the combination of the human hand model and the hind limb of a dog model that Bromocriptine causes vasospasm in human beings? . . . A. Well, okay. In isolation, that does not—that does not prove that Bromocriptine causes vasospasm.") (Att.3B)

505. Dr. Petro admits that evidence a drug can cause vasoconstriction in some blood vessels in a *human* does not necessarily mean it can cause vasospasm in the cerebral arteries sufficient to cause a stroke. *See, e.g.,* Petro/*Siharath* Dep. at 189 (conceding that, in humans, peripheral vessels differ from cerebral vessels; Dr. Petro cannot say that because bromocriptine allegedly causes constriction of hand veins it also causes spasm of the cerebral or coronary arteries) (Att.3B).

506. Dr. Petro admits that: (1) a drug may have a different effect on an animal and a human being, Petro/*B/G/Q* Dep. at 213–14 (Att.3C); Petro/*Siharath* Dep. at 187–88 (Att.3B); (2) he does not know whether effects seen in animals whose nervous systems have been destroyed would be seen in human beings whose nervous systems are intact; (3) he is aware of no methodology to test the hypothesis, *e.g.,* that the results of a study involving the hind limb of a dog can be extrapolated to intact humans, Petro/*B/G/Q* Dep. at 215–16 (it is "unknowable" whether observation in "hind-limb 'study'" of a dog would be found in humans) (Att.3B); Petro/*Siharath* Dep. at 187–88 (conceding that canine blood vessels are different from human vasculature) (Att.3B); and, (4) notwithstanding his acceptance that a basic principle of toxicology is the concept of dose-response, Petro/*B/G/Q* Dep. at 175 (Att.3C), and that the animal models involve doses far in excess of therapeutic human doses, he has made no attempts whatsoever to correlate the doses used in the animal models with the doses relevant to women taking the drug for PPL, such as plaintiff. *See, e.g.,* Petro/*B/G/Q* Dep. at 204, 213–17 (Att.3C).

507. Dr. Petro testified that no one has ever established a dose-response relationship with respect to bromocriptine and stroke. Petro/*B/G/Q* Dep. at 155–56 (Att.3C).

508. Dr. Petro is not aware of any studies in intact animals showing that bromocriptine causes high blood pressure, stroke, seizures, or myocardial infarction. *See* Petro/*B/G/Q* Dep. at 172 (no studies in intact animals showing hypertension) (Att.3C).

(viii) Dr. Petro's Reliance on Evidence of Drugs Other Than Bromocriptine

509. Although he concedes that bromocriptine causes vasodilation and hypotension, *see, e.g.,* Petro/*Rider* Dep. at 113 – 117–18 ("There were many cases of hypotension in the Sandoz-related studies") (Att.3A); Petro/*Siharath* Dep. at 127 (Att.3B), Dr. Petro nevertheless argues that—in plaintiff (and others in an otherwise unidentifiable subset of women)—bro-

mocriptine causes the opposite effect, vasoconstriction, because, according to Dr. Petro, it shares properties with other ergot-derived drugs, some of which have vasoconstrictive properties. Petro/*Rider* Dep. at 115–17, 132–33, 137 (Att.3A); Petro/*Siharath* Dep. at 140–42, 192 (Att.3B).

510. He agrees that there is no statistically-significant epidemiologic study showing that *any* ergot increases the risk of stroke. *See* Petro/*B/G/Q* Dep. at 335 (Att.3C).

(ix) Dr. Petro's Opinions Regarding Specific Causation

(a) High Risk of Stroke in the Postpartum Period

511. Dr. Petro agrees that the postpartum period itself presents an increased risk for stroke. *See, e.g.* Petro/*B/G/Q* Dep. at 318–25 (postpartum period involves significant hormonal and blood volume changes and hypercoagulation, thus increasing the risk of stroke) (Att.3C).

512. Dr. Petro does not cite evidence to support his view that, absent eclampsia, postpartum women are not at an increased risk for stroke; he instead challenges the studies showing the increased risk, even though he is not an expert in epidemiology. Petro/*Siharath* Dep. at 208 (Att.3B).

513. As does Dr. Kulig, Dr. Petro disregards the *express* conclusion of recent studies, *i.e.,* that eclampsia is not a sufficient explanation for the increased risk of postpartum stroke. *E.g.,* Kittner Study, *supra;* Petro Dep. at 255, 227 (Att.3E); Petro/*Rider* Dep. at 242–43 (Att.3A).

514. Dr. Petro concedes that the Kittner Study's finding of a 28.3 relative risk of stroke for women in the postpartum period is statistically significant. Petro Dep. at 218–19 (Att.3E).

515. Dr. Macones, plaintiff's epidemiologist, rejects Dr. Petro's hypothesis. Macones/*Brasher* Dep. at 90–99 (epidemiology clearly showed an increased risk of stroke in the postpartum period, even excluding preeclampsia and eclampsia) (Att.4A).

516. Dr. Petro concedes that strokes occur in the absence of any obvious risk factors and that ICH can be caused by unknown causes. Petro Dep. at 117 (Att.3E); *see, e.g.,* Petro/*P/G/Q* Dep. at 263–66 (Att.3C).

(b) Other Causal Factors

517. Dr. Petro has no scientifically reliable means of excluding amphetamine, diet pills, or sympathomimetic amines as the cause of plaintiff's stroke. Dr. Petro concedes that plaintiff had been taking amphetamine or amphetamine-like drugs, possibly Contac, at the time of her stroke. Petro Dep. at 187 (Att.3E).

518. Dr. Petro opines that the active ingredient of Contac, most likely PPA, would appear on a drug screen as amphetamine. Petro Dep. at 191 (Att.3E).

519. Dr. Petro concedes that sympathomimetic amines such as PPA or pseudoephedrine cause vasoconstriction. Petro Dep. at 194–95 (Att.3E).

520. Dr. Petro has never compared the alleged vasoconstrictive properties of bromocriptine to the known vasoconstrictive properties of PPA or pseudoephedrine. Petro Dep. at 195 (Att.3E).

521. Dr. Petro can identify no epidemiologic studies or controlled clinical studies that demonstrate that the combination of Parlodel® and sympathomimetic amines can cause ICH. Petro Dep. at 209–11 (Att.3E).

522. Dr. Petro cannot describe the mechanism by which Parlodel® and sympathomimetic amines would cause an ICH. Petro Dep. at 212 (Att.3E).

523. Dr. Petro relies on animal studies involving the concurrent administration of Parlodel ® and amphetamine as support for his opinion that Parlodel ® and sympathomimetic amines can cause ICH, Petro Dep. at 215 (Att.3E), but these studies did not involve either PPA or pseudoephedrine. *Id.*

524. Dr. Petro relies upon the abstract and charts of an animal study of ambulatory mice being administered Parlodel ® and methamphetamine as support for his opinion about the cause of plaintiff's injuries. Petro Dep. at 301–02 (Att.3E). Except for the abstract and charts, the study is in Japanese. Petro Dep. at 307 (Att.3E).

525. Dr. Petro concedes that the methamphetamine/Parlodel ® ambulatory mice study involved much higher doses of Parlodel ® (1–2 mg/kg in the mice vs. 2.5 mg/50 kg in plaintiff) administered in a different fashion (injected vs. taken orally) from the dose and method used by plaintiff. Petro Dep. at 307–08 (Att.3E).

526. Dr. Petro concedes that methamphetamine and PPA do not have the same vasoconstrictive properties. Petro Dep. at 304 (Att.3E).

527. Dr. Petro relies upon studies involving the use of Parlodel ® and cocaine as the basis for his opinion that Parlodel ® and sympathomimetic amines can cause ICH. Petro Dep. at 213–14 (Att.3E).

528. Dr. Petro concedes that cocaine and PPA do not have the same vasoconstrictive properties. Petro Dep. at 304 (Att.3E).

(c) Plaintiff's Medical History

(1) Dr. Petro's causation theory is not supported by plaintiff's medical history

529. Dr. Petro states that "localized vasospasm in the area of the hemorrhage was a precipitant of [plaintiff's] hemorrhage," Petro Dep. at 229 (Att.3E), but he acknowledges he has seen no evidence of vasospasm in plaintiff's medical records, which he reviewed. Petro Dep. 75 (reviewed plaintiff's medical records); *id.* at 232 (no knowledge of evidence of vasospasm in medical records) (Att.3E).

530. Dr. Petro concedes that plaintiff's stroke is not due to hypertension. Petro Dep. at 228 (Att.3E).

(2) Dr. Petro cannot demonstrate that plaintiff was taking Parlodel ® at or near the time of her ICH.

531. Dr. Petro concedes that plaintiff would have completed her Parlodel ® therapy eight days before her stroke if she started on December 27 and took Parlodel ® according to her prescription. Petro Dep. at 133 (Att.3E).

532. Dr. Petro "assumes" that plaintiff took Parlodel ® until one or two days prior to her hemorrhage, and bases this assumption entirely on plaintiff's deposition. Petro Dep. at 130, 135 (Att.3E).

533. There is no evidence in plaintiff's medical records when she completed her Parlodel ® therapy.

534. Dr. Petro concedes that plaintiff's medical records at the time of her stroke do not reflect that she was taking Parlodel ® at that time. Petro Dep. at 137 (Att.3E).

535. Dr. Petro concedes there is no scientifically reliable way to determine when plaintiff actually took her last dose of Parlodel ®. Petro Dep. at 139–140 (Att.3E).

536. Dr. Petro can only guess that plaintiff "could have missed doses" of her Parlodel ® therapy. Petro Dep. at 337, 353–55 (Att.3E).

537. Dr. Petro concedes there is no scientifically reliable way to determine that

plaintiff's last dose of Parlodel ® was fewer than eight days before her stroke. Petro Dep. at 141 (Att.3E).

(x) Dr. Petro's Use of Differential Diagnosis

538. Dr. Petro's theory is that plaintiff's cerebral arterial wall was structurally changed and weakened by a repeated vasospasm secondary to Parlodel ®, resulting ultimately in rupture of the blood vessel (ICH). 11/15 Tr. at 6–7.

539. Dr. Petro did not adequately attempt to rule out an idiopathic stroke—that is, address the fact that stroke occurs in the general population with no known cause and in persons with no known risk factors. 11/10 Tr. at 215 ("You cannot rule out what you cannot rule out.") In addition:

(a) Dr. Petro did not validly rule out the risk of stroke in the postpartum period as an alternate cause of plaintiff's ICH.

540. Dr. Petro previously testified that the postpartum period is a risk factor for stroke. Petro/*Brasher* Dep. at 322 (Att.2).

541. Dr. Petro offered no valid basis to "rule out" this well-documented risk factor as the cause of plaintiff's stroke. *See generally* 11/10 Tr. at 105 ("there's no reason to believe that just having a child three weeks prior will in fact make that person susceptible to stroke").

(b) Dr. Petro did not validly rule out a possible role of sympathomimetic amines in plaintiff's ICH

542. All the sympathomimetic drugs commonly found in over-the-counter medications are vasoconstrictors. 11/15 Tr. at 23.

543. It is unknown how much sympathomimetic-containing drug plaintiff had ingested prior to her ICH. 11/15 Tr. at 18.

544. Dr. Petro testified that PPA could have been a contributing factor to plaintiff's ICH. 11/10 Tr. at 121.

545. Dr. Petro did not offer a scientifically valid basis to rule out sympathomimetic amines as a plausible cause of plaintiff's stroke.

(c) Dr. Petro did not offer a valid basis by which to rule out endogenous vasoconstrictors as an alternate cause of plaintiff's ICH.

546. Dr. Petro did not compare the vasoconstrictive effects of endogenous vasoconstrictors, such as serotonin and angiotensin, to bromocriptine. 11/15 Tr. at 25.

547. There is no "sufficient diagnostic technique" for ruling out endogenous vasoconstrictors, and it is in fact impossible to do so. Kulig/*Globetti* Dep. at 135 (Att.11).

548. Dr. Petro did not present any evidence that he validly attempted to rule out endogenous vasoconstrictors as an alternate cause of plaintiff's ICH.

(d) Dr. Petro concedes that there is no physical evidence in plaintiff's medical records that supports his causation hypothesis of vasoconstriction leading to ICH.

549. There is no pathological specimen from which Dr. Petro could deduce that the arterial wall had structurally changed. 11/15 Tr. at 6–7.

550. Plaintiff's arteriogram taken shortly after she was admitted to the hospital does not show that the arterial wall had structurally changed. 11/15 Tr. at 8.

551. Plaintiff's arteriogram does not support any conclusion that plaintiff exhibited signs of cerebral vasospasm. 11/15

Tr. at 185–87; *see also* Petro/*Soldo* Dep. at 252 (Att.22).

552. Plaintiff's neurosurgeon did not report any evidence of a ruptured blood vessel when he conducted a craniotomy to evacuate plaintiff's cerebral hematoma. 11/15 Tr. at 9.

(e) Dr. Petro did not validly rule out the possibility of arterial venous malformation ("AVM") as an alternate cause of plaintiff's ICH.

553. An AVM is an arterial wall defect. 11/15 Tr. at 9.

554. AVM is a relatively common cause of ICH in young people. 11/15 Tr. at 10.

555. An arteriogram cannot rule out an AVM after an ICH has occurred because the AVM can be obliterated by the hemorrhage itself. 11/15 Tr. at 10.

556. Dr. Petro did not present a valid basis to rule out AVM as a plausible cause of plaintiff's stroke.

(f) Dr. Petro conceded that plaintiff's medical history did not support his theory of "forme fruste."

557. Dr. Petro testified that he uses "forme fruste," or the appearance of reduced symptoms such as skin mottling and digital vasospasm, as a basis for his opinion that Parlodel ® acts similarly to other ergot alkaloids. 11/10 Tr. at 31.

558. Dr. Petro conceded that plaintiff showed none of the symptoms that he described as indicative of "forme fruste" of ergotism: gangrene, dementia, digital vasoconstriction, mottling of the skin, erythromelalgia, muscle cramps or numbness. 11/15 Tr. at 41.

559. Dr. Petro concedes that patients who experienced digital vasospasm while taking Parlodel ® were taking 40 to 60 milligrams of the drug per day, while plaintiff was taking less than 5 milligrams of the drug per day—eight to twelve times less than the individuals who experienced digital vasospasm. 11/10 Tr. at 150–51 (Petro).

(g) Dr. Petro did not validly rule out stress, caffeine or smoking as a plausible alternate cause of plaintiff's ICH

560. Stress can provoke a stroke. 11/15 Tr. at 43.

561. Dr. Petro is aware of several significant events in plaintiff's life immediately preceding her stroke that were sources of stress: loss of sleep from a crying newborn child, moving from her home in Virginia to Pennsylvania, leaving her husband, feeling not loved by her husband. 11/15 Tr. at 43–46.

562. Plaintiff was a regular coffee drinker. 11/17 Tr. at 40–41.

563. Caffeine is a component of many over-the-counter medications. 11/15 Tr. at 3.

564. Caffeine is a vasoconstrictor. 11/15 Tr. at 3.

565. According to Dr. Petro, smoking, combined with the use of sympathomimetic drugs, combined with stress, could cause ICH. 11/15 Tr. at 47–48.

566. Dr. Petro did not demonstrate any diagnostic technique by which he could validly rule out stress, caffeine, smoking, or some combination of those things with or without sympathomimetic drugs and/or endogenous drugs as plausible alternate causes for plaintiff's ICH.

567. Dr. Petro opines that studies showing a link between smoking and risk of subarachnoid hemorrhage are unhelpful to analysis of plaintiff's ICH, because a subarachnoid hemorrhage is distinct from an ICH, which occurs in a different area of the brain. 11/15 Tr. at 51.

568. At the same time, Dr. Petro opines that evidence of digital vasospasm from high doses of Parlodel ® is helpful to the analysis of the cause of plaintiff's ICH, even though digital vasospasm, which occurs in fingers and toes, is distinct from ICH that occurs in the brain. 11/15 Tr. at 51.

569. Dr. Petro's purported ability to draw conclusions about ICH from digital vasospasm but not from subarachnoid hemorrhage is not premised on any neurologic text or other evidence presented to the Court and does not form a valid basis to rule plausible causes of plaintiff's stroke either "in" or "out."

(h) Dr. Petro did not validly rule out the blood abnormalities or hormones as the cause of plaintiff's ICH.

570. A hypercoagulable state is a risk factor for stroke. 11/15 Tr. at 170.

571. Dr. Petro concedes that no diagnostic tests were performed on plaintiff following her ICH to determine the adhesive nature of her blood platelets or test plaintiff for hypercoagulable blood. 11/10 Tr. at 218.

572. Dr. Petro admits that protein C and S deficiencies and antithrombin III deficiency are all potential risk factors for stroke. 11/10 Tr. at 221.

573. Dr. Petro concedes that plaintiff was never checked for protein C and S deficiencies or antithrombin III deficiency after her ICH. 11/10 Tr. at 221.

574. Dr. Petro did not present any evidence that he validly ruled out blood protein deficiencies as an alternate cause for plaintiff's ICH.

575. Dr. Petro concedes that hormones have an effect on blood pressure, and that the postpartum period involves significant hormonal changes. 11/10 Tr. at 215.

576. Dr. Petro did not present any evidence that he validly ruled out hormones as an alternate cause for plaintiff's ICH.

577. Dr. Petro did not demonstrate any diagnostic technique by which he ruled out blood protein deficiencies or hormones as a plausible alternate cause of plaintiff's stroke.

578. Dr. Petro did not demonstrate that any statistically-significant epidemiology exists that supports the hypothesis that the use of Parlodel ® can cause ICH.

579. Dr. Petro did not demonstrate that the results of any clinical trials and other studies conducted with humans support the hypothesis that the use of Parlodel ® can cause ICH.

580. Dr. Petro did not demonstrate that the results of any animal studies support the hypothesis that the use of Parlodel ® can cause ICH.

581. Dr. Petro did not identify any mechanism by which Parlodel ® can cause ICH or cerebral vasospasm.

582. Dr. Petro did not demonstrate that his hypothesis that Parlodel ® can cause ICH has been tested by the scientific method.

583. Dr. Petro did not present evidence that his methods were generally accepted.

584. Dr. Petro has not presented evidence concerning the error rate of his causation methodology.

585. Dr. Petro did not present evidence that his causation methodology or his opinion has been tested by peer review.

586. Dr. Petro did not reliably rule out the postpartum period as a plausible alternate cause of plaintiff's stroke.

587. Dr. Petro did not reliably rule out a sympathomimetic compound as a plausible alternate cause of plaintiff's ICH.

588. Dr. Petro did not attempt to rule out endogenous vasoconstrictive substances as a plausible alternate cause of plaintiff's ICH.

589. Dr. Petro did not demonstrate use of any diagnostic techniques for ruling out plausible causes of plaintiff's stroke.

590. Dr. Petro did not present any objective or corroborating evidence that supports any finding that plaintiff's stroke was caused by cerebral vasoconstriction or cerebral vasospasm.

591. Dr. Petro did not present scientifically valid evidence to support a finding that plaintiff's ICH was caused by Parlodel ®.

O. Findings of Fact Regarding Plaintiff's Expert Dr. George Macones

(i) Dr. Macones' Qualifications

592. Dr. Macones is an expert in obstetrics and epidemiology.

593. Dr. Macones is not a neurologist. Macones/*B/G/Q* Dep. at 177.

594. Dr. Macones is not an expert in pharmacology. Macones/*B/G/Q* Dep. at 213.

(ii) Methodology

595. According to Dr. Macones, the scientific method includes the formulation and testing of hypotheses. Macones/*B/G/Q* Dep. at 273.

596. Dr. Macones admits that "case reports are very useful for generating hypotheses but not really for testing hypotheses. . . ." Macones/*Hernandez* Dep. at 72.

597. According to Dr. Macones, case series and case reports cannot be used to calculate relative risks. Macones/*B/G/Q* Dep. at 57–58, 272–73.

598. In Dr. Macones' own research, to test causal hypotheses, he utilizes randomized and blinded clinical trials. Macones/*Colangelo* Dep. at 115.

(iii) Scientific Knowledge—Risk Factors for Postpartum Stroke Independent of Use of Parlodel ®

599. According to Dr. Macones, postpartum stroke may occur in women who have had normal pregnancies and who have been deemed healthy up to the time of their strokes. Macones/*B/G/Q* Dep. at 94.

600. According to Dr. Macones, the background risk of postpartum stroke has been known since the dawn of medical history. Macones/*Hernandez* Dep. at 88–89.

601. According to Dr. Macones, the frequency of postpartum strokes occurring at his own hospital is between one and four per year. Macones/*Hernancez* Dep. at 35.

602. Dr. Macones recognizes that pregnancy and the postpartum period are very different physiologic states for a woman than other periods in her life. Macones/*Hernandez* Dep. at 83.

603. Dr. Macones recognizes that the physiologic changes during the postpartum period provide an explanation for the substantially increased risk of ICH shown in the Kittner Study. Macones/*Hernandez* Dep. at 87–88.

604. Dr. Macones admits that the increased risk of postpartum stroke shown in the Kittner Study cannot be explained by preeclampsia or eclampsia. Macones/*B/G/Q* Dep. at 89–90.

605. According to Dr. Macones, data from the Kittner Study can be used to reasonably calculate a relative risk of postpartum stroke, among women who did not have preeclampsia or eclampsia, of 11.9, indicating that such women are almost 12 times more likely to have postpartum stroke than similarly-aged women who are

not postpartum. Macones/*B/G/Q* Dep. at 95.

606. According to Dr. Macones, the same methodology allows one to calculate a relative risk of 19 for ICH of indeterminate cause, showing that such ICHs are 19 times more likely in postpartum women compared to similarly-aged women who are not postpartum. Macones/*B/G/Q* Dep. at 102–03.

607. According to Dr. Macones, using methodologies that he prefers, the risk of stroke among postpartum women, even excluding women with preeclampsia or eclampsia, is still roughly twice the risk in similarly-aged women who are not postpartum. Macones/*B/G/Q* Dep. at 94.

608. Neither Dr. Macones nor any other expert for plaintiff has shown that Parlodel ® was used for PPL at any of the hospitals in the Kittner Study during the two years that were studied in that publication, or, if so, the extent of such Parlodel ® usage.

609. During that time, Dr. Macones, who himself prescribed Parlodel ® for PPL, prescribed it to no more than 5% of his postpartum patients. Macones/*Hernandez* at 14.

610. Dr. Macones is apparently taking the position that the Kittner Study should be deemed irrelevant to the questions before this Court, because the majority of women found to have stroke in that study were not Caucasian. However, the Court notes that this commentary from Dr. Macones was not contained in his Rule 26 expert disclosure in this case and in fact was presented for the first time in an affidavit supplied by Dr. Macones on August 12, 1999, after the close of discovery.

611. At his deposition in another Parlodel ® case, a few months prior to the submission of his August 12, 1999 affidavit, Dr. Macones was unable to testify that the results of the Kittner Study could not be used for all racial groups. Macones/*B/G/Q* Dep. at 85–86.

612. Furthermore, Dr. Macones admits that the majority of women studied in the Kittner Study were Caucasian. Macones/*B/G/Q* Dep. at 85.

613. Plaintiff's experts rely on a study by Petitti, et al, *Incidence of Stroke and Myocardial Infarction in Women of Reproductive Age,* which provided an estimate of the rate of stroke associated with pregnancy of 5.6/100,000 deliveries. However, plaintiff's experts, including Dr. Macones, have not shown that this estimate includes strokes in the postpartum period, when women are not pregnant. As defined in this study, one would expect a background rate of 560 strokes associated with 10,000,000 pregnancies. Macones/*B/G/Q* Dep. at 135–36.

614. Dr. Macones admits that the human body itself produces vasoconstrictor substances such as norepinephrine, angiotensin II, and renin. Macones/B/G/Q Dep. at 241–42, 265.

(iv) Lack of Scientific Knowledge That Parlodel ® is a Risk Factor for Postpartum Stroke

615. According to Dr. Macones, there are "no epidemiologic studies showing a statistically-significant increased relative risk of stroke caused by Parlodel ® in postpartum women. . . ." Macones/*Hernandez* Dep. at 79.

616. According to Dr. Macones, there is no indication that the risk of postpartum stroke increased after 1980, when Parlodel ® first came on the market for PPL, or declined after 1994, when that indication was removed. Macones/*Colangelo* Dep. at 93–94.

617. Dr. Macones cannot testify to a reasonable degree of medical certainty

that Parlodel ® increases the risk of postpartum stroke. Macones/*Hernandez* Dep. at 81.

618. According to Dr. Macones, "there is no evidence" that Parlodel ® increases the risk of postpartum stroke. Macones/*Hernandez* Dep. at 48.

619. Dr. Macones admits that he "do[es not] know if there's a positive association or if there is a negative association" between Parlodel ® and postpartum stroke. Macones/*Hernandez* Dep. at 65–66.

620. Although Dr. Macones' expert affidavit contains the statement that the epidemiologic data are "suggestive" that Parlodel ® increases the risk of postpartum stroke, he acknowledges that "suggestive" refers to the "generation of a hypothesis that might require further research." Macones/*Hernandez* Dep. at 81.

621. Dr. Macones admits that the ERI study on Parlodel ® and postpartum stroke, upon which plaintiff's other experts rely, is "uninformative" on that issue and does not even begin to address the question. Macones/*Hernandez* Dep. at 65.

622. Dr. Macones apparently opines that, if the ERI study had fully "captured readmissions," *i.e.,* found every woman in the study populations who had had postpartum stroke, then the study would have shown a purportedly stronger association between the use of Parlodel ® and the occurrence of postpartum stroke. However, such a statement is not contained in the Rule 26 expert witness disclosure submitted by Dr. Macones in this case.

623. Dr. Macones admits that, if additional stroke cases had been found in the ERI study, it is entirely speculative as to whether such stroke cases would have been women who used Parlodel ® or women who did not. Macones/*B/G/Q* Dep. at 78–80. Similarly, Dr. Macones admits that, if additional stroke cases had been found, additional controls would have been selected and it is entirely speculative as to whether such controls would have been women who used Parlodel ® or women who did not. *Id.*

624. Accordingly, Dr. Macones admits that any opinions concerning what the ERI would have shown if full admissions had been recaptured are entirely speculative. Macones/*B/G/Q* Dep. at 81–82.

625. According to Dr. Macones, the HCIA study, sponsored by SPC after completion of the ERI study, also cannot be used to say that Parlodel ® increases the risk of postpartum stroke. Macones/*B/G/Q* Dep. at 186.

626. The HCIA study was twice as big as the ERI study in terms of the number of deliveries studied and three times as big as the ERI study in terms of the number of postpartum strokes ascertained. Macones/*B/G/Q* Dep. at 181, 186.

627. Dr. Macones acknowledges that the Witlin–Sibai Study might also reasonably be described as an epidemiologic study. Macones/*B/G/Q* Dep. at 22, 121.

628. Dr. Macones admits that the relative risk calculation in the Witlin–Sibai Study, showing the relative risk of postpartum stroke in Parlodel ® users of 0.12, with confidence intervals from 0.01 to 0.83, is correct, assuming that the numbers used as input for that calculation [130,000 total deliveries, 40,000 Parlodel ® users, 20 postpartum strokes, 1 postpartum stroke in a Parlodel ® user] are also correct. Macones/*B/G/Q* Dep. at 37–38, 152–53.

629. Although Dr. Macones criticizes various aspects of the Witlin–Sibai Study, he admits that it fails to show that Parlodel ® increases the risk of postpartum stroke.

630. Although Dr. Macones notes the possibility of confounding by indication in

the Witlin–Sibai Study, he admits that, based on the factual statements of the authors concerning which of their postpartum patients were more likely to receive Parlodel ®, any correction of such confounding would tend to show that Parlodel ® had an even more protective effect against postpartum stroke than the calculated relative risk shows. Macones/*B/G/Q* Dep. at 157–59.

P. Findings of Fact Regarding Plaintiff's Expert Dr. Leslie Iffy

(i) Dr. Iffy's Qualifications

631. Dr. Iffy is a clinical obstetrician. Iffy Curriculum Vitae (Att.1G); 12/2/97 Iffy Dep. at 41 (scope of practice is obstetrics) (Att.1A).

632. Dr. Iffy is not a neurologist. 12/2/97 Iffy Dep. at 162 (general and adult neurology not his area of expertise) (Att.1A), 5/14/98 Iffy Dep. at 251 (not a neurologist or radiologist) (Att.1A); *see also* Iffy/*Brumbaugh* Dep. at 219 (doesn't hold himself out as a neurologist) (Att.1H); Iffy/*Song* Dep. at 65 (doesn't hold himself out as a neurologist) (Att.1J); Iffy/*Smith* Dep. at 185 ("I'm not going to guess what a neurologist might say") (Att.1I).

633. Dr. Iffy is not an epidemiologist. 12/2/97 Iffy Dep. at 23 (Att.1A).

634. Dr. Iffy concedes that he is not competent to respond to the Kittner Study because he is not an epidemiologist. 12/2/97 Iffy Dep. at 125–26 (Att.1A).

635. Dr. Iffy is not a pharmacologist. 12/2/97 Iffy Dep. at 66 (Att.1A); *see also, e.g.,* Iffy/*Song* Dep. at 71 (Att.1J); Iffy/*Roberts* Dep. at 31 ("I am not a pharmacologist and my orientation doesn't go that far.") (Att.1K).

636. Dr. Iffy has been cited as an example of an expert engaging in gross carelessness and/or intentional perjury. Fisher, *et al. The Expert Witness: Real Issues and Suggestions,* 172 Am. J. Obstet. Gynecol. 1792, 1794 (1995) (Att.33); *see also* Letter to Editor from Dr. Iffy and Reply, 173 Am.J. Obstet. Gynecol. 1898–99 (1995) (Att.34).

(ii) Dr. Iffy's Lack of Scientific Knowledge

637. Dr. Iffy's causation opinion regarding alleged adverse effects of Parlodel ® has been excluded as being scientifically unreliable under *Daubert* in *Brumbaugh v. Sandoz Pharmaceutical Corp.,* 77 F.Supp.2d, 1153 (D.Mont.1999).

638. Dr. Iffy's causation opinion regarding alleged adverse effects of Parlodel ® has been excluded as being scientifically unreliable in *Revels v. Sandoz Pharmaceuticals Corp.,* No. 95–11076, Orders of Mar. 31 and Apr. 1, 1998 (201st Jud. Dist., Travis County, Tex.) (Texas *Daubert* analog) (excluding general causation evidence in similar Parlodel ® case as "not sufficiently scientifically reliable or relevant" and granting summary judgment) (Att.35), *aff'd,* 1999 WL 644732, No. 03–98–00231–CV (Tex.App. Aug. 26, 1999) (Aboussie, C.J.) (Att.29), *petition for review denied.*

639. When asked to cite a learned treatise that states that Parlodel ® causes strokes in postpartum women, Dr. Iffy has inappropriately cited Gabbe's *Obstetrics,* which actually states that a "causal relationship with bromocriptine has not been established." 5/14/98 Iffy. Dep. at 181–82 (Att.1A).

(iii) The Testing or Testability of Dr. Iffy's Opinions

(a) Epidemiology

640. Dr. Iffy admits that the scientific standard to establish that a drug causes a particular effect requires the use of con-

trolled studies showing a statistically-significant effect, usually to a 95% degree of confidence. Iffy/*Revels* Dep. at 75 (Att.1C).

641. Dr. Iffy concedes that no epidemiologic study has found a statistically-significant association between Parlodel ® and stroke. Iffy/*Simonson* Dep. at 160 (Att.1L).

642. Dr. Iffy concedes that no epidemiologic study has found a statistically-significant association between Parlodel ® and hypertension (the mechanism by which he proposes Parlodel ® causes stroke). Iffy/*Song* Dep. at 92–93 (Att.1J).

643. Dr. Iffy cannot cite any epidemiologic study showing a statistically-significant increased incidence of vasospasm in any patient population using Parlodel ®. Iffy/*NJC* Dep. at 46–48 (Att.1A). Nor can he cite any controlled scientific study showing that bromocriptine causes vasospasm in cerebral arteries. Iffy/*Hollander* Dep. at 25 (Att.1E).

(b) Dr. Iffy's Reliance on Anecdotal Human Data

644. In the absence of epidemiologic evidence, Dr. Iffy relies predominantly on case reports as the basis for his causation opinion. 12/2/97 Iffy Dep. at 143 (Att.1A); Iffy/*Hollander* Dep. at 122–23 (Att.1E).

645. All of Dr. Iffy's published case reports—on which he relies for support of his causation opinion in this case—are the result of cases brought to his attention by plaintiff's lawyers seeking his expert testimony. Iffy/*Nussel* Dep. at 69 (Att.1M).

646. Dr. Iffy's published case reports regarding Parlodel ®, on which he relies for support, never state that Parlodel ® has adverse causal events; they are, at best, suggestive of this possibility. *See* Iffy, TenHove & Frisoli 1986 at 372 (case reports and adverse drug experience reports to FDA "suggest a possible vasopressor effect of bromocriptine.") (Att.37); Iffy, Lindenthal, Szodi & Griffin 1989 at 171 (bromocriptine is "an agent *suspected* of causing" various serious adverse effects.) (Att.38); Iffy & McArdle 1994 at × ("the outcomes *suggest* that women ... *may* suffer rare and unpredictable, yet serious untoward sequelae in response to treatment with the recommended doses.") (Att.39); Iffy 1994 at 248 (scientists "*have begun to consider the possibility* of a relationship between bromocriptine ablactation and [adverse events].") (Att.40); Iffy 1995 at 102 (Case reports "*lend support to the proposition* that, in some women so predisposed, bromocriptine has powerful vasoconstrictive propensities.") (Att.41); Iffy, TenHove, Hopp & McArdle 1995 at 78 ("Therefore, we consider our [current] and previously published cases of postpartum MI *supportive* of the *interpretation* presented ... concerning a *potential vasopressive side effect* of this drug.") (Att.42); Iffy, Lindenthal, McArdle & Ganesh 1996 at 309 ("Description of the following three incidents ... appears, therefore, *of heuristic value.*") (Att.43); Iffy, McArdle & Hopp 1996 at 300 ("*It is conceded* that the cause-effect relationship in any particular case *is difficult to prove conclusively.*") (Att.44); Hopp, Haider & Iffy 1996 at 231 ("Duly recognizing that, *in any particular case, the association may be coincidental,* its relative frequency *raises the level of suspicion about a cause-effect relationship* between the use of bromocriptine and the ensuing MI [myocardial infarction].") (Att.45); Hopp, Weisse & Iffy 1996 at 417 (case report finding "*suggests* that bromocriptine *may cause* MI [myocardial infarction] through severe vasoconstriction.") (Att.46) (emphasis supplied in all citations).

(c) Dr. Iffy's Opinion on Mechanism

647. Dr. Iffy opines that the cause of plaintiff's stroke is "Parlodel ®-related ce-

rebral hemorrhage generally, secondary to intensive vasospasm." 5/14/98 Iffy Dep. at 219 (Att.1A).

648. Dr. Iffy states that one *possible* mechanism for Parlodel ® to cause stroke is the occurrence of vasospasm (constriction of the cerebral arteries), leading to hypertension that leads to an ICH. 12/2/97 Iffy Dep. at 59 (Att.1A).

649. Dr. Iffy cannot explain how Parlodel ® causes vasoconstriction of cerebral arteries. He is unable to explain how bromocriptine allegedly causes vasospasm or stroke. 12/2/97 Iffy Dep. at 59 (Att.1A).

650. Dr. Iffy concedes the existence of a large body of scientific literature demonstrating that Parlodel ® is vasodilatory, not vasoconstrictive, and causes hypotension, not hypertension. 12/2/97 Iffy Dep. at 60 (Att.1A). He concedes that the primary effect of Parlodel ® is hypotension. 5/14/98 Iffy Dep. at 234 (Att.1A).

651. Dr. Iffy concedes that Parlodel ® is quite unlikely to cause hypertension (and thus stroke), 12/2/97 Iffy Dep. at 114 ("very rare effect") (Att.1A); Iffy/*Smith* Dep. at 153 ("occurs very, very rarely" and Iffy does not expect "any statistical significance to show this effect" [sic]) (Att.1I).

652. Dr. Iffy concedes that the cause of plaintiff's stroke would be "obscure and unresolved" if plaintiff had not been taking Parlodel ®. 5/14/98 Iffy Dep. at 229–230 (Att.1A).

(iv) Dr. Iffy's Methodology

653. Dr. Iffy's theory of sensitivity to Parlodel ® cannot be tested or proven; "sensitivity" to Parlodel ® is allegedly demonstrated only by the actual occurrence of an adverse event. There is no way to test for this "sensitivity" prior to the actual event. Iffy/*Nussel* Dep. at 85 (Att.1M).

654. Dr. Iffy believes that the burden of proof is not on plaintiff to demonstrate proximate cause, but on NPC to prove absence of risk. Iffy and McArdle 1990 at ix (". . . the burden of proving the absence of risk was the obligation of the distributors [of Parlodel ®] rather than that of their critics") (Att.47); Iffy/*Revels* Dep. at 75 ("But when it comes to an agent which is used more or less over the counter or almost over the counter and without medical indication, in other words it is not a medical necessity to take it, I would expect scientific proof that the drug is innocuous. In other words, I would expect that it is proven by a 95 percent probability that it is innocuous.") (Att.1C).

655. Dr. Iffy believes that attorneys, not he, are responsible for collecting evidence for him to analyze in reaching his expert opinion in a lawsuit. Iffy/*Revels* Dep. at 44 (Att.1C).

656. NPC asserts that Dr. Iffy's causation opinions change to meet the facts of each Parlodel ® case in which he testifies. For example, he has repeatedly testified that an adverse reaction after less than three days of Parlodel ® therapy suggests an unlikely connection between the event and Parlodel ® usage. Iffy/*Soldo* Expert report at 5 ("These reports indicate that on no occasion was there evidence of catastrophic side effects deriving from the use of the drug during the first three days of administration,") (Att.1F); Iffy/*Nussel* Dep. at 42 (Att.1M); Iffy/*Simonson* Dep. at 90 (Att.1L), but he has also opined that Parlodel ® was likely at fault when Parlodel ® was first taken 1.5 hours before the occurrence of the adverse event. Iffy/*Kuhn* Dep. at 61 (Att. 1D).

(v) Rate of Error

657. Dr. Iffy concedes that one cannot derive relative risk assessments from case reports, and that they are mere "suggestive evidence of causation." 12/2/97 Iffy

Dep. at 141–42 (Att.1A); Iffy/*Song* Dep. at 89 (relative risk cannot be calculated from case reports) (Att.1J); *see also* Iffy/*Simonson* Dep. at 166–67 (case reports are observations, without controls, and cannot be used to determine whether Parlodel ® causes a statistically increased risk of stroke) (Att.1L).

(vi) General Acceptance in the Scientific Community

658. Dr. Iffy has characterized his expert witness analysis of cases as "medicolegal" analysis. *E.g.,* Iffy/*Revels* Dep. at 202–03 (describing work as "medicolegal review") (Att.1C).

659. Dr. Iffy concedes that the medical and academic communities tend not to credit "medicolegal" investigation as a meaningful approach to clinical research, and therefore do not generally accept this methodology. Iffy and McArdle 1990 at viii (Att.47).

660. Dr. Iffy concedes that his theory that Parlodel ® causes hypertension is not generally accepted in the medical community. Iffy/*Smith* Dep. at 156–57 (Att.1I); *see also* Iffy/*Simonson* Dep. at 23 (Iffy's theory is hypothesis and is not proven) (Att.1L).

(vii) Dr. Iffy's Reliance on Animal and Other Studies

661. Dr. Iffy bases his opinion in part on animal studies, but he is not aware of any studies in intact animals showing that bromocriptine causes high blood pressure, or stroke, or any other injury purportedly secondary to cerebral vasospasm. *See, e.g.,* Iffy/*Kuhn* Dep. at 34–35 (no studies showing stroke, seizure, or myocardial infarction) (Att. 1D); *id.* at 89–90 (animal studies generally show that Parlodel ® *lowers* blood pressure).

(viii) Dr. Iffy's Opinions regarding Specific Causation

(a) High Risk of Stroke in the Postpartum Period

662. Dr. Iffy concedes that cerebral vasospasm can occur in a postpartum woman independent of any drug usage. 5/14/98 Iffy Dep. at 271, 273 (Att.1A).

663. Dr. Iffy concedes that ICHs can occur in the postpartum period independent of any drug use; he has seen cases of this personally. 12/2/97 Iffy Dep. at 108, 109 (Att.1A).

664. Dr. Iffy's own writings discuss the risk of postpartum cerebrovascular accidents that can occur in the absence of *any* drug use. "Pregnancy may complicate or be complicated by one or more vascular disorders of diverse cause having hypertension as a common component." Iffy, Diseases Specific to Pregnancy at 759, *Gynecology & Obstetrics* (Romney *et al.,* eds., 1975) "Maternal death associated with the hypertensive disorders of pregnancy is caused by cerebral accidents, heart failure, acute pulmonary edema, abruptio placenta, hemorrhage from coagulation defects, adrenal failure, pneumonia, and hepatic rupture or failure." (Att.36) *Id.* at 761.

665. Dr. Iffy concedes he is not competent to respond to the Kittner Study (regarding the epidemiology of stroke in the postpartum period). 12/2/97 Iffy Dep. at 125–26 (Att.1A)

(ix) Other Causal Factors

(a) Dr. Iffy has no scientifically reliable means of excluding amphetamine, diet pills, or sympathomimetic amines as the cause of plaintiff's stroke

666. Dr. Iffy failed to consider records documenting plaintiff's use of amphetamines, diet pills, or sympathomimetic

agents in reaching his opinion that Parlodel ® was the cause of her stroke. 5/14/98 Iffy Dep. at 221–22 (has no opinion on plaintiff's use of amphetamines or diet pills) (Att.1A).

667. Dr. Iffy would concede that amphetamine can cause cerebral hemorrhage if there were published reports of such a link. 5/14/98 Iffy Dep. at 220 (Att.1A).

668. Petti, *Stroke and Cocaine or Amphetamine Use*, 9 Epidemiology 597 (November 1998) (Att.48), and Harrington, *Intracerebral Hemorrhage and Oral Amphetamine*, 40 Arch. Neurol 503 (August 1983) (Att.49), are two published reports suggesting a link between amphetamine and cerebral hemorrhage.

669. A January 19, 1991 urine drug screen conducted by Sharon General Hospital, where plaintiff was first admitted following her stroke, notes a "large amount present" of amphetamine. (Att.92).

670. Dr. Iffy did not consider plaintiff's January 18, 1991 Emergency Room record entry, "Patient apparent OD of amphetamines with large intracerebral bleed," in reaching his causation opinion. 12/2/97 Iffy Dep. at 227–28 (Att.1A).

671. Dr. Iffy concedes that Emergency Room records are generally honest because of a desire to get appropriate treatment. 12/2/97 Iffy Dep. at 229 (Att.1A).

672. Dr. Iffy inaccurately states that there is "no indication" in plaintiff's medical records about diet pill use. 5/14/98 Iffy Dep. at 225 (Att.1A).

673. A January 19, 1991 Emergency Room record completed at St. Elizabeth Hospital Medical Center contains the entry, "questionably taking diet pills." (Att.50).

674. A January 19, 1991 medical history and physician examination taken at St. Elizabeth Hospital Medical Center by Dr. Michael Boyd contains the notation, "She may possibly have been taking diet pills since her delivery." (Att.51).

675. Dr. Iffy concedes that sympathomimetic drugs can cause cerebral vasospasm. 12/2/97 Iffy Dep. at 220 (Att.1A).

676. Plaintiff stated in her deposition that she was taking Contac, an over-the-counter medicine that contains PPA, a sympathomimetic drug. Lisa Soldo Dep. at 126 (Att.8).

677. Dr. Iffy did not consider records of plaintiff's prior pregnancy in reaching his causation opinion, despite the fact that her body's reaction to prior pregnancies should be highly relevant to her reaction to her 1990 pregnancy. Iffy Expert Report at 1–2 (listing records analyzed in preparing his opinion, listing only records from 1990 pregnancy) (Att.1F).

(b) Dr. Iffy's causation theory is not supported by plaintiff's medical history

678. Although Dr. Iffy's opinion is that plaintiff's stroke was due to "intensive vasospasm," 5/14/98 Iffy Dep. at 219, he concedes that plaintiff's medical history contains no record that demonstrates evidence of vasospasm. 5/14/98 Iffy Dep. at 219–20 (Att.1A).

(c) Dr. Iffy cannot demonstrate that plaintiff was taking Parlodel ® at or near the time of her ICH.

679. Dr. Iffy concedes that if plaintiff had been taking Parlodel ® according to prescription, she would have completed her Parlodel ® therapy by January 10, 1991. 5/14/98 Iffy Dep. at 217 (Att.1A).

680. Dr. Iffy has stated that Parlodel ® would be an unlikely cause of plaintiff's stroke if she had completed a Parlodel ®

therapy on January 10 (and had her stroke on January 18). 5/14/98 Iffy Dep. at 217 (Att.1A).

681. Dr. Iffy has "no view" on when plaintiff completed her Parlodel ® therapy. 5/14/98 Iffy Dep. at 217 (Att.1A).

682. Dr. Iffy concedes that there is no evidence other than the testimony of plaintiff that she completed Parlodel ® therapy "one or two days" before her stroke. 5/14/98 Iffy Dep. at 218 (Att.1A).

683. The January 18, 1991 Sharon General Hospital Emergency Room intake record does not list Parlodel ® as a current or recent medication. (Att.52).

684. The January 18, 1991 Sharon General Hospital Emergency Room intake record lists aspirin as a current medication. (Att.52).

685. Dr. Iffy has testified in another case that severe adverse events usually occur 6–10 days after delivery. Iffy/*Nussel* Dep. at 59–60 (Att.1M).

686. Dr. Iffy has testified in another case that adverse events associated with Parlodel ® typically appear 5–7 days after initiation of treatment. 12/2/97 Iffy Dep. at 97 (Att.1A).

687. Plaintiff's stroke would have occurred approximately *twenty-three days* after initiation of treatment if she began Parlodel ® therapy on or around December 27, 1990.

Q. Findings of Fact Regarding Plaintiff's Expert James O'Donnell

688. Dr. James O'Donnell is "self-taught" on the subject of Parlodel ®. O'Donnell Dep. at 27 (Att.53A).

689. Dr. O'Donnell is not a medical doctor, O'Donnell Dep. At 9 (Att.53A), and does not have a degree in medicine. O'Donnell/*Revels* Dep. at 8 (Att.53B); O'Donnell/*Simonson* Dep. at 72 (Att.53C).

690. Dr. O'Donnell is not a toxicologist. O'Donnell Dep. At 9 (Att.53A); O'Donnell/*Simonson* Dep. at 7 (Att.53C).

691. Dr. O'Donnell does not consider himself an expert in neurology. O'Donnell/*Simonson* Dep. at 90 (Att.53C).

692. Dr. O'Donnell does not consider himself an expert in obstetrics and gynecology (O'Donnell/*Simonson* Dep. at 90) (Att.53C) and concedes that he would not be considered an expert in obstetrics and gynecology in the scientific community. O'Donnell/*Simonson* Dep. at 100 (Att.53C). None of Dr. O'Donnell's teaching responsibilities have been related to obstetrics or gynecology. O'Donnell/*Simonson* Dep. at 83 (Att.53C).

693. Dr. O'Donnell does not consider himself an expert in epidemiology, pharmo-epidemiology, or statistics, O'Donnell/*Simonson* Dep. at 90–91 (Att.53C), and has never conducted an epidemiologic study. O'Donnell/*Simonson* Dep. at 99 (Att.53C).

694. Dr. O'Donnell is a nutritionist. O'Donnell/*Simonson* Dep. at 70 (Att.53C).

695. Dr. O'Donnell has done no laboratory research on bromocriptine. O'Donnell Dep. at 132 (Att.53A).

696. Dr. O'Donnell has never been involved in any bromocriptine toxicology studies. O'Donnell Dep. at 76 (Att.53A).

697. Dr. O'Donnell has never conducted a clinical trial regarding Parlodel ®. O'Donnell/*Simonson* Dep. at 96 (Att.53C).

698. Dr. O'Donnell has never conducted an animal study or a human study of the effects of bromocriptine. O'Donnell Dep. at 20 (Att.53A).

699. Dr. O'Donnell does not rely upon the results of animal studies regarding bromocriptine for his opinion about Parlodel ®'s pharmacologic and physiologic ef-

fects. O'Donnell Dep. at 76–77 ("not interested" in animal studies) (Att.53A).

700. Dr. O'Donnell has never conducted laboratory or clinical research regarding ergot alkaloids ("ergots"), the group of compounds derived from the organic compound ergot of which bromocriptine is a member. O'Donnell/*Simonson* Dep. at 99 (Att.53C).

701. Dr. O'Donnell concedes that he would not be considered an expert in ergot alkaloids within the scientific and medical communities. O'Donnell/*Simonson* Dep. at 99–100 (Att.53C).

702. Dr. O'Donnell has never discussed Parlodel ® with any prescribing physicians. O'Donnell/*Simonson* Dep. at 192 (Att.53C).

703. While working as a pharmacist, Dr. O'Donnell has never filled a prescription for Parlodel ®, nor has he ever provided Parlodel ® to a postpartum woman. O'Donnell Dep. at 24 (Att.53A).

704. Dr. O'Donnell has received no honors or awards in pharmacology. O'Donnell/*Simonson* Dep. at 76 (Att.53C).

705. Dr. O'Donnell testified that he could neither defend nor attack the causation opinions of his co-experts because he had "essentially disqualified [himself] from giving causation opinions." O'Donnell/*Revels* Dep. at 46 (Att.53B); *see also* O'Donnell Expert Report at 1 (O'Donnell does not intend to render any cause specific causation opinions in this case) (Att. 53D).

706. Dr. O'Donnell concedes that scientific studies have not proven a "cause and effect" relationship between Parlodel ® and stroke. O'Donnell/*Simonson* Dep. at 102 (Att.53C).

707. Dr. O'Donnell has never conducted a study on adverse events, including strokes, that can occur in the postpartum period. O'Donnell/*Simonson* Dep. at 99, 178 (Att.53C).

708. Dr. O'Donnell further opines that "we don't know what the actual incidence is" of stroke occurrence in the postpartum period to compare the occurrence of stroke in women taking Parlodel ® for PPL to similarly situated women not taking Parlodel ®. O'Donnell Dep. at 72 (Att.53A).

709. Dr. O'Donnell relies on case reports as support for his opinion that Parlodel ® can cause strokes. *See, e.g.,* O'Donnell Dep. at 53, 55, 57 (referring to and relying upon case report allegedly demonstrating link between Parlodel ® and myocardial infarction) (Att.53A).

710. Dr. O'Donnell concedes that case reports merely report one physician's observation regarding that physician's particular patients. O'Donnell/*Simonson* Dep. at 42 (Att.53C).

711. Dr. O'Donnell agrees that general causation cannot be demonstrated by a case report. O'Donnell/*Simonson* Dep. at 42–43 (Att.53C).

712. Dr. O'Donnell agrees that case reports are, by definition, anecdotal. O'Donnell/*Simonson* Dep. at 43 (Att.53C).

713. Dr. O'Donnell agrees that case reports typically do not control for chance, bias, or confounding effects. O'Donnell/*Simonson* Dep. at 43 (Att.53C).

714. At best, Dr. O'Donnell suggests two alternate mechanisms that can cause Parlodel ® to be both hypotensive and hypertensive (and thus cause strokes): (1) that Parlodel ® attaches to the "wrong" dopamine receptors, which react differently depending on the dose administered; and (2) that the human body "mistakes" bromocriptine for a "regular ergot" and reacts to it as if it were such. Dr. O'Donnell readily admits, though, that "These are posits. Those are hypotheses. Those

are explanations but they are not dogma." O'Donnell Dep. at 82–84 (Att.53A).

715. Dr. O'Donnell relies on the transcript of a portion of the 8/24/94 "investigative journalism" television program "NBC NOW" as the basis for his opinion regarding the safety and pharmacologic effects of Parlodel®. O'Donnell Expert Report at 1 (Att. 53D).

716. The NBC NOW program segment, which is less than a quarter of a transcript of the hour-long show, cites no scientific studies in support of its statements about the safety and pharmacologic effects of Parlodel®. The FDA representative interviewed on the program emphasized that Parlodel® had no proven risk. (Att. 54 at DS001161 (page 14 of the program transcript)).

717. Dr. O'Donnell believes that Parlodel® is safe and efficacious for the treatment of endocrine and pituitary disorders, based on the fact that Parlodel® was approved by the FDA for these uses. O'Donnell Dep. at 25 (Att.53A).

718. Dr. O'Donnell concedes that neither the 1988 nor the 1989 FDA Fertility and Maternal Health Drugs Advisory Committees determined that Parlodel® had serious risks when used for the PPL indication. O'Donnell/*Simonson* Dep. at 123 (Att.53C).

719. "Virtually all" of Dr. O'Donnell's income is derived from consulting in and testifying in litigation. O'Donnell/*Revels* Dep. at 82 (Att.53B); O'Donnell Dep./ *Simonson* at 159 (Att.53C).

720. As of October 21, 1997, Dr. O'Donnell stated that he had testified at trial in excess of 140 times and in deposition in excess of 250 times.

721. In the 1995 edition of Moch, Borga and O'Donnell, *Pharmacy Law: Litigating Pharmaceutical Cases* (Lawyers & Judges Publishing Co.), Dr. O'Donnell is described as having consulted in over 1,500 matters in civil and criminal courts. (Att.55).

722. Dr. O'Donnell performed no independent literature research to reach his opinions in this case; other than scientific literature already in his personal files, all material that Dr. O'Donnell reviewed before reaching his expert opinion in this case was selected for his review by attorneys representing plaintiffs in Parlodel® litigation. O'Donnell/*Simonson* Dep. at 175–76 (Att.53C).

723. Dr. O'Donnell has been advertising his services as an expert since at least February 1983. O'Donnell/*Simonson* Dep. at 162 (Att.53C).

724. Dr. O'Donnell has advertised his services in the *Chicago Daily Law Bulletin*, *Trial* Magazine, *Barrister* Magazine, *Ohio Academy of Trial Lawyers' Journal*, *Essex County* (New Jersey) *Bar Association Journal*, *Bar Association Journal* (suburban San Francisco), *Washington State Bar Journal*, *Michigan Bar Journal*, *Illinois Bar Journal*, *Case and Comment*, *Chicago Lawyer*, *New York Jury Verdict Reporter*, *Kansas Trial Lawyers Association Journal*, *Georgia Trial Lawyers Association Journal*, *Kentucky Trial Lawyers Association Journal*, *Fulton County Legal Reporter*, *U.S. Business Litigation*, *A.B.A. Journal*, *Indiana Lawyer*, *Wisconsin Opinion* and *Legal Times* (Washington D.C.). (Att. 56 (list of publications)); O'Donnell/*Simonson* Dep. at 184–85 (agreeing that list of publications is accurate and noting additional publications); (Att. 57 (advertisement from August 16, 1999 issue of Washington, D.C. Legal Times)).

725. Dr. O'Donnell does not have a Doctor of Philosophy (Ph.D.) degree in any discipline. O'Donnell Dep. at 137

(Att.53A). Rather, he states he has a degree in pharmacology.

726. NPC claims that in material sent out with business solicitation letters, Dr. O'Donnell falsely held himself out as having a doctorate degree in pharmacology. O'Donnell/*Simonson* Dep. at 163 (Att.53C); *see also* (Att.58).

727. NPC claims that in advertisements placed in legal publications, Dr. O'Donnell falsely held himself out as having a doctorate degree in pharmacology. O'Donnell/*Simonson* Dep. at 163–64 (Att.53C); *see also* (Att.59).

728. NPC claims that in the Rolodex card handed out for promotional purposes, Dr. O'Donnell falsely held himself out as having a doctorate degree in pharmacology. O'Donnell/*Simonson* Dep. at 164 (Att. 53C; *see also* (Att.60)).

729. NPC claims that in the case of *Thomas v. Hoffman–LaRoche,* 949 F.2d 806 (5th Cir.1992), Dr. O'Donnell is described by the Court, based on his false information, as an expert with a Ph.D. in the field of pharmacy. 949 F.2d at 809. Dr. O'Donnell denies he testified that he has a Ph.D. in the field of pharmacy.

R. Supplemental Findings of Fact Summarizing Court's Appointment of Rule 706 Experts

730. With the assistance of the Duke University School of Law Registry of Independent Scientific and Technical Advisors, the Court appointed three Rule 706 experts to provide their opinions regarding "whether the methodology or technique employed by plaintiff's medical witnesses, Dr. Kenneth Kulig and Dr. Dennis Petro, in formulating their opinions, is scientifically reliable and whether the methodology or technique properly can be applied to the facts in issue."

731. The appointed Rule 706 experts are: (1) David A. Flockhart, M.D., Ph.D., a pharmacologist, (2) William J. Powers, M.D., a neurologist, and (3) David A. Savitz, Ph.D., an epidemiologist. The credentials of the experts are more fully set forth in the curriculum vitae previously filed and incorporated by reference herein.

732. Two of the Rule 706 experts, Dr. Powers and Dr. Savitz, concluded that plaintiff's experts, Dr. Kulig and Dr. Petro, failed to utilize a scientifically reliable methodology to demonstrate general causation (*i.e.,* that Parlodel ® can cause ICH in general). *See generally* Powers Report (Ex. 2); Savitz Report (Ex. 3). Rule 706 expert Dr. Flockhart concluded that plaintiff's experts had utilized a reliable methodology to demonstrate the possibility that Parlodel ® causes ICH, based on his assumption that the differential diagnosis is a reliable methodology for assessing general causation. *See generally* Flockhart Report (Ex. 4). As discussed below, the Court agrees with Dr. Powers and Dr. Savitz that plaintiff's experts have failed to utilize a reliable scientific methodology to demonstrate general causation. Two of the Rule 706 experts, Dr. Flockhart and Dr. Powers, concluded that plaintiff's expert, Dr. Petro, failed to utilize a scientifically reliable methodology to demonstrate specific causation (*i.e.,* that Parlodel ® caused plaintiff's stroke). *See generally* Flockhart Report; Powers Report. Dr. Powers also concluded that Dr. Kulig failed to utilize a reliable scientific methodology to demonstrate specific causation. *See generally* Powers Report. Because Dr. Savitz did not believe plaintiff's experts had reliably established general causation, he did not consider specific causation. *See generally* Savitz Report. As discussed below, the Court agrees with Dr. Flockhart and Dr. Powers that plaintiff's expert, Dr. Petro, did not utilize a reliable scientific methodology to dem-

onstrate specific causation. The Court further agrees with Dr. Powers that the same is true of Dr. Kulig.

733. The Court's instructions to the Rule 706 experts, previously filed and incorporated by reference, provided specific questions for which the Court requested answers and provided instructions to guide the Rule 706 experts in their efforts. *See* Instructions (Ex. 1).

734. The Rule 706 experts were provided with and were asked to respond to the Court's questions based on the evidentiary materials cited by the parties at the *Daubert* hearing and the transcripts from that hearing. *Id.*

735. The parties had an opportunity to review and file objections regarding the Court's proposed instructions to the Rule 706 experts, and the Court considered and ruled upon those objections.

736. The parties also had an opportunity to review and file objections regarding the identity of the appointed Rule 706 experts, and the Court considered and ruled upon those objections.

737. Plaintiff did not object to the appointment of Dr. Flockhart, whom she described as "extremely qualified to serve as a 706 expert." *See* Plaintiff Lisa Soldo's Response to Sandoz Pharmaceuticals Corporation's Objections to Potential Appointment of David A. Flockhart, M.D., Ph.D., as an Expert Under Federal Rule of Evidence 706 (Ex. 5).

738. NPC objected to Dr. Flockhart's appointment. The Court overruled NPC's objections to the appointment of Dr. Flockhart. *See* 5/14/01 Order (Ex. 7).

739. Plaintiff objected to the appointment of Dr. Powers. The Court found these objections to be without merit. *See* 12/6/00 Order (Ex. 8).

740. NPC did not object to the appointment of Dr. Powers.

741. Plaintiff stated that "Dr. Savitz is an unbiased, qualified candidate," and offered no objections to his appointment. *See* Plaintiff's Response to Defendant's Objections to David A. Savitz, Ph.D. at 3 (Ex. 9).

742. The Court overruled NPC's objections to the appointment of Dr. Savitz. *See* 1/24/01 Order (Ex. 10).

743. The Rule 706 expert reports followed extensive *Daubert* briefing and the extensive exhibits annexed to the briefing.

S. Supplemental Findings of Fact Regarding the Scientific Method

744. The scientific method requires consideration and evaluation of all of the available scientific evidence regarding the issue of interest. *See* Flockhart Report at 1; Powers Report at 1; Savitz Report at 1.

745. The scientific method requires objective inferences from the relevant scientific evidence, not mere subjective belief. *See* Flockhart Report at 1–2; Powers Report at 1; Savitz Report at 1.

746. "As one moves further and further out along the continuum between interpretation of scientific evidence into the territory of opinion with modest contributions from the research itself, the inference is increasingly removed from being one that is based in science." Savitz Report at 1.

747. "One of the principal hallmarks of the application of a scientifically reliable method of interpreting data is that as new data emerges, a method that is based on science will result in a modified interpretation." *Id.*

748. Where opinions are based on mere subjective judgment as opposed to objective inferences from reliable scientific evidence, "the question of how new information would be factored in and shape the

expert's opinion becomes less clear." *Id.* at 1–2.

749. Before such objective inferences can be made, there must exist sufficient reliable scientific evidence to support the conclusion. *See* Flockhart Report at 1–2 (hypotheses must be ruled in or out by specific tests; facts must be carefully applied to evidence from peer-reviewed literature); Powers Report at 1 (to be scientifically valid, methodology must provide reasonable and plausible scientific explanations for any cause and effect conclusions based on scientific evidence); Savitz Report at 2 (important element of scientifically reliable conclusion is existence of sufficient scientific evidence upon which to draw).

750. The Court agrees that "[o]pinions can readily be offered, and those opinions may even make appropriate use of all of the available information, but in the absence of some minimum amount or level of scientific evidence, the opinions cannot be scientifically derived because there is too little science from which to derive them." Savitz Report at 2.

751. Although it is sometimes necessary in clinical, regulatory, or business practice to make decisions based on less than sufficient and/or reliable scientific evidence due to practical demands requiring immediate decision-making, such guesses, although perhaps reasonable hypotheses based on the best available evidence, do not constitute a scientifically reliable approach when used to assess causality via the scientific method. Savitz Report at 1–4.

752. A methodology based on insufficient scientific evidence can result in "wildly different views among qualified experts because the available knowledge base is so deficient." Savitz Report at 2.

753. It is not surprising, therefore, given the lack of available reliable scientific evidence regarding Parlodel ® and stroke, that application of plaintiff's experts' methodology could result in divergent opinions because the methodology is so inherently subjective. *See, e.g.,* Powers Report at 6; Savitz Report at 2, 5.

754. Although an insufficient body of reliable scientific evidence may nevertheless be enough to justify that a hypothesis or possibility is worth testing, it cannot establish causation in a manner consistent with the scientific method. Savitz Report at 3; *see generally* Flockhart Report (using variations of word "possible," sometimes emphasized, at least 13 times to describe relationship between evidence regarding Parlodel ® and stroke).

755. However, "of the many things that could plausibly occur, empirical evaluations through research often determines that they do not." Savitz Report at 3, 6.

756. "Establishing the *plausibility* of a hypothesis is not the same as demonstrating that the hypothesis is correct." *Id.* (Emphasis in original).

T. Supplemental Findings of Fact Regarding the Increased Incidence of Stroke in the Postpartum Period

757. There is an important background risk of stroke in the postpartum period. *See* Flockhart Report at 4; Powers Report at 3, 5; Savitz Report at 4, 5.

758. There is "a demonstrably high risk of stroke late in pregnancy and in the early postpartum period." Savitz Report at 4, 5; *see also* Powers Report at 3, 5 (noting the increased risk of stroke during the postpartum period). Skidmore, *et al,* "Presentation, Etiology, and Outcome of Stroke in Pregnancy and Puerperium," *Journal of Stroke and Cerebrovascular Diseases,* Vol. 10, No. 1, pp. 1–10 (Janu-

ary–February, 2001) (finding 36 cases of stroke out of 58,429 deliveries, 64% of which occurred during the postpartum period (Ex. 12)); Deev and Zakharushkina, "Cerebral Strokes at a Young Age," *Zhurnal Nevrologii i Psikhiatrii,* 1:14–17 (2000) (of 322 women in study who had stroke, 48 were in pregnancy or postpartum period) (English and Russian versions attached as Ex. 11); Jaigobin, *et al,* "Stroke and Pregnancy," *Stroke,* 31:2948 (2000) (incidence of stroke: 26/100,000 pregnancies; none taking Parlodel ®) (study attached as Ex. 13 and letter to editor/reply attached as Ex. 14); Witlin–Sibai Study, 183 *Am. J. Obstet. Gynecol.* 83, 87 (July 2000) (significant background incidence of postpartum stroke; "Although bromocriptine is no longer approved for use in postpartum lactation suppression, in this series it does not appear to have been causal for postpartum stroke, as has previously been reported.") (Ex. 15); Lanska and Kryscio, "Risk Factors for Peripartum and Postpartum Stroke and Intracranial Venous Thrombosis," *Stroke* (2000) (provides national estimate of 24.6 strokes per 100,000 deliveries) (Ex. 16).

759. Plaintiff's experts offer no credible evidence to dismiss the postpartum period as a time of increased risk of stroke. Powers Report at 5.

U. Supplemental Findings of Fact Regarding Plaintiff's Experts' Failure to Faithfully Apply the Scientific Method in Testing Whether Parlodel ® Causes ICH

760. The methodologies and techniques employed by Dr. Kulig and Dr. Petro in concluding that Parlodel ® causes stroke in general and plaintiff's ICH in particular are not scientifically reliable. *See* Powers Report at 1–2, 4–5; Savitz Report at 5.

761. The elements of evidence relied upon by Dr. Kulig and Dr. Petro are insufficient to satisfy the scientific method whether viewed separately or as a whole. *See generally* Powers Report; Savitz Report, *But cf.* Flockhart Report at 2–4 (evidence taken separately does not prove causation, but as a whole demonstrates possibility that Parlodel ® could cause stroke).

762. The available information regarding Parlodel ® and stroke "is so indirectly applicable and hypothetical in nature, the application of it to form an opinion is not a 'scientifically reliable' process," and "[t]he linkage between those shreds of potentially relevant information and the opinion that results is so murky that it is very difficult to see how the evidence leads to the opinions that are offered." Savitz Report at 4; *see also* Powers Report at 2.

763. If the method of weighing the available evidence regarding Parlodel ® and ICH were sufficiently reliable to establish general causation, plaintiff's experts would be obliged to concede that general causation existed with respect to other drugs or compounds that have generated data of similar quality to that generated in the case of Parlodel ®. Plaintiff's experts fail to do this, indicating either that the method is unreliable, or that they fail to faithfully apply it, or both.

764. The Court finds in accordance with the views of Rule 706 experts, Dr. Powers and Dr. Savitz, that the opinions of plaintiff's experts, Dr. Kulig and Dr. Petro, that Parlodel ® causes stroke are not scientifically reliable.

(i) Lack of Epidemiology Reliably Demonstrating that Parlodel ® Can Cause ICH

765. Notwithstanding Dr. Flockhart's comments regarding the potential imperfections of epidemiologic studies, all of the Rule 706 experts agree that epidemiology

is of "unquestionable value" in assessing causation. Flockhart Report at 2; *see also* Powers Report at 2; Savitz Report at 3.

766. There is no epidemiology demonstrating that Parlodel ® increases the risk of stroke. *See* Flockhart Report at 2; Powers Report at 2; Savitz Report at 4.

767. Dr. Kulig has judged one epidemiologic study (the ERI Study) to be critical in his analysis of causation. *Compare* Flockhart Report at 3 (incorrectly stating that Dr. Kulig places "little reliance" on epidemiologic studies) *with* Powers Report at 2 (noting Dr. Kulig finds ERI study "critical").

768. The ERI Study does not reliably demonstrate that Parlodel ® increases the risk of stroke. *See generally* Powers Report; Savitz Report.

769. Epidemiology is not an absolute requirement in order to prove causation. *See* Flockhart Report at 2; Powers Report at 5; Savitz Report at 3–4.

770. For example, Dr. Flockhart provides an example of a situation in which he alleges a drug (the anti-allergin Seldane) was removed from the market in the absence of epidemiologic studies because "clear *in vitro* evidence of the possibility of an adverse event, combined with excellent case reporting and *trials in normal volunteers* resulted in sufficient evidence for regulators to act to remove the drug from the market around the world." Flockhart Report at 2 (emphasis added). Even if such evidence would reliably establish causation, no such combination of evidence exists with respect to Parlodel ® and ICH.

771. Rule 706 expert Dr. Powers also states that he does not consider epidemiology to be an absolute prerequisite to establishing causation, but finds that a reliable scientific methodology would not support a finding of causation based upon the other evidence relied upon by plaintiff's experts. Powers Report at 4–5 (stating that "it is reasonable not to require clinical trials or epidemiology as the standard of evidence for uncommon adverse reactions," but finding no other data reliably linking Parlodel ® to ICH).

772. Similarly, Rule 706 expert Dr. Savitz states that he does not consider epidemiology to be an absolute prerequisite to establishing causation, but also finds that a reliable scientific methodology would not support a finding of causation based upon the other evidence relied upon by this plaintiff's experts. *See* Savitz Report at 3–4 (discussing methods of proving causation in the absence of epidemiology).

773. Dr. Savitz states that a scientifically reliable methodology in this case (involving a widely-used drug, an adverse event with multiple known contributing causes, and a demonstrably high risk of stroke in the postpartum period) could utilize epidemiologic research, other types of clinical research, or a "tremendous amount of indirect evidence." *Id.* Plaintiff's experts' methodology, however, does not utilize epidemiologic research, other types of clinical research, or a tremendous amount of indirect evidence demonstrating that Parlodel ® causes ICH. *Id.;* Powers Report at 4–5. For example, a scientifically valid understanding of the alleged mechanism by which Parlodel ® allegedly causes vasoconstriction could be important indirect evidence, but it does not exist in this case.

(ii) Lack of Other Human Studies Reliably Demonstrating That Parlodel ® Can cause ICH

774. There are no data from any clinical trials regarding Parlodel ® demonstrating an increased incidence of stroke. Powers Report at 2.

775. There are no case control studies of any kind demonstrating an increased incidence of stroke in patients taking Parlodel ®. Powers Report at 2.

776. There are no data from any human study reliably linking Parlodel ® to ICH. Powers Report at 2.

777. None of the Rule 706 experts state that clinical trial data are an absolute requirement in order to prove causation. *See* Flockhart Report at 4–5; Powers Report at 5; Savitz Report at 3–4; *see also supra* at ¶¶ 45–48 (discussing Rule 706 experts' views regarding the types of evidence that could reliably demonstrate causation in this case).

778. Rule 706 experts Dr. Powers and Dr. Savitz do not find the remaining evidence relied upon by plaintiff's experts to be scientifically reliable evidence of causation.

779. Rule 706 expert Dr. Flockhart states that most clinical practice is not guided by data from randomized, placebo-controlled trials because they are difficult and expensive to conduct. Flockhart Report at 4–5.

780. Dr. Flockhart also states that "[i]t is reasonable for Dr. Petro to conclude that Parlodel ® *can* cause stroke in the absence of prospective randomized placebo controlled trial[s] to answer this question because no trial of sufficient power was ever conducted." Flockhart report at 4–5 (emphasis in original). The Court finds that such reasoning attempts to place the burden of proving a negative onto the defendant.

781. The Court agrees with Dr. Savitz, however, that in clinical practice physicians must often act upon reasonable guesses based on whatever information happens to be available because they must take some action to treat their patients and thus do not have the option of inaction in the face of incomplete, inconclusive, and unreliable evidence. Savitz Report at 4.

782. A clinical guess made because a physician simply does not have the option of saying "we don't have enough information to render a scientifically informed opinion" is not a scientifically reliable approach when used to assess causality. Savitz Report at 2, 4.

783. A conclusion that Parlodel ® can cause stroke simply because there is an *absence* of evidence (*i.e.,* no studies proving that Parlodel ® cannot cause stroke as opposed to reliable scientific evidence proving that it does) is not grounded in reliable scientific methodology. *Id.*

784. In any event, Dr. Petro himself stated that prospective, randomized placebo controlled studies or epidemiological studies were necessary to reach a scientifically reliable conclusion that a drug causes an adverse event.

(iii) The Case Reports Relied Upon by Plaintiff's Experts Do Not reliably Demonstrate That Parlodel ® Can Cause Intracerebral Hemorrhage

785. Plaintiff's experts rely on case reports to support their conclusions. *See* Flockhart Report at 3.

786. All of the Rule 706 experts agree that case reports cannot prove causation in this case. *See id.;* Powers Report at 2; Savitz Report at 4.

787. Rule 706 expert Dr. Flockhart states that the strength of case reports is "in making clear the *possibility* of an event, such as the possibility that Parlodel ® can cause vasoconstriction." Flockhart Report at 3 (emphasis in original). In a somewhat contradictory fashion, Dr. Flockhart later states that "[a] cause and effect relationship can be established even

with a single case report if it is excellent." *Id.*

788. Rule 706 expert Dr. Powers notes that "[a] series of well-documented case reports linking [Parlodel ®] to stroke would *be supportive but not conclusive.*" Powers Report at 2 (emphasis added).

789. However, there is no such series of well-documented case reports linking Parlodel ® to stroke. *Id.*

790. Even if the Court were to find that a single case report could establish causation in certain contexts, plaintiff's experts do not provide reliable evidence that the issue of whether Parlodel ® causes stroke in postpartum women presents such a context. *Id.;* Flockhart Report (failing to explain why one case report would be sufficient reliable evidence in the context of Parlodel ® and ICH).

791. Rule 706 expert Dr. Savitz provides examples of contexts where individual case studies could provide meaningful information, such as when the causal pathway is so clear that comparisons with controls are not needed. Savitz Report at 4. Dr. Savitz provides an example of a tornado hitting a mobile home, causing a person to die of injury. There is no need to ask whether the person might have suffered injury even without the occurrence of the tornado because the causal pathway linking the tornado and injury is simple and direct. *Id.*

792. Dr. Savitz stated and the Court agrees: "In evaluating a widely used drug [such as Parlodel ®], a disease with multiple known contributing causes [such as stroke], and especially a demonstrably high risk of stroke late in pregnancy and in the early postpartum period, some more rigorous evidence [than case reports] is needed to make the specific judgment about the linkage between taking medication and the occurrence of the Intracerebral hemorrhage." *Id.; see also* 11/16/99 *Daubert* Hearing Tr. at 45–53 (Dr. Buchholz explaining types of evidence capable of demonstrating causation where background rate exists for adverse event in question) (Ex. 17).

793. The Court finds that "[g]iven the purpose for which Parlodel was prescribed, to reduce lactation after delivery, the separation of the effects of Parlodel use from the effects of the pregnancy itself demand some information on risk of Intracerebral hemorrhage among women who do and do not use Parlodel." *See* Savitz Report at 4.

794. Plaintiff's experts have not articulated the rate of ICH among postpartum women who do and do not use Parlodel ®.

795. "In the absence of clinical or epidemiologic research, it would require a tremendous amount of indirect evidence to reach the point that even in the absence of research, the linkage is 'obvious' in the way that the tornado leading to injury is obvious." *See* Savitz Report at 4.

796. There is not a sufficient amount of indirect evidence linking Parlodel ® to stroke to satisfy the scientific method. *Id.*

797. Nor is the Court presented with the type of "excellent" case reports to which Dr. Flockhart refers. Flockhart Report at 3; Powers Report at 2; Savitz Report at 4.

798. Dr. Flockhart and plaintiff's experts cite an alleged challenge and dechallenge case report published in the Annals of Internal Medicine ("Larrazet case report") as persuasive evidence that Parlodel ® might cause stroke. Flockhart Report at 3.

799. The Larrazet case report suffers from numerous methodological flaws, and does not constitute a valid dechallenge/rechallenge.

800. The authors of the report wrote: "The mechanism whereby bromocriptine could have precipitated coronary artery spasm is not clear." Larrazet, *et al*, "Possible Bromocriptine–Induced Myocardial Infarction," 118 Ann. Intern. Med. 199 (1993) (Ex. 18).

801. Even the title of the case report, "*Possible* Bromocriptine–Induced Myocardial Infarction," shows that the authors could not state that there was a causal relationship. *Id.* (Emphasis added).

802. However, this case report involved alleged vasoconstriction of the coronary arteries, not cerebral vasoconstriction or stroke. Flockhart Report at 3.

803. Neither Dr. Flockhart nor plaintiff's experts provide a reliable explanation for how one can extrapolate evidence of alleged coronary vasoconstriction to vasoconstriction of the cerebral arteries or stroke.

804. For example, as noted by Rule 706 expert Dr. Powers, the pathophysiology and causes of ICH are different from those of ischemic stroke. Powers Report at 2. Thus, data linking Parlodel® to stroke in general would not be relevant unless it links drug exposure to ICH. *Id.* This same reasoning applies with equal if not greater force to evidence of alleged coronary vasoconstriction.

805. Cerebral arteries also respond differently to ergots than do other arteries in the body. *Id.*

806. Rule 706 expert Dr. Flockhart does not explain why it is scientifically reliable to give no weight to studies in patients taking Parlodel® for Parkinson's Disease showing the absence of hypertension, and yet rely upon a case report allegedly demonstrating coronary vasoconstriction as evidence that Parlodel® causes cerebral vasoconstriction or ICH. *Compare* Flockhart Report at 5 (giving no weight to studies in Parkinson's patients in part because plaintiff did not have Parkinson's Disease) *with id.* at 3 (relying on case report allegedly involving coronary vasoconstriction).

807. Dr. Flockhart opines that caffeine, a substance he states is an acknowledged vasoconstrictor, can be eliminated as a possible cause of stroke because there is no reliable evidence specifically proving caffeine causes stroke as opposed to merely vasoconstriction. *Id.* at 5. He does not explain, however, why it is scientifically reliable to exclude caffeine for this reason, yet rely upon a case report allegedly demonstrating coronary vasoconstriction as evidence that Parlodel® possibly causes stroke. *Id.* at 3, 5.

(iv) DMC Causality Assessments Do not Reliably Demonstrate That Parlodel® Can Cause Intracerebral Hemorrhage

808. None of the Rule 706 experts cite the DMC causality assessments, relied upon by plaintiff's experts, as scientifically reliable evidence that Parlodel® causes ICH.

809. The Court agrees with Rule 706 expert Dr. Savitz that "[t]he standards for expressing a concern among pharmaceutical industry employees or for making a notation on a drug package insert are not necessarily derived from a scientifically reliable method of inference." Savitz Report at 3.

810. Statements by pharmaceutical industry employees regarding the ability of Parlodel® to cause ICH are no better or worse than the scientific methodology and evidence on which they are based. *Id.* at 3.

811. Objective scientific evaluation of the evidence requires the assessment of testing and research findings, not the *ipse dixit* of others. *Id.*

812. Plaintiff's experts have not demonstrated that the methodology utilized in making these "causality assessments" is scientifically reliable or that they even know what the methodology is.

(v) The Animal Studies Relied Upon by Plaintiff's Experts Do Not Reliably Demonstrate That Parlodel ® Can Cause Intracerebral Hemorrhage

813. At best, "animal data can demonstrate the *possibility* of an effect, but they cannot carry the same weight as studies conducted in people or in human tissues." Flockhart Report at 3 (Emphasis in original).

814. Animal studies "must be used very carefully" because the "[d]oses used in animals can often not be equated to doses used in humans," and because the affinities of the pharmacologic receptors of interest "may well be significantly different" between animals and humans. *Id.*

815. The animal studies relied upon by plaintiff's experts are not sufficient evidence, either alone or in combination with other evidence, that Parlodel ® causes ICH. *See* Powers Report at 2, 5 (no data provided from either human or animal studies linking Parlodel ® to ICH); Savitz Report at 4 (generally describing evidence regarding Parlodel ® as "indirectly applicable and hypothetical in nature").

816. Even Rule 706 expert Dr. Flockhart can say no more than that the animal studies raise a "*possibility* that [Parlodel ®] can bring about vasoconstriction in a mammalian blood vessel in vivo." Flockhart Report at 3.

817. Both Dr. Flockhart and plaintiff's experts admit the inherent problems in extrapolating results from animal studies utilizing high doses of the drug to effects in humans taking therapeutic doses. Flockhart Report at 3.

818. Both Dr. Flockhart and plaintiff's experts admit that the doses of Parlodel ® utilized in the animal studies on which they rely were high doses. Flockhart Report at 3.

819. Neither Dr. Flockhart nor plaintiff's experts adequately explain how one can reliably translate the admittedly high doses of the drug used in these animal studies to the therapeutic doses allegedly consumed by plaintiff and arrive at a reliable conclusion that Parlodel ® *possibly* causes vasoconstriction in humans, much less that it actually *does* cause vasoconstriction in humans. Flockhart Report at 3, 5.

820. Both Dr. Flockhart and plaintiff's experts admit that the affinities of the relevant pharmacologic receptors of animals may be significantly different than those of humans. Flockhart Report at 3.

821. Neither Dr. Flockhart nor plaintiff's experts provide reliable scientific evidence to demonstrate that the animal receptors at issue in the studies on which they rely are sufficiently comparable to those found in humans to allow a reliable conclusion that Parlodel ® *possibly* causes vasoconstriction in humans, much less that it actually *does* cause vasoconstriction in humans. Flockhart Report at 3, 5.

822. Neither Dr. Flockhart nor plaintiff's experts adequately explain the relationship between the affinities of the particular receptors at issue in the animal studies and the affinities of the comparable receptors in humans (to the extent comparable receptors even exist), much less in receptors found in human cerebral arteries. Flockhart Report at 3, 5.

823. Even were the Court to find these animal studies translatable in any meaningful way to humans, none of these stud-

ies purports to demonstrate cerebral vasoconstriction, stroke, or ICH in the animals studied. *See* Powers Report at 2, 5.

824. Both Dr. Flockhart and plaintiff's experts agree that animal studies cannot carry the same weight as studies conducted in people. Flockhart Report at 3.

825. Were the Court to find that the several animal studies referenced by plaintiff's experts demonstrated the possibility that Parlodel ® could cause ICH in animals, neither Dr. Flockhart nor plaintiff's experts adequately explain how this possibility could be applied to humans, given the substantial evidence that Parlodel ® is known to cause hypotension and vasodilation in animals and humans, and the absence of reliable human evidence that Parlodel ® causes cerebral vasoconstriction, hypertension, stroke, or ICH. Flockhart Report at 3; Powers Report at 2, 5.

826. For example, Rule 706 expert Dr. Flockhart gives *no* weight to the fact that no hypertension was reported in a study of 200 patients taking Parlodel ® for Parkinson's Disease, in part because plaintiff did not have Parkinson's Disease. Flockhart Report at 5 (study has "no bearing").

827. Yet, despite the fact that Dr. Flockhart and plaintiff's experts recognize that human studies carry greater weight than animal studies, they provide no explanation for why they give more weight to an animal study showing alleged effects in the "dependent ear margins in dogs with long hanging ears" than negative human studies or human studies demonstrating vasodilation, given that plaintiff is not a dog and does not have long hanging ears. Flockhart Report at 3. (Dr. Petro testified that comparing mongrel ten kilogram dog used in Parlodel ® animal study relied upon by plaintiff's experts to a postpartum woman "is a stretch").

828. Although Dr. Flockhart and plaintiff's experts raise the possibility that Parlodel ® may cause both vasodilation and vasoconstriction, they cite only animal studies as proof of this phenomenon. Flockhart Report at 5 (citing animal studies and raising the hypothesis of Parlodel ® causing both vasoconstriction and vasodilation as a "possibility," not a proven phenomenon).

829. The Court finds that these animal studies do not reliably support the hypothesis that Parlodel ® is capable of causing both vasodilation and vasoconstriction in animals generally, much less in humans.

830. Even if the Court found that these animal studies reliably demonstrated that Parlodel ® is capable of causing vasoconstriction in certain vessels and vasodilation in others in the same animal, neither Dr. Flockhart nor plaintiff's experts adequately explain how such a finding would reliably translate into a conclusion that Parlodel ® causes vasoconstriction in certain people and vasodilation in others. Flockhart Report at 5.

(vi) FDA Regulatory Proceedings Regarding Parlodel ® Do Not Reliably Demonstrate That Parlodel ® Can Cause ICH

831. Dr. Flockhart cites the withdrawal of Parlodel ® for the indication PPL as "[p]erhaps the most persuasive among the data presented." Flockhart Report at 3.

832. Dr. Flockhart also relies on the allegation that FDA officials have stated that Parlodel ® can cause vasoconstriction, although he provides no citations for this statement and there is no such statement in the record. *Id.*

833. The Court finds that the FDA has never concluded that Parlodel ® is causally related to stroke in general or ICH in particular.

834. In its letter to the FDA, NPC noted that it was "voluntarily withdrawing this indication despite the fact that we continue to have every confidence in the safety and efficacy of Parlodel ® for this indication . . . [and] it remains true that *no credible scientific evidence has established a causal connection between Parlodel and an increased risk of stroke or seizure in the postpartum period* . . . . " Letter from Thomas Koestler to Solomon Sobel, August 18, 1994 (Ex. 23) (emphasis added).

835. The current FDA-approved labeling for Parlodel ® continues to state that the causal relationship between Parlodel ® and stroke "has not been established."

836. Rule 706 expert Dr. Savitz notes, and the Court agrees, that the decisions made in the regulation of pharmaceutical companies do not necessarily reflect methodologies or conclusions considered acceptable in the scientific arena and are not necessarily based on the scientific method. Savitz Report at 1, 3.

837. Such regulatory decisions are no better or worse than the scientific methodology and evidence on which they are based. *Id.* at 3.

838. Plaintiff's experts have themselves admitted that FDA decision-making is based on a different standard than tort law-based scientific proof of causation.

(vii) There is No Reliable Evidence of an Alleged Mechanism by Which Parlodel ® Can Cause ICH

839. No scientifically plausible explanation for how Parlodel ® can cause ICH has been provided by plaintiff's experts. Powers Report at 2, 5; Flockhart Report at 5.

840. The mechanisms for ICH and ischemic stroke are different. Powers Report at 2, 5.

841. There are no data from either human or animal models demonstrating any mechanism by which Parlodel ® allegedly causes cerebral vasoconstriction or ICH. Powers Report at 2, 5.

842. Nor are there human or animal data substantiating the assumption made by plaintiff's experts that cerebral vasoconstriction can cause ICH. Powers Report at 2, 5.

843. Even if there were such data, there is no reliable evidence in animals or humans that Parlodel ® actually causes cerebral vasoconstriction. Powers Report at 2, 5.

844. Although plaintiff's experts cite alleged evidence that Parlodel ® may cause peripheral vasoconstriction and a clinical syndrome of ergotism, there is no scientifically valid evidence that peripheral vasoconstriction or ergotism causes cerebral vasoconstriction. Powers Report at 2, 5.

845. Plaintiff's experts, who claim that Parlodel ® acts like all other ergots to allegedly cause vasoconstriction, provide no reliable means of distinguishing studies showing that cerebral arteries respond differently to ergots than do peripheral vessels. Powers Report at 2, 5.

846. Studies showing that cerebral arteries respond differently to ergots than do peripheral vessels invalidate plaintiff's experts' efforts to reason by analogy from scientific data regarding alleged vasoconstriction of the peripheral vessels. Powers Report at 2, 5.

847. Although plaintiff's experts cite a case report in an effort to bolster their assumption that Parlodel ® can cause cerebral vasoconstriction, that case report involves a different ergot (ergotamine tartrate) and at best demonstrates abnormalities in extra cranial carotid arteries, not cerebral arteries. Powers Report at 2.

848. In any event, the findings described in the case report are not specific

for vasoconstriction and have the appearance of carotid artery dissection. *Id.*

849. Although plaintiff's experts raise various possibilities for a mechanism by which Parlodel ® might cause vasoconstriction as a general matter, they are unable to articulate any such mechanism to a reasonable degree of medical certainty. *See also* Flockhart Report at 5 (also raising possibilities for mechanism, but agreeing that mechanism is not known to reasonable degree of medical certainty).

850. Rule 706 expert Dr. Flockhart states that lack of understanding regarding the mechanism by which Parlodel ® allegedly causes vasoconstriction should not detract from a conclusion that Parlodel ® can cause vasoconstriction if "*the preponderance of the evidence makes clear it can do so.*" Flockhart Report at 5.

851. However, there is no such preponderance of the evidence making it clear that Parlodel ® can cause vasoconstriction.

852. Even if there were, there is no preponderance of the evidence making it clear that vasoconstriction causes ICH. *See id.* (rejecting caffeine as a possible cause of plaintiff's stroke because although scientists agree caffeine can be a vasoconstrictor there is no credible evidence that it causes stroke); Powers Report at 2, 5 (evidence of general vasoconstriction does not equate with evidence of cerebral vasoconstriction or ICH).

(viii) Plaintiff's Experts Cannot Reliably Demonstrate That Parlodel ® Can Cause ICH Through Application of the Bradford–Hill Criteria to the Evidence in this Case

853. Application of the Bradford–Hill criteria to this case does not provide reliable evidence of causation. Powers Report at 3; Savitz Report at 4. Rule 706 expert Dr. Flockhart does not rely upon or discuss the Bradford–Hill criteria. *See generally* Flockhart Report.

854. The Bradford–Hill criteria "were developed as a mean[s] of interpreting *an established association* based on a body of epidemiologic research for the purpose of trying to judge whether the observed association reflects a causal relation between an exposure and disease." Savitz Report at 4 (emphasis added).

855. "Not only is there not a consistently observed association between Parlodel and Intracerebral hemorrhage to which the criteria could be applied, but there is not even a single epidemiologic study that addresses the issue in a meaningful way." *Id.*

856. Plaintiff's experts' efforts to apply the Bradford–Hill principles to the available evidence in this case are not scientifically reliable. *Id.*

857. Even given the absence of any observed positive association from epidemiology, Rule 706 expert Dr. Powers demonstrates the futility of attempting to otherwise apply the Bradford–Hill principles, noting that only one of the nine criteria is satisfied in this case in any event (Powers Report at 3–4):

a. Consistency and unbiasedness of findings:

1) An association between Parlodel ® and ICH has not been established by valid scientific methods. Powers Report at 3; Savitz Report at 4.

2) Plaintiff's experts are unable to point to a single study in animals or humans demonstrating a positive association between Parlodel ® and ICH or Parlodel ® and stroke generally.

3) This criterion is not satisfied. Powers Report at 3.

b. Strength of association:

1) No association between Parlodel ® and ICH has been established, much less a strong association. *Id.*; Savitz Report at 4.

2) Plaintiff's experts have not cited reliable scientific evidence establishing such an association.

3) This criterion is not satisfied. Powers Report at 3.

c. Temporal sequence:

1) The exposure to Parlodel ® occurred prior to the onset of plaintiff's ICH. *Id.*

2) This is the one criterion that is satisfied, assuming the Bradford–Hill criteria could be applied properly in the absence, as here, of a positive association based on epidemiology. *Id.*

3) This particular criterion is trivial, given that in the absence of its fulfillment all would agree Parlodel ® could not even theoretically be a cause of stroke.

d. Dose Response Relationship:

1) "No dose response relationship for Parlodel and the occurrence of Intracerebral hemorrhage has been documented." *Id.*

2) Plaintiff's experts have not articulated a known dose response relationship for Parlodel ® and ICH.

3) This criterion is not satisfied. Powers Report at 3.

e. Specificity:

1) "Parlodel use has not been shown to specifically be associated with changes in the occurrence of Intracerebral hemorrhage." *Id.* at 3.

2) Plaintiff's experts have not cited reliable scientific evidence that Parlodel ® is specifically associated with changes in the occurrence of ICH.

3) This criterion is not satisfied. Powers Report at 3.

f. Coherence of the biological background and previous knowledge:

1) "No evidence linking an increase in postpartum Intracerebral hemorrhage with the marketing of Parlodel has been presented." *Id.*

2) Plaintiff's experts have not cited reliable scientific evidence linking an increase in postpartum ICH with the marketing of Parlodel ® either before or after the marketing of Parlodel ®.

3) This criterion is not satisfied. Powers Report at 3.

g. Biological plausibility:

1) "The proposed mechanism of cerebral vasoconstriction by which Parlodel might cause Intracerebral hemorrhage is not substantiated by scientific evidence. It is unlikely given that there is little evidence that cerebral arteries constrict in response to the class of ergot drugs, as distinct from well-documented constriction of the peripheral vasculature." *Id.* at 3.

2) Nor is the proposed mechanism by which Parlodel ® might cause vasoconstriction substantiated by scientific evidence.

3) Plaintiff's experts have been unable to articulate the mechanism by which Parlodel ® might cause vasoconstriction, or the mechanism by which cerebral vasoconstriction might cause ICH. *Id.*

4) This criterion is not satisfied. Powers Report at 3.

h. Reasoning by analogy:

1) "Reasoning by analogy is not valid under these circumstances due to the differential response of the cerebral vasculature to the class of ergot drugs as compared to the peripheral vasculature." *Id.* at 4.

2) Plaintiff's experts have not adequately explained why reasoning by analogy would be appropriate in this case. *See id.*

3) This criterion is not satisfied. Powers Report at 4.

i. Experimental evidence:

1) No dechallenge or rechallenge data exist with respect to Parlodel ® and ICH. Powers Report at 4.

2) Although Dr. Flockhart cites (and plaintiff's experts rely upon) a case report allegedly demonstrating coronary vasoconstriction in a dechallenge/rechallenge setting, the Court has already discussed the problems inherent with reliance on this case report. *See supra* at ¶¶ 73–83.

3) This criterion is not satisfied. Powers Report at 4.

V. Supplemental findings of Fact Regarding Plaintiff's Experts' Misuse of Differential Diagnosis

(i) Failure to Rule in Parlodel ® by Scientifically Reliable Means

858. Dr. Kulig and Dr. Petro have expressly disavowed the use of differential diagnosis to establish general causation (*i.e.,* that Parlodel ® causes ICH in general).

859. Although Dr. Kulig and Dr. Petro do rely on the differential diagnosis for purposes of attempting to establish specific causation (*i.e.,* that Parlodel ® caused plaintiff's ICH), they have expressly admitted that they must first establish general causation *before* they may reliably apply a differential diagnosis.

860. Notwithstanding his charge to assess plaintiff's experts' methodology, Dr. Flockhart states that it is implicit in his opinion that differential diagnosis is a reasonable technique to *rule in* or out possible causes of adverse events. Flockhart Report at 1. Thus, Dr. Flockhart assumes for purposes of his analysis that a differential diagnosis may not only be used to demonstrate *specific* causation, but can also be used to demonstrate *general* causation.

861. To the extent Dr. Flockhart is suggesting that it is scientifically reliable to place Parlodel ® on the differential diagnosis simply because it is hypothesized that Parlodel ® might *possibly* cause vasoconstriction or stroke, and then somehow prove causation simply by crossing out other alternative causes identified in this particular case, the Court finds such reasoning fatally circular, particularly since plaintiff's experts use the fact that plaintiff took Parlodel ® (which they assume causes stroke) as a *reason* to rule out other alternative causes. *See, e.g.,* Powers report at 6. The Court agrees with Rule 706 experts Dr. Powers and Dr. Savitz that the differential diagnosis is not a reliable methodology for determining *general* causation for the reasons discussed below, although it has been recognized as a valid methodology for assessing *specific* causation (once general causation has first been established).

862. First, to the extent Dr. Flockhart is positing a new methodology for determining general causation other than that of plaintiff's experts, it is not relevant to the Court's task.

863. Second, Dr. Flockhart cannot articulate a known error rate for his application of the differential diagnosis, except to state that erroneous conclusions based on the differential diagnosis are "constantly sober[ing]," thereby admitting an impermissibly high error rate. Flockhart Report at 1. Although Dr. Flockhart states that this unknown error rate can be reduced by careful application of the relevant facts to knowledge imparted by the peer-

reviewed literature, as discussed elsewhere in these findings, plaintiff's experts' methodologies do not rely on sufficient established knowledge imparted by the peer-reviewed literature or on a careful application of the facts of this case to that literature.

864. Third, Dr. Flockhart's proposed use of the differential diagnosis to show *general* causation also ignores the substantial evidence that a discernible cause is never identified with respect to a significant number of strokes, despite careful evaluation. *See also* Buchholz/*Soldo* Dep. at 155–56 (etiology of stroke or hemorrhage unknown in approximately one-third of all stroke cases) (Ex. 24); Jaigobin, *et al,* Stroke and Pregnancy, *Stroke* 31:2948–51 (2000) (49% of strokes in study were of unknown etiology) (Ex. 13); Kittner, *et al,* "Cerebral Infarction in Young Adults: The Baltimore Washington Young Stroke Study," *Neurology* 50:890–94 (1998) (nearly one-third of both first and recurring strokes had no identified cause) (Ex. 25); Kittner, *et al,* "Pregnancy and the Risk of Stroke," *New Engl. J. Med.* 335:768–74 (1996) (half of ICHs in postpartum period were of unknown cause despite careful evaluation by pairs of neurologists) (Ex. 26); Gorelick and Alter, *Handbook of Neuroepidemiology* (Marcel Dekker 1994) at 151–53 (a clear cause of arterial rupture is found in only approximately 20% of patients with an ICH) (Ex. 27).

865. Dr. Flockhart dismisses the possibility that the cause of stroke is often unidentified even after careful evaluation, but does not explain the basis upon which he disregards the scientific studies demonstrating exactly that. *See* Flockhart Report at 4.

866. In any event, given plaintiff's experts' admissions that many strokes occur for which a particular cause cannot be ascertained even after extensive investigation, consistent application of their own methodology requires them to rule out such idiopathic stroke before reliably concluding that Parlodel ® caused the stroke.

867. It is impossible to reasonably rule out a cause that cannot even be specifically identified. (Dr. Petro testifying regarding his inability to rule out idiopathic stroke: "You cannot rule out what you cannot rule out.").

868. Thus, even if Parlodel ® were the only remaining identifiable possible cause of stroke left on the differential diagnosis, this fact could not equate to a conclusion that Parlodel ® can cause stroke because it is known that a significant number of strokes are caused by unidentifiable factors.

869. Reliable scientific evidence proving that Parlodel ® can cause ICH is thus necessary to "rule in" Parlodel ® and justify its placement on the differential diagnosis. *See* Powers Report at 3, 5 (Parlodel ® must be implicated as a cause and other reasonable causes must be ruled out); Savitz Report (never reaching specific causation analysis due to insufficient evidence to establish general causation.)

870. "[Without a knowledge base that establishes] general causation for [hypothesized] factors, *i.e.,* evidence that the agent can cause the disease more generally, judgment that those factors contribute to the disease in this specific patient is unwarranted, no matter how well we understand the immediate sequence of biologic events that culminated in the disease." Savitz Report at 2.

871. Even Dr. Flockhart states that a potential cause must be ruled on by specific tests, and that a differential diagnosis is only scientifically reliable if there is a reasonable basis for accepting that Parlodel ® can cause ICH. *See* Flockhart Report at 1.

872. No such specific tests, reasonable basis, or reliable scientific evidence exists in this case with respect to the hypothesis of whether Parlodel ® can cause ICH. *See generally* Powers Report; Savitz Report.

873. Even if there were reliable evidence that Parlodel ® causes ICH, there is no reliable evidence in the medical records of plaintiff that she experienced vasoconstriction or ergotism to justify placing and/or keeping Parlodel ® on the differential diagnosis in the first place. *See* Powers Report at 3, 5.

874. The Court, therefore, finds that neither Dr. Kulig nor Dr. Petro had a reasonable scientific basis for including and/or keeping Parlodel ® on the differential diagnosis in this case.

(ii) Failure to Rule Out Other Putative Causes of Plaintiff's Stroke by Scientifically Reliable Means

875. A differential diagnosis is scientifically reliable only if every reasonable alternative cause is considered and there is a reasonable basis articulated for rejection of each alternative cause that is rejected. *See* Flockhart Report at 1; Powers Report at 3, 6.

876. Reasonable alternative causes should be ruled out by specific diagnostic tests. *See* Flockhart Report at 1 (differential diagnosis involves posing series of testable hypotheses which can be ruled in or out by specific tests).

877. Dr. Kulig failed to articulate a reasonable basis for ruling out certain alternative causes of plaintiff's stroke that need to be included in the differential if Dr. Kulig's methodology is consistently applied. *See* Powers Report at 2; *cf.* Flockhart Report at 4, 6 (noting that Dr. Petro failed to faithfully apply his methodology to exclude plaintiff's exposure to sympathomimetic amines, but not addressing Dr. Kulig).

878. Dr. Petro failed to articulate a reasonable scientific basis for ruling out certain alternative causes of plaintiff's stroke that need to be included in the differential if Dr. Petro's methodology is consistently applied. *See* Flockhart Report at 6; Powers Report at 5–6; (not addressed by Dr. Savitz).

(a). Dr. Kulig Fails to Rule Out Alternative Possible Causes of Plaintiff's ICH

1. Dr. Kulig did not offer a reasonable basis to rule out the postpartum period or idiopathic stroke as possible alternative causes of plaintiff's Intracerebral hemorrhage"

879. There is a statistically significant, massive increased risk of stroke in the postpartum period.

880. Dr. Flockhart states that it was reasonable for Dr. Kulig to exclude the postpartum period as the cause of plaintiff's stroke because it was untenable to believe that such strokes happen for no describable reason that could be detected in plaintiff. Flockhart Report at 4 (referring to the Kittner/Buchholz study finding postpartum ICH risk increased 28–fold). He asserts that "[i]t is likely that were each of these [postpartum ICHs] to be as closely examined as was Ms. Soldo's [ICH], that a scientifically plausible cause [other than the post-partum period] might well be found for each of them." *Id.*

881. Dr. Flockhart offers no support for these statements other than his own *ipse dixit. Id.*

882. The Court finds that the weight of the reliable evidence and the admissions of plaintiff's experts contradict Dr. Flockhart's statements in this regard.

883. The Court agrees with Dr. Powers, who is the only Rule 706 neurologist in this case, that Dr. Kulig did not offer a reasonable basis for excluding the postpartum period itself as the cause of plaintiff's stroke. Powers Report at 3; *see also* Savitz Report at 4, 5 (noting generally that plaintiff's experts were unable to exclude the postpartum period as cause of strokes in patients taking Parlodel ®).

884. The Court also finds that Dr. Kulig did not offer a reasonable basis for excluding idiopathic stroke (*i.e.,* stroke with no known cause in persons with no known risk factors). Dr. Kulig's basis for ruling out idiopathic causes of plaintiff's ICH—his belief that there was an obvious alternative explanation for the stroke in that plaintiff had taken Parlodel ®—is fatally circular. *See, e.g.,* 11/9/99 *Daubert* Hearing Tr. at 156:20–23 (Dr. Kulig testifying that he ruled out idiopathic causes of plaintiff's stroke because there was an obvious explanation found in Parlodel ®) (Ex. 28); *see also* Powers Report at 6 (noting that Dr. Petro's attempt to rule out AVM as an alternative cause of plaintiff's stroke by relying on the fact that she had taken Parlodel ® is circular and evidence of an unreliable scientific methodology).

2. Dr. Kulig did not offer a reasonable basis to rule out sympathomimetic amines as a possible alternative cause of plaintiff's ICH

885. A consistent and faithful application of plaintiff's experts' methodology used to place Parlodel ® on the differential diagnosis for plaintiff (which relies heavily, for example, on unreliable case reports) requires that plaintiff's ingestion of a sympathomimetic drug must also be considered. *See* Flockhart Report at 6; Powers Report at 3.

886. Assuming the validity of the methodology offered by plaintiff's experts, Dr. Kulig failed to offer a reasonable explanation for ruling out a sympathomimetic drug as the cause of plaintiff's ICH. Powers Report at 3; Flockhart Report at 6 (addressing Dr. Petro's inconsistent application of methodology regarding sympathomimetic drug, but not addressing Dr. Kulig).

3. Dr. Kulig did not offer a reasonable basis to rule out arteriovenous malformation ("AVM") as a possible alternate cause of plaintiff's ICH

887. Although Rule 706 expert Dr. Flockhart concludes that Dr. Kulig reliably performed a differential diagnosis with respect to specific causation, he does not discuss why he believes Dr. Kulig reliably ruled out an AVM as a plausible alternative cause of plaintiff's ICH. *See generally* Flockhart Report.

888. Rule 706 expert Dr. Powers notes Dr. Petro's failure to reliably rule out AVM as an alternative cause of plaintiff's stroke, but also does not discuss this issue with respect to Dr. Kulig. *See* Powers Report at 6.

889. Dr. Kulig admitted that AVM is a cause of ICH, and that he must consider AVM as part of his differential diagnosis in this case. *See* 11/8/99 *Daubert* Hearing Tr. at 67:17–23 (testifying that AVM, which can be asymptomatic until it ruptures, is a cause of ICH and must be included on his differential diagnosis) (Ex. 29).

890. Dr. Kulig's only stated reason for ruling out AVM is that one was not seen on plaintiff's arteriogram. *See id.* at 83:7–22.

891. Plaintiff's experts have admitted, however, that an arteriogram cannot rule out an AVM after an ICH has occurred because the AVM can be obliterated by the hemorrhage itself.

892. The Court finds that Dr. Kulig did not offer a reasonable explanation for ruling out AVM as the cause of plaintiff's ICH.

4. Dr. Kulig did not offer a reasonable basis to rule out caffeine or smoking as possible alternative causes of plaintiff's ICH.

893. Although Dr. Flockhart concludes that Dr. Kulig reliably performed a differential diagnosis with respect to specific causation, he does not discuss why he believes Dr. Kulig reliably ruled out caffeine as a plausible alternative cause of plaintiff's ICH.

894. Dr. Flockhart does discuss caffeine with respect to his analysis of Dr. Petro's differential diagnosis, stating that Dr. Petro reliably ruled out caffeine as a possible cause of plaintiff's stroke because "[w]hile there is agreement that caffeine can be a vasoconstrictor, no credible evidence was presented indicating that it can cause stroke in healthy young women." *Id.* at 5.

895. Neither Dr. Flockhart nor plaintiff's experts Dr. Petro and Dr. Kulig explain why the alleged evidence regarding Parlodel ® and stroke is more credible than the evidence regarding caffeine and stroke.

896. Neither Dr. Flockhart nor plaintiff's experts Dr. Petro and Dr. Kulig explain why the alleged evidence that Parlodel ® possibly causes vasoconstriction is sufficient to place and keep Parlodel ® on the differential diagnosis but evidence that caffeine can be a vasoconstrictor is not sufficient to place and keep caffeine on the differential diagnosis.

897. The Court finds that Dr. Kulig failed to follow faithfully or consistently the method he espouses and did not provide a reasonable explanation for ruling out caffeine as a cause of plaintiff's stroke.

898. The Court also finds that Dr. Kulig did not provide a reasonable explanation for ruling out smoking as a cause of plaintiff's stroke.

899. Although Rule 706 expert Dr. Flockhart concludes that Dr. Kulig reliably performed a differential diagnosis with respect to specific causation, he does not discuss why he believes Dr. Kulig reliably ruled out smoking as a plausible alternative cause of plaintiff's ICH. *See generally* Flockhart Report.

900. Rule 706 expert Dr. Powers states that Dr. Petro dismisses the possible causative role of smoking without a reasonable explanation, but does not discuss this issue with respect to Dr. Kulig. *See* Powers Report at 6.

5. Dr. Kulig did not offer a reasonable basis to rule out blood abnormalities as a possible alternative cause of plaintiff's ICH.

901. Although Rule 706 expert Dr. Flockhart concludes that Dr. Kulig reliably performed a differential diagnosis with respect to specific causation, he does not discuss why he believes Dr. Kulig reliably ruled out blood abnormalities as a plausible alternative cause of plaintiff's ICH. *See generally* Flockhart Report.

902. Dr. Flockhart does discuss blood abnormalities with respect to Dr. Petro, stating that Dr. Petro reasonably ruled out blood abnormalities as a possible alternative cause of plaintiff's ICH. *Id.* at 5.

903. However, there is no dispute that certain tests for endogenous coagulating factors, which might have pre-disposed plaintiff to ICH, were not done. *Id.*

904. Dr. Flockhart states that Dr. Petro reasonably ruled out the value of such testing because there was no evidence in the medical records to suggest that plaintiff suffered from a clinically relevant coag-

ulopathy. Flockhart Report at 5. The Court assumes that Dr. Flockhart believes Dr. Kulig reasonably ruled out blood abnormalities on the same basis.

905. The Court finds this "reasoning" circular in that without such testing there is no evidence that all abnormalities in coagulating factors would be discovered.

906. Further, the Court finds that the fact that plaintiff was in the postpartum period and had sustained an ICH as adequate evidence in the medical record to at least suggest the possibility that plaintiff suffered from a clinically relevant coagulopathy that might have been detected had additional testing been done.

907. In any event, a consistent application of Dr. Kulig's methodology placing and keeping Parlodel ® on the differential diagnosis in spite of no evidence in the medical records of vasoconstriction or ergotism, would require Dr. Kulig to place and keep blood abnormalities on the differential diagnosis. *See, e.g.,* Powers Report at 5.

908. Dr. Flockhart further states that it is reasonable to conclude that plaintiff did not have abnormalities in coagulating factors because "she has apparently not suffered any episodes since that would indicate this to be the case." Flockhart Report at 5.

909. However, there is no evidence that plaintiff has since been in the postpartum period, a time of known increased risk of ICH. *See* Powers Report at 5 (postpartum period is time of increased risk for stroke); Savitz Report at 5 (same).

910. The Court finds that Dr. Kulig did not offer a reasonable explanation for ruling out blood abnormalities as an alternative cause of plaintiff's stroke.

6. Dr. Kulig did not offer a reasonable explanation to rule out stress, hormones, or endogenous vasoconstrictors as possible alternative causes of plaintiff's ICH

911. Although Rule 706 expert Dr. Flockhart concludes that Dr. Kulig reliably performed a differential diagnosis with respect to specific causation, he does not discuss why he believes Dr. Kulig reliably ruled out stress, hormones, or endogenous vasoconstrictors as plausible alternative causes of plaintiff's ICH. *See generally* Flockhart Report.

912. The Court finds that Dr. Kulig has not reliably ruled out these other plausible causes of plaintiff's stroke.

(b) Dr. Petro Fails to Rule Out Alternative Possible Causes of Plaintiff's ICH

1. Dr. Petro did not offer a reasonable basis to rule out the postpartum period or idiopathic stroke as possible alternative causes of plaintiff's ICH

913. As discussed above, there is an increased risk of stroke in the postpartum period.

914. Dr. Flockhart states that it was reasonable for Dr. Kulig to exclude the postpartum period as the cause of plaintiff's stroke because it was untenable to believe that such strokes happen for no describable reason that could be detected in plaintiff. Flockhart Report at 4. He asserts that "[i]t is likely that were each of these [postpartum ICHs] to be as closely examined as was Ms. Soldo's [ICH], that a scientifically plausible cause [other than the postpartum period] might well be found for each of them." *Id.*

915. Although Dr. Flockhart does not discuss this issue in connection with Dr. Petro, the Court assumes he would ad-

vance the same statements with respect to him as well.

916. Dr. Flockhart offered no support for these statements other than his own *ipse dixit. Id.*

917. As discussed above, the Court finds that the weight of the reliable evidence and the admissions of plaintiff's experts contradict Dr. Flockhart's statements in this regard.

918. The Court agrees with the neurologist, Dr. Powers, that Dr. Petro did not offer a reasonable basis for excluding the postpartum period itself as the cause of plaintiff's stroke. Powers Report at 5; *see also* Savitz Report at 4, 5 (noting generally that plaintiff's experts were unable to exclude the postpartum period as cause of strokes in patients taking Parlodel ®).

919. The Court also finds that Dr. Petro did not offer a reasonable basis for excluding idiopathic stroke (*i.e.,* stroke with no known cause in persons with no known risk factors).

2. Dr. Petro did not offer a reasonable basis to rule out sympathomimetic amines as a possible alternative cause of plaintiff's ICH

920. A consistent application of plaintiff's experts' methodology used to place Parlodel ® on the differential diagnosis for plaintiff (which relies heavily, for example, on unreliable case reports) requires that plaintiff's ingestion of a sympathomimetic drug must also be considered. *See* Flockhart Report at 6; Powers Report at 3.

921. Dr. Petro failed to offer a reasonable explanation for ruling out a sympathomimetic drug as the cause of plaintiff's ICH. Flockhart Report at 6; Powers Report at 3.

3. Dr. Petro did not offer a reasonable basis to rule out arteriovenous malformation as a possible alternative cause of plaintiff's ICH

922. Dr. Petro's attempt to rule out AVM as an alternative cause of plaintiff's stroke by relying on the fact that she had taken Parlodel ® is circular and evidence of an unreliable scientific methodology. *See* Powers Report at 6.

923. Such circular "reasoning" is particularly suspect where Parlodel ® is placed on the differential diagnosis based on an alleged "possibility" it causes ICH, as opposed to being based on reliable scientific evidence that it does cause ICH. *See, e.g.,* Flockhart Report at 4 ("Parlodel . . . *possible* cause of the plaintiff's stroke") (emphasis in original).

924. The Court agrees with neurologist Dr. Powers that Dr. Petro did not offer a reasonable explanation for ruling out the possibility of AVM as an alternative cause of plaintiff's stroke. *See* Powers Report at 6.

4. Dr. Petro did not offer a reasonable basis to rule out caffeine or smoking as possible alternative causes of plaintiff's ICH.

925. Dr. Flockhart states that Dr. Petro reliably ruled out caffeine as a possible cause of plaintiff's stroke because "[w]hile there is agreement that caffeine can be a vasoconstrictor, no credible evidence was presented indicating that it can cause stroke in healthy young women." Flockhart Report at 5.

926. Neither Dr. Flockhart nor Dr. Petro explain why the evidence regarding Parlodel ® and stroke is more credible than the evidence regarding caffeine and stroke.

927. Neither Dr. Flockhart nor Dr. Petro explain why alleged evidence that Par-

lodel ® possibly causes vasoconstriction is sufficient to place and keep Parlodel ® on the differential diagnosis but evidence that caffeine can be a vasoconstrictor is not sufficient to place and keep caffeine on the differential diagnosis.

928. The Court finds that Dr. Petro failed to follow faithfully or consistently the method he espouses and did not provide a reasonable explanation for ruling out caffeine as a cause of plaintiff's stroke.

929. The Court agrees with Dr. Powers that Dr. Petro dismisses the possible causative role of smoking without a reasonable explanation. *See* Powers Report at 6; Bonita, R., *et al*, "Passive Smoking as Well as Active Smoking Increases the Risk of Acute Stroke," *Tobacco Control* 8:156–60 (1999) (study found active smokers had four-fold risk of stroke compared with people who reported they never smoked; smoking found to have strong association with both ischemic and hemorrhagic stroke) (Ex. 30).

930. Dr. Flockhart fails to address the consequences or reliability of Dr. Petro's failure to provide a reasonable explanation for ruling out smoking as playing a causative role in plaintiff's stroke. *See* Flockhart Report at 5–6.

5. Dr. Petro did not offer a reasonable explanation to rule out blood abnormalities as a possible alternative cause of plaintiff's ICH

931. Dr. Flockhart states that Dr. Petro reasonably ruled out blood abnormalities. Flockhart Report at 5.

932. However, Dr. Flockhart and Dr. Petro admit that certain tests for endogenous coagulating factors which might have pre-disposed plaintiff to ICH, were not done. *Id.*

933. Dr. Flockhart states that Dr. Petro reasonably ruled out the value of such testing because there was no evidence in the medical records to suggest that plaintiff suffered from a clinically relevant coagulopathy. Flockhart Report at 5.

934. The Court finds that "reasoning" circular in that without such testing there is no evidence that all abnormalities in coagulating factors would be discovered.

935. Further, the Court finds that the fact that plaintiff was in the postpartum period and had sustained an ICH as adequate evidence in the medical records to at least suggest the possibility that plaintiff suffered from a clinically relevant coagulopathy that might have been detected had additional testing been done.

936. In any event, a consistent application of Dr. Petro's methodology placing and keeping Parlodel ® on the differential diagnosis in spite of no evidence in the medical records of vasoconstriction or ergotism, would require Dr. Petro to place and keep blood abnormality on the differential diagnosis. *See, e.g.,* Powers Report at 5.

937. Dr. Flockhart further states that it is reasonable to conclude that plaintiff did not have abnormalities in coagulating factors because "she has apparently not suffered any episodes since that would indicate this to be the case." Flockhart Report at 5.

938. However, there is no evidence that plaintiff has since been in the postpartum period, a time of known increased risk for ICH. *See* Powers Report at 5 (postpartum period is time of increased risk for stroke); Savitz Report at 5 (same).

939. The Court finds that Dr. Petro did not offer a reasonable explanation for ruling out blood abnormalities as an alternative cause of plaintiff's stroke.

6. Dr. Petro did not offer a reasonable explanation to rule out stress, hormones, or endogenous vasoconstrictors as possible alternative causes of plaintiff's ICH

940. Rule 706 expert Dr. Flockhart does not discuss why he believes Dr. Petro reliably ruled out stress, hormones, or endogenous vasoconstrictors as plausible causes of plaintiff's ICH. *See generally* Flockhart Report.

941. The Court finds that Dr. Petro has not reliably ruled out these other plausible causes of plaintiff's ICH.

W. Judicial Estoppel

942. NPC is the manufacturer of Tavist–D, a drug which contains the active ingredient PPA. Plaintiff has also claimed that NPC manufactures Contac, the drug apparently ingested by the plaintiff prior to her ICH.

943. The plaintiff asserts that because of its prior position in other cases, to-wit, *Buggs v. Novartis* and hundreds of PPA cases in the MDL Court in Seattle and in state courts throughout the country, that PPA cannot cause stroke, NPC should be judicially estopped from making any argument that Contac (PPA) or (sympathomimetic) played a role in plaintiff's stroke or that plaintiff's experts properly failed to rule out the role of Contac.

944. Plaintiff argues that NPC should not obtain the benefit of the argument that PPA is a viable alternative cause of plaintiff's ICH. Otherwise, NPC is to be rewarded by its "playing fast and loose with the courts."

945. Distilled to its essence, NPC's position is that the failure of the plaintiff's medical experts to properly rule out Contac or other amphetamine-type drugs in arriving at their differential diagnosis that Parlodel ® caused plaintiff's ICH renders their methodology or technique scientifically unreliable.

946. Additionally, NPC's position is that it has not claimed that PPA as well as other possible causes of plaintiff's stroke have been proven by scientifically reliable evidence to cause stroke, but rather because of the low threshold plaintiff's experts applied in order to place Parlodel ® on the differential diagnosis requires that these alternatives be considered and reasonably ruled out if using sufficient diagnostic technology.

947. The three medical experts appointed by the Court recognize the need for plaintiff's medical experts to rule out PPA or other amphetamine-type drugs in arriving at their differential diagnosis, and for the most part, even plaintiff's experts admit that PPA or other amphetamine-type drugs can cause stroke or in the least, can cause vasoconstriction or vasospasm.

Conclusions of Law

A. Conclusions of Law Regarding the Elements Required to Sustain a Pharmaceutical Products Liability Action Under Pennsylvania Law and Plaintiff's Burden of Proof Thereunder

[1] 1. Proof of causation is a necessary element in a products liability action. Absent a causal relationship between the defendant's product and the plaintiff's injury the defendant cannot be held liable on a theory of negligence, strict product liability, or misrepresentation. *O'Brien v. Sofamar, S.N.C.,* 1999 WL 239414 (E.D.Pa. 1999); *see also Mellon v. Barre–National Drug Co.,* 431 Pa.Super. 175, 636 A.2d 187, 191 (Pa.Super.1993), *appeal denied,* 538 Pa. 658, 648 A.2d 789 (1994).

[2–4] 2. As plaintiff's experts acknowledge, to meet her causation burden, plaintiff must first establish that Parlodel ®

is capable of causing ICH (general causation). She must then establish that, in her particular case, Parlodel ® *did in fact cause* her ICH (specific causation). *See Heller v. Shaw Indus.,* 1997 WL 535163 at *6 (E.D.Pa.1997), *aff'd,* 167 F.3d 146 (3d Cir.1999); *DeLuca v. Merrell Dow Pharm., Inc.,* 911 F.2d 941, 958 (3d Cir. 1990); *In re Consol. Parlodel ® Litig.,* 182 F.R.D. 441, 445 n. 3 (D.N.J.1998). If plaintiff has not demonstrated sufficiently reliable evidence of *general* causation, her claims fail and there is no need to consider *specific* causation. *Wade–Greaux v. Whitehall Labs.,* 874 F.Supp. 1441, 1485 (D.Vi.), *aff'd without op.,* 46 F.3d 1120 (3d Cir.1994) ("[t]o prove specific causation, plaintiff must *first* prove that the products at issue can cause [injury] and must *then* exclude other possible causes for the plaintiff's injury") (emphasis in original); *see also Merrell Dow Pharm., Inc. v. Havner,* 953 S.W.2d 706 (Tex.1997) (opinion based on "differential diagnosis" is excluded where there is no scientific basis for general causation). Plaintiff must prove medical causation to a "reasonable degree of medical certainty." *Wilson v. Wigen,* 1998 WL 199649, at *4 (E.D.Pa.1998) (setting out standard in medical malpractice action); *Watkins v. Hospital of the University of Pa.,* 1999 Pa.Super. 181, 737 A.2d 263 (1999) (same).

3. Far from constituting some type of dubious "shield," as plaintiff contends, the requirement of general causation as an aspect of a scientifically-reliable causation opinion is the very essence of *Daubert. See General Elec. Co. v. Joiner,* 522 U.S. 136, 146, 118 S.Ct. 512, 139 L.Ed.2d 508 (1997) (tenuous temporal link and lack of studies linking product to disease impermissibly left only the "*ipse dixit* of the expert" to support his conclusion). Without admissible evidence that Parlodel ® is capable of causing postpartum stroke in the first place, plaintiff's experts cannot reliably perform the differential diagnoses that they contend they have employed.

4. There are a number of cases in which summary judgment has been granted to NPC on comparable Parlodel ® claims. *See Brumbaugh v. Sandoz Pharm. Corp.,* 77 F.Supp.2d 1153, 1999 WL 1104539 (D.Mont.1999) (Att.39); *Revels v. Sandoz Pharm. Corp.,* No. 95–11076, Orders of Mar. 13 and Apr. 1, 1998 (201st Jud. Dist., Travis County, Tex.) (excluding general causation evidence in similar Parlodel ® case as "not sufficiently scientifically reliable or relevant" and granting summary judgment) (Att.40), *aff'd,* 1999 WL 644732 (Tex.App.—Austin Aug. 26, 1999) (Aboussie, C.J.), *petition for review denied.*

5. This Court agrees with *Brumbaugh:* "The issue of specific causation is material, however, only if plaintiff can demonstrate general causation between Parlodel ® and her injury." *Brumbaugh,* 77 F.Supp.2d at 1155 n. 1; *see also Revels,* at *5 ("we must hold that in the absence of a scientifically reliable basis for a conclusion regarding general causation, the trial court did not abuse its discretion by excluding expert testimony that Parlodel ® was the specific cause of Mrs. Revel's death.").

[5] 6. In a case such as this one involving complex issues of causation not readily apparent to the finder of fact, plaintiff must present admissible expert testimony to carry her burden. *See Heller v. Shaw Indus., Inc.,* 167 F.3d 146, 153 (3d Cir.1999) (expert testimony required to establish that alleged respiratory ailments were caused by carpet fumes). If her expert testimony cannot support both general and specific causation, summary judgment for the defendant must be granted.

[6] 7. Such opinions must be expressed to a reasonable degree of medical certainty. *Heller,* 167 F.3d at 153 n. 4; *In*

re: Paoli, 2000 WL 1279922 at *2 (E.D.Pa. 2000). Opinions merely expressing "possibilities" do not suffice to support the admissibility of expert testimony. *See Saldana v. Kmart Corp.,* 260 F.3d 228, 234 (3d Cir.2001) ("the mere possibility that something occurred in a particular way is not enough, as a matter of law, for a jury to find it probably happened that way"); *Booth v. Black & Decker, Inc.,* 166 F.Supp.2d 215, 222–23 (E.D.Pa.2001) (metaphysical possibility of causation insufficient to establish product liability claim); *In re: Paoli,* 2000 WL 1279922 at *5 ("possible" link between vaccine and illness "not enough to support expert testimony") (*citing Mazur v. Merck & Co.,* 742 F.Supp. 239, 265 (E.D.Pa.1990)); *In re: Paoli R.R. Yard PCB Litig.,* 2000 WL 274262 at *6 (E.D.Pa.2000) ("possible" diagnosis too speculative to satisfy Rule 702).

[7] 8. Plaintiff bears the burden of demonstrating that each of her proffered experts is qualified to render an expert opinion, that the opinion is reliable, and that the opinion would assist the trier of fact in resolving a disputed issue of material fact—here, causation. Fed.R.Evid. 702; *see, e.g., Daubert v. Merrell Dow Pharm.,* 43 F.3d 1311, 1316 (9th Cir.), *cert. denied,* 516 U.S. 869, 116 S.Ct. 189, 133 L.Ed.2d 126 (1995) (*Daubert II*).

9. In challenging plaintiff's proposed expert testimony, defendant is not required to come forward with "scientific evidence" negating plaintiff's claims. Rather, defendant is entitled to point out deficiencies in plaintiff's proof. *E.g., Celotex Corp. v. Catrett,* 477 U.S. 317, 325, 106 S.Ct. 2548, 91 L.Ed.2d 265 (1986) ("the burden on the moving party may be discharged by 'showing'—that is pointing out to the district court—that there is an absence of evidence to support the nonmoving party's case").

10. When a claimant produces insufficient competent evidence in support of an element she would be required to prove at trial, summary judgment is required. *See Celotex,* 477 U.S. at 322–23, 106 S.Ct. 2548 ("Rule 56(c) mandates the entry of summary judgment ... against a party who fails to make a showing sufficient to establish the existence of an element essential to that party's case, and on which that party will bear the burden of proof at trial"); *Estate of Zimmerman v. Southeastern Penn. Transp. Auth.,* 168 F.3d 680, 684 (3d Cir.1999) (failure of plaintiffs in personal injury case to establish triable issue of fact on any element on which they would bear burden of proof at trial, including causation, is grounds for summary judgment).

B. Standards Regarding the Review of Proposed Expert Testimony Under Fed.R.Evid. 702, *Daubert, Kumho Tire,* and Court of Appeals for the Third Circuit Jurisprudence

11. Federal Rule of Evidence 702 states:

> If scientific, technical, or other specialized knowledge will assist the trier of fact to understand the evidence or to determine a fact in issue, a witness qualified as an expert by knowledge, skill, experience, training, or education, may testify thereto in the form of an opinion or otherwise, if (1) the testimony is based upon sufficient facts or data, (2) the testimony is the product of reliable principles and methods, and (3) the witness has applied the principles and methods reliably to the facts of the case.

[8] 12. Under *Daubert v. Merrell Dow Pharmaceuticals, Inc.,* 509 U.S. 579, 113 S.Ct. 2786, 125 L.Ed.2d 469 (1993), a two-step analysis is used to assess the admissibility of the proffered expert testimony on scientific issues under Rule 702.

First, the expert testimony must be reliable, so that it must be "scientific," meaning grounded in the methods and procedures of science, and must constitute "knowledge," meaning something more than subjective belief or unsupported speculation. *Daubert,* 509 U.S. at 590, 113 S.Ct. 2786.

[9] 13. Guideposts that the Court may consider in assessing the reliability of the proffered expert testimony include, but are not limited to: (1) whether the expert's methodology has been tested or is capable of being tested; (2) whether the technique has been subjected to peer review and publication; (3) the known and potential error rate of the methodology; and (4) whether the technique has been generally accepted in the proper scientific community. *See Daubert,* 509 U.S. at 593–94, 113 S.Ct. 2786; *In re TMI Litig.,* 193 F.3d 613, 663–64 (3d Cir.1999); *Heller,* 167 F.3d at 152. In addition, other non-exclusive factors that the Court may consider are the (1) existence and maintenance of standards controlling the methodology's operation; (2) relationship of the technique to methods that have been established to be reliable; (3) expert witness' qualifications; and (4) nonjudicial uses to which the method has been put. *Paoli II,* 35 F.3d at 742 n. 8.

[10] 14. In addition, *Daubert* requires an appropriate "fit" with respect to the offered opinion and the facts of the case. *See Daubert,* 509 U.S. at 591, 113 S.Ct. 2786. The "fit" requirement stems from the instruction of Federal Rule of Evidence 702 that proffered expert testimony must "assist... the trier of fact." Under *Daubert,* scientific testimony does not assist the trier of fact unless the testimony has a *valid scientific connection* to the pertinent inquiry. *See Daubert,* 509 U.S. at 591, 113 S.Ct. 2786; *Heller,* 167 F.3d at 152; *Paoli II,* 35 F.3d at 742–43. For example, there is no fit where there is "simply too great an analytical gap between the data and the opinion offered," as when an expert offers animal studies showing one type of cancer in mice to establish causation of another type of cancer in humans. *General Electric Co. v. Joiner,* 522 U.S. 136, 118 S.Ct. 512, 139 L.Ed.2d 508 (1997); *See Heller,* 167 F.3d at 156 ("[a] court may conclude that there is simply too great an analytical gap" (citing *Joiner*)).

15. This Court is thus required to act as a gatekeeper "to make certain that an expert, whether basing testimony upon professional studies or personal experience, employs in the courtroom the practice of an expert in the relevant field." *Kumho Tire Co. v. Carmichael,* 526 U.S. 137, 152, 119 S.Ct. 1167, 143 L.Ed.2d 238 (1999).

16. When an expert's testimony "relies in part on his own *ipse dixit,* rather than on something more readily verifiable ... it is open to attack." *In re TMI Litig.,* 193 F.3d at 687. "[S]omething doesn't become 'scientific knowledge' just because it's uttered by a scientist; nor can an expert's self-serving assertion that his conclusions were 'derived by the scientific method' be deemed conclusive." *Id.* (*quoting Daubert II,* 43 F.3d at 1315–16).

[11] 17. Expert opinions generated as the result of litigation have less credibility than opinions generated as the result of academic research or other forms of "pure" research. *E.g., Daubert,* 509 U.S. at 593, 113 S.Ct. 2786 (one factor to consider is whether opinion was generated to further litigation or was subject to peer review); *Wade–Greaux,* 874 F.Supp. at 1465, 1476 (witness educated as a pediatrician, pharmacologist, and toxicologist unqualified to testify regarding the cause of birth defects because he had merely re-

viewed, for purposes of litigation, selected literature on that subject); *see also National Bank of Commerce v. Dow Chem. Co.,* 965 F.Supp. 1490, 1516 (E.D.Ark.1996) ("[T]he expert's motivation for his/her study and research is important.... [W]e may not ignore the fact that a scientist's normal work place is the lab or field, not the courtroom or the lawyer's office.") (*quoting Daubert*) (internal quotations omitted).

18. The Court has "considerable leeway in deciding in a particular case how to go about determining whether particular expert testimony is reliable," *Kumho Tire,* 526 U.S. at 152, 119 S.Ct. 1167, but the Court's discretion in choosing the manner of testing expert reliability "is not discretion to abandon the gatekeeping function." *Id.* at 158, 119 S.Ct. 1167 (Scalia, J., concurring).

[12] 19. In this Circuit, it is appropriate for the Court to conduct an evidentiary hearing to determine whether plaintiff's experts' reasoning or methodology is admissible under the standards of *Daubert v. Merrell Dow Pharm.,* 509 U.S. 579, 592, 113 S.Ct. 2786, 125 L.Ed.2d 469 (1993); *In re TMI Litig.,* 199 F.3d 158, 159 (3d Cir. 2000) (citations omitted).

20. While the Court has engaged in its own independent analysis regarding the admissibility of plaintiff's experts' testimony and is not suggesting that the conclusions of the Rule 706 experts or the body of existing case law excluding nearly identical or similar testimony precluded its admissibility here, the consistency of this Court's findings and conclusions with those of the majority of the Rule 706 experts and a number of other federal courts suggests that this Court is "not operating on the outer fringe of its discretion" in concluding as it does that the testimony is inadmissible. *See, e.g., Allison v. McGhan Med. Corp.,* 184 F.3d 1300, 1311 (11th Cir.1999).

21. As will be discussed in greater detail below, this Court agrees with the conclusions of Dr. Powers, Dr. Savitz, and the other federal courts holding that expert testimony such as that proffered in this case is inadmissible because, *inter alia:*

a. The body of scientific evidence relating to Parlodel ® and stroke is simply insufficient to support a scientifically reliable application of plaintiff's experts' methodology.

b. Plaintiff's experts did not demonstrate general causation (*i.e.,* that Parlodel ® can cause ICH) through application of a reliable methodology, and thus, did not reliably "rule in" Parlodel ® as a cause of ICH for purposes of their differential diagnoses.

c. Specifically, plaintiff's experts offered no human studies reliably demonstrating that Parlodel ® causes vasoconstriction or ICH, or adequately separating the risk of stroke related to Parlodel ® from the risk of stroke related to the postpartum period.

d. Plaintiff's experts offered no animal studies reliably demonstrating that Parlodel ® causes vasoconstriction in humans, and could not point to a single animal study concluding that Parlodel ® causes ICH in animals or humans.

e. Plaintiff's experts offered no indirect evidence of sufficient amount, specificity, and reliability to overcome the lack of direct evidence of causation.

f. Without sufficient reliable evidence of general causation, plaintiff's experts could not reliably apply a differential diagnosis that comports with the scientific method, notwithstanding the fact that physicians in clinical practice may be required to proceed with a differential diagnosis on the basis of guesses or hypotheses due to the exi-

gency of the need to treat their patients.

g. Even if plaintiff's experts had reliably "ruled in" Parlodel ® for the purposes of their differential diagnoses, their failure to reliably "rule out" possible causes of plaintiff's ICH that a consistent application of their methodology would require be placed on the differential diagnosis, renders their methodology unreliable.

See generally Powers Reports; Savitz Report; *Glastetter v. Novartis Pharm. Corp.,* 252 F.3d 986 (8th Cir.2001); *Glastetter v. Novartis Pharm. Corp.,* 107 F.Supp.2d 1015 (E.D.Mo.2000); *Caraker v. Sandoz Pharm. Corp.,* 172 F.Supp.2d 1046; *Siharath v. Sandoz Pharm. Corp.,* 131 F.Supp.2d 1347 (N.D.Ga.2001); *Hollander v. Sandoz Pharm. Corp.,* 95 F.Supp.2d 1230 (W.D.Okla.2000) *aff'd. in all respects,* 289 F.3d 1193 (10th Cir.2002); *Brumbaugh,* 77 F.Supp.2d 1153. The Court concludes that the methodology and conclusions in Dr. Flockhart's report, which speak in terms of "possibilities" and speculation, represent too significant a departure from the Court of Appeals for the Third Circuit *Daubert* standards to be reliable and suffer from the same methodological flaws as those of plaintiff's experts.

C. The Court of Appeals for the Third Circuit Guidance in *In re TMI Litigation,* 193 F.3d 613 (3d Cir.1999)

22. The Court of Appeals for the Third Circuit has given guidance concerning the appropriate application of *Daubert* and *Paoli II,* in a toxic tort case. In *In re TMI Litigation,* 193 F.3d 613 (3d Cir. 1999), the Court of Appeals for the Third Circuit affirmed the district court's grant of summary judgment for defendants as to ten named plaintiffs who had alleged that exposure to high levels of ionizing radiation emanating from the TMI accident caused various forms of cancer.

23. *In re TMI Litigation* confirms the importance of testing of hypotheses as a critical aspect of the application of the scientific method. In the instant case, NPC contends that plaintiff's experts have failed to demonstrate that their causal hypotheses have ever been tested. For example, the general causation hypothesis (*i.e.,* Parlodel ® can cause postpartum stroke) is one that can be tested by an epidemiologic study, but no such study shows a statistically-significant increased risk of postpartum stroke in women using Parlodel ®. Likewise, the general causation hypothesis that bromocriptine can cause cerebral vasoconstriction is one that can be tested by controlled animal and human studies, but no such study shows bromocriptine to have that effect.

24. The Court of Appeals for the Third Circuit in *In re TMI Litigation* affirmed exclusion of the testimony of exposure experts by noting that their "hypothesis is testable, and it was in fact tested. However, the results of that testing undermined [the] conclusions." *Id.* at 675. In particular, one of plaintiffs' experts sent soil to a laboratory in a failed attempt to identify specific radionuclides that could be attributed to the TMI nuclear facility. Rather, these tests showed only "ubiquitous" radionuclides. In affirming the district court's exclusion of the opinions of this expert, the Court of Appeals for the Third Circuit commented:

> [The expert] did not modify his hypothesis as a result of the ... findings.... ***Daubert* recognized that science is "an empirical endeavor in which testing plays a crucial role."** REFERENCE MANUAL ON SCIENTIFIC EVIDENCE, at 71. Indeed, a "key question to be answered in determining whether a theory ... is scientific knowledge that will assist the trier of fact [is] whether it can (and has been) tested."

Id. at 675 (emphasis added). The failure of plaintiffs' experts to modify their opinions in light of the negative testing "undermined" their hypothesis. *Id.* at 676. The Court of Appeals for the Third Circuit deemed their approach "the antithesis of good science." *Id.*

25. Similarly, the importance of testing—or the lack of testing—underlay the Court of Appeals for the Third Circuit's affirmance of the exclusion of another expert, whose methodology was deemed subjective. The Court of Appeals for the Third Circuit commented that "significantly, **it is impossible to test a hypothesis generated by a subjective methodology** because the only person capable of testing or falsifying the hypothesis is the creator of the methodology." *Id.* at 704 n. 144 (emphasis added).

26. *In re TMI Litigation* also provides important guidance concerning how this Court should evaluate the assumptions made by plaintiff's experts. For example, the testimony of Drs. Petro and Kulig was based in part on their review of various animal studies in which bromocriptine was tested and in which certain allegedly vasoconstrictive phenomena (*e.g.,* necrosis of the tips of dog ears, necrosis of the tips of rat tails, arterial constriction in the hind limb of a dog) were observed. NPC demonstrated—and Dr. Petro admitted—that the doses administered to these animals were hundreds and thousands of times higher than would obtain in a woman using Parlodel ® for the prevention of lactation. (Indeed, Dr. Engelman's unopposed testimony was that a woman would need to consume 5,000 Parlodel ® pills at once to obtain the same doses that existed in the "hand vein study." 11/16 Tr. at 154–55 (Engelman).) Although plaintiff's experts did not explain clearly why such studies were relevant to the present case, such relevance, if it exists, must be premised on the assumption that, if bromocriptine can cause a vasoconstrictive effect on any part of the body, at any dose, bromocriptine must therefore be capable of causing cerebral vasoconstriction in a woman using Parlodel ® for the prevention of lactation, even if the dose is thousands of times lower. *In re TMI Litigation* cautions us that an assumption must be "sufficiently grounded in sound methodology, and reasoning to allow the conclusion it supports to clear the reliability hurdle. Assumption-based conclusions that do not meet that test can hardly be relied upon as 'good science.' " *Id.* at 677.

27. One of the critical issues in this case, to which *In re TMI Litigation.* is most relevant, is the issue of specific causation. The Court of Appeals for the Third Circuit noted that, even where general causation has been established ("there is a scientific consensus that ionizing radiation *can cause* cancer," *In re TMI Litig.,* 193 F.3d at 643) (emphasis added), "[m]edical examinations and laboratory tests . . . rarely (if ever) provide definite information as to" specific causation. *Id.* The inability of examinations and tests to determine specific causation results from the fact that "ionizing radiation . . . [does not] leave a tell-tale marker in those cells which subsequently become malignant." *Id.* Similarly, plaintiff in this case has not advanced the hypothesis that the cause of her ICH can be determined by any "tell-tale marker" in her brain or blood cells.

28. The Court of Appeals for the Third Circuit went on to note that "the task of establishing causation is greatly complicated by the reality that a given percentage of a defined population will contract cancer even absent any exposure to ionizing radiation." *Id.* at 643–44. In the instant case, it is undisputed that stroke, including ICH, occurs in the background population even

absent any exposure to Parlodel ® or other drugs.

[13] 29. In this case, the timing of plaintiff's last ingestion of Parlodel ® is a critical step in plaintiff's experts' path toward specific causation. Had plaintiff taken her Parlodel ® prescription as prescribed, she would have finished it on or about January 10, 1990, *i.e.,* eight days prior to her stroke. 11/9 Tr. at 146 (Kulig). In order to posit Parlodel ® as an even potential cause of plaintiff's stroke, plaintiff's experts assume that she took her last dose on the day of or the day before her stroke. *See id.* at 72–73 (Kulig).[6] The sole evidence in this case to indicate when plaintiff last took Parlodel ®, however, is plaintiff's own deposition testimony. Plaintiff admits that her memory has been affected by her ICH. In other words, there is no blood test of bromocriptine levels; there is no testimony of a neutral third-party witness; there is no indication on plaintiff's emergency room admission records, etc., that she had recently taken Parlodel ®. The Court of Appeals for the Third Circuit in *In re TMI Litigation* instructs that "a physician who evaluates a patient in preparation for litigation should seek more than a patient's self-report of symptoms or illness . . . ." 193 F.3d at 698 (*quoting Paoli II,* 35 F.3d at 762). Likewise, a physician opining on specific causation must have more than the patient's self-report on her last ingestion of the drug in question, where the timing of that last ingestion is critical to specific causation and, had the patient taken the drug as directed, the drug would no longer qualify as a suspect cause.

30. Another aspect of *In re TMI Litigation* that bears on the opinion testimony of plaintiff's experts addresses the alleged application of "causal criteria." *In re TMI Litig.,* 193 F.3d at 702. Plaintiff's experts here rely heavily on so called "causality assessments" performed by a Swiss affiliate of NPC. These "causality assessments" were based on the checking-off of listed criteria in a form completed for regulatory purposes by unidentified personnel at Sandoz Ltd.'s DMC. These forms, in turn, were supposedly based on the "Karch–Lasagna criteria." The Court of Appeals for the Third Circuit in *In re TMI Litigation* faced a similar proffer of evidence, *i.e.,* the opinions of Dr. Molholt based on his application of comparable criteria. Even though Dr. Molholt had testified at length in the district court, the Court confessed that it was "at a loss to determine how [he] scored each parameter to arrive at his causation conclusion." 193 F.3d at 703. The Court concluded that "the methodology . . . used to score and weight [these] parameters to determine causation is purely subjective." *Id.* The Court stated:

> obviously [the methodology] does not satisfy a number of the *Daubert* factors. It was never peer reviewed, there is no known or potential rate of error, there are no discernable standards governing its operation, and it is not generally accepted.

Id. n. 144 (*citing Daubert,* 509 U.S. at 593–94, 113 S.Ct. 2786). Likewise, plaintiff's experts here have not established that the DMC "causality assessments" have ever been peer reviewed; nor have plaintiff's experts established their known or potential rate of error; nor standards governing

6. As *Heller v. Shaw Industries* shows, a failure to establish a "valid and strong temporal relationship" between the alleged toxic exposure and the adverse event in question constitutes sufficient reason to exclude a plaintiff's expert testimony on specific causation. 167 F.3d at 154. *See also id.* at 158 ("the temporal relationship between the exposure . . . and the onset of . . . illness was questionable at best and exculpatory at worst").

their operation; nor that these criteria are generally accepted for the purposes of establishing causation. Similarly, as with the "Karch–Lasagna criteria," plaintiff's experts here have not established their known or potential rate of error; nor standards governing their operation; nor that these criteria are generally accepted for the purposes proposed by plaintiff's experts.

31. Notwithstanding *In re TMI Litig.,* as well as *DeLuca* and *In re Consolidated Parlodel® Litigation,* plaintiff has cited the Court of Appeals for the Third Circuit's opinion in *Heller* for the proposition that (a) a temporal relationship between ingestion of a drug and an adverse event and (b) a subsequent differential diagnosis attributing causation to that drug are sufficient, in and of themselves, to establish medical causation. Plaintiff's experts' testimony on the scientific method does not support this notion, and *Heller* does not so hold, in any event. *Heller* holds only that general causation need not always be established by "definitive published studies." *See* 167 F.3d at 154. *See also id.* at 155 ("we do not read the Supreme Court as requiring a medical expert to always rely on *published studies* indicating the exposure necessary to cause a particular illness" (emphasis added)). Thus, in considering the question of general causation, the Court does not require plaintiff to demonstrate the existence of *published* studies as a *sine qua non* for proving that bromocriptine can cause ICH. Nevertheless, plaintiff's proposed evidence of general medical causation—published or unpublished—must still meet the reliability and "fit" tests of Rule 702 and *Daubert.*

D. Conclusions of Law Regarding Plaintiff's Proposed Use of Epidemiologic Evidence

32. Epidemiology is "the primary generally accepted methodology for demonstrating a causal relation between a chemical compound and a set of symptoms or a disease." *Conde v. Velsicol Chem. Corp.,* 804 F.Supp. 972, 1025–26 (S.D.Ohio 1992), *aff'd,* 24 F.3d 809 (6th Cir.1994), *cited in* Federal Judicial Center, REFERENCE MANUAL FOR SCIENTIFIC EVIDENCE ("MANUAL") at 126 n. 10, *see also e.g. Allen v. Pennsylvania Eng'g Corp.,* 102 F.3d 194, 197 (5th Cir.1996) (where no epidemiologic study has found a statistically-significant link between the product and the alleged injury, expert testimony of an association does not meet the standard of reliability required under *Daubert*); *Turpin v. Merrell Dow Pharm., Inc.,* 959 F.2d 1349, 1351–56, 1360 (6th Cir.1992) (affirming grant of summary judgment for defendants because the evidence relied upon by plaintiffs, which did not include epidemiologic studies, was insufficient basis for opinion on causation), *cert. denied,* 506 U.S. 826, 113 S.Ct. 84, 121 L.Ed.2d 47 (1992); *see generally In re Breast Implant Litig.,* 11 F.Supp.2d 1217, 1224 (D.Colo.1998) (collecting cases standing for the proposition that epidemiologic studies are the best evidence of causation).[7]

7. *See also, e.g., Allison v. McGhan Med. Corp.,* 184 F.3d 1300, 1316 (11th Cir.1999) (excluding plaintiff's proffered epidemiologic studies; "proffered conclusions in studies with questionable methodologies were out of sync with the conclusions in the overwhelming majority of the epidemiological studies presented to the court"); *Raynor v. Merrell Pharm., Inc.,* 104 F.3d 1371, 1375–76 (D.C.Cir.1997) (affirming j.n.o.v. and exclusion of plaintiff's experts' testimony because, among other reasons, experts' conclusions regarding causation were directly contradicted by the significant body of epidemiologic data); *Richardson v. Richardson–Merrell, Inc.,* 857 F.2d 823, 831 n. 59 & 832 (D.C.Cir. 1988) (affirming j.n.o.v. for defendant drug manufacturer because none of the great

33. Courts have emphasized that epidemiologic proof must be statistically significant. *E.g., DeLuca v. Merrell Dow Pharm., Inc.,* 791 F.Supp. 1042, 1048–50, 1058–59 (D.N.J.1992) (rejecting plaintiff's experts' "reanalysis" of epidemiologic studies where original investigators found no statistically-significant association between Bendectin and birth defects), *aff'd, without op.,* 6 F.3d 778 (3d Cir.1993), *cert. denied,* (1994); *Wade–Greaux v. Whitehall Labs., Inc.,* 874 F.Supp. 1441, 1485 (D.Vi.) (opinions excluded because none of the studies showed a statistically-significant increased risk of the relevant injury due to exposure to the drug at issue), *aff'd without op.,* 46 F.3d 1120 (3d Cir.1994); *see also, e.g., Daubert II,* 43 F.3d at 1316 ("*Daubert II* "), *cert. denied,* (rejecting plaintiffs' expert testimony as inadmissible under *Daubert,* noting that none of plaintiffs' experts could testify that the epidemiologic data showed a relative risk of greater than two, and that relative risk of less than two actually tended to disprove legal causation); *Brock v. Merrell Dow Pharm., Inc.,* 884 F.2d 166, 167 (5th Cir.1989) (plaintiff's failure to present statistically-significant epidemiologic proof of causation required dismissal).

34. The very purpose of epidemiology is to serve the type of testing function required by *Daubert, i.e.,* to discern accurately the effect of a particular agent on a disease against the background of the natural occurrence of the disease in the relevant population. Stated otherwise, epidemiology is the scientific methodology that allows testing of the hypothesis that Substance A causes Effect B. *See* MANUAL, at 125–26.

35. The need for statistically-significant epidemiology is particularly acute in the instant case. Plaintiff's experts did not rebut the showing by NPC that stroke occurs in the general population. Nor did they rebut the showing by NPC that postpartum stroke in particular has been known to occur in medical history since ancient times and that there are various estimates of the incidence of postpartum stroke in the general population going back long before the invention of Parlodel®. Therefore, to determine whether any given case of postpartum stroke could possibly be attributable to a particular drug, epidemiology would be the favored methodology for scientifically testing the hypothesis that use of the drug increases the risk of postpartum stroke.

36. This Court is persuaded by the reasoning of the Court in *Brumbaugh v. Sandoz,* wherein that Court analyzed plaintiff's use of epidemiology in a Parlodel® case:

> Defendant points to five studies (two of them epidemiological studies, which study the causal relationship between an agent and disease) which show no statistically significant relationship between Parlodel® and seizure . . .
>
> . . .
>
> . . . None of the five studies cited by defendant and designed to analyze the causal relationship between Parlodel® and hypertension, stroke, and seizure supports Dr. Iffy's theory that Parlodel® generally causes seizure. The plaintiff criticizes certain aspects of these studies, but **she produced no epidemiological study, or other reliable scientific proof that does make the causal link between Parlodel® and**

wealth of epidemiologic data found a statistically-significant relationship; and [i]n mass tort cases . . . epidemiological studies are of critical significance"); *Haggerty v. Upjohn Co.,* 950 F.Supp. 1160, 1165 (S.D.Fla.1996) ("Epidemiological studies [or the lack thereof] . . . are an important factor in determining the admissibility of an expert's opinion on causation."), *aff'd without op.,* 158 F.3d 588 (11th Cir.1998).

her condition, or any related condition. Plaintiff's lawyers['] attack on defendant's studies does not meet the law's requirements. She must come forward with reliable scientific evidence of her own to defeat a summary judgment motion when her case is based on the expert's proof.

. . .[Plaintiff] is left with anecdotal reports and an untested theory as evidence of causation. **Correlation of two events in time does not necessarily establish causation. That is why anecdotal reports are not generally accepted as reliable scientific evidence to establish causation. Further, Dr. Iffy's opinions have not been analyzed with the safeguards of a controlled experiment to see if his causal mechanism theory is valid**. . . . While *Daubert* does not require absolute precision in identifying the medical mechanism of injury, there still must be "sufficiently compelling proof that the agent must have caused the damage somehow." *Kennedy [v. Collagen Corp.,* 161 F.3d 1226], 1230 [9th Cir.1998], *cert. denied,* 526 U.S. 1099, 119 S.Ct. 1577, 143 L.Ed.2d 672 (1999) , quoting *Daubert* on remand, 43 F.3d 1311, 1314 (9th Cir. 1995). No such proof was advanced in this case.

Brumbaugh, 77 F.Supp.2d at 1155–57 (distinguishing *Kennedy v. Collagen Corp.,* 161 F.3d 1226 (9th Cir.1998), *cert. denied,* 526 U.S. 1099, 119 S.Ct. 1577, 143 L.Ed.2d 672 (1999), relied upon by plaintiff in this case as well) (Att.39).

[14] 37. The Court concludes that plaintiff's experts' hypothesis about medical causation is not scientifically reliable because it is not based on statistically-significant epidemiologic studies—published or unpublished—that show that the use of Parlodel ® increases the risk of postpartum ICH or postpartum stroke of any kind.

38. Plaintiff contends that the Court should discount or distinguish those *Daubert* cases, including *Daubert* itself, in which there were allegedly a substantial number of *negative* epidemiologic studies. It is not a defendant's burden to disprove causation, however, nor is it a defendant's burden to prove that a plaintiff's expert testimony is unreliable. Rather, it remains plaintiff's burden to show that her experts' opinions *are* scientifically reliable and otherwise admissible under Rule 702 and other rules. Accordingly, in none of the cited cases did the courts granting summary judgment to defendants do so simply on the basis of an accumulation of negative epidemiologic studies.

39. The one epidemiologic study upon which plaintiff's experts purport to rely, the ERI study, admittedly shows no statistically-significant association between Parlodel ® and postpartum stroke. The situation is akin to that in *General Electric Company v. Joiner,* 522 U.S. 136, 118 S.Ct. 512, 139 L.Ed.2d 508 (1997), where the plaintiff's experts based their opinions in part on two epidemiologic studies that showed a relative risk for cancer due to exposure to PCBs somewhat higher than the background rate, but without statistical significance. The authors of the studies concluded that they thus failed to establish a causal link between PCBs and cancer. The Supreme Court upheld the district court's exclusion of expert opinions based in part upon this uninformative epidemiologic evidence, because use of the data was contrary to the conclusions of the studies themselves. *Id.*

40. The Court concludes that the ERI study upon which plaintiff's experts rely is uninformative on the issue of whether Parlodel ® causes any form of postpartum stroke.

41. Negative epidemiologic studies, to the extent they reflect failed attempts to show that there *is* in fact a statistically-significant association between a particular drug and a particular adverse outcome, may provide useful background information. In this regard, the Court concludes that four studies looking at the possible association between Parlodel ® and postpartum stroke in human beings have all failed to find any such statistically-significant relationship. The ERI study has already been discussed. The other three studies are discussed below.

42. The HCIA Study—whether properly deemed an "epidemiologic" study or not—is a study allowing the calculation of relative risks and confidence intervals. It involved hundreds of thousands of deliveries in which the postpartum experience of women who were prescribed Parlodel ® for PPL was compared to the postpartum experience of women who were not prescribed Parlodel ®. No statistically-significant difference was observed between the experiences of the two groups. Accordingly, the HCIA Study is a negative "human" study; it shows no association between the use of Parlodel ® and postpartum stroke.

43. The Herings and Stricker study—whether or not properly characterized as an "epidemiologic" study—is another human study that attempted to determine if there was an association between use of Parlodel ® and postpartum stroke. No such association could be established. Although this is a small study, it is nevertheless a study published in the medical literature and is negative.

44. Another study forming part of the background of the Court's analysis of this case is the Witlin–Sibai Study. The Witlin–Sibai Study was accepted in writing for publication by the American Journal of Obstetrics and Gynecology, following a peer-review process, on August 3, 1999. 11/17 Tr. at 62–63 (Green). Additionally, the abstract of that study was in fact published earlier in the Proceedings of the Society for Gynecological Investigation. *Id.* at 62 (Green). The Witlin–Sibai Study calculated a statistically-significant Odds Ratio of 0.12, for postpartum stroke in users of Parlodel ®. An Odds Ratio of 1.0 would mean that Parlodel ® had no effect—positive or negative—on the risk of postpartum stroke. The calculated Odds Ratio of 0.12 in the Witlin–Sibai Study means that women in the study appeared to be eight times *less* likely to have postpartum stroke when using Parlodel ® compared to when not using Parlodel ®. Stated otherwise, the calculated Odds Ratio in the Witlin–Sibai Study suggests that Parlodel ® has a strong protective effect against postpartum stroke.

45. The Court recognizes that the Witlin–Sibai Study was subsequently rejected by the American Journal of Obstetrics and Gynecology. The unchallenged testimony of Dr. Green in this regard is that she obtained information from Dr. Witlin that plaintiff's attorneys "wrote to the journal editor ... [and] that the journal editor then knuckled under." 11/17 Tr. at 73 (Green). Whether or not Dr. Witlin's version of what happened is true—plaintiff did not present a contrary version—the Court's conclusions as set forth in this opinion would be the same. Moreover, even if the Witlin–Sibai Study had not been presented to the Court, the Court's conclusions in this case would be the same. Nonetheless, the Court comments on the Witlin–Sibai Study because it constitutes a strong piece of evidence undercutting plaintiff's allegations concerning general causation.

[15] 46. With specific reference to the ERI study—the only epidemiology study upon which plaintiff's experts purport to rely—the Court concludes that, even if

evidence of a non-statistically-significant epidemiologic study could be reliable and relevant under Rule 702, the probative value of such evidence would be substantially outweighed by its unfair prejudicial effect, its tendency to confuse and mislead the jury, and its waste of precious judicial time. Thus, reference to, and reliance upon, the ERI study must be excluded under Rule 403: "[e]vidence may be excluded if its probative value is substantially outweighed by the danger of unfair prejudice, confusion of the issues, or misleading the jury, or by considerations of . . . waste of time." Fed.R.Evid. 403. *See Brumbaugh,* 77 F.Supp.2d at 1157 ("[h]ere, the limited probative worth of Dr. Iffy's testimony is outweighed by the substantial probability of misleading the jury so the evidence is inadmissible pursuant to Fed.R. Evid. 403"); *Daubert II,* 43 F.3d at 1321 n. 17; *see also id.* at 1315 ("were we to conclude that the expert testimony is not per se inadmissible, the district court on remand would nevertheless have discretion to reject it under Rule 403 or 702"); *Allison,* 184 F.3d at 1310 ("Rule 403, working in conjunction with Rules 702 and 703, . . . giv[es] courts discretion to preclude expert testimony unless it passes more stringent standards of reliability and relevance . . . because of the potential impact on the jury of expert testimony. While the district court did not expressly exclude any testimony on the basis of Rule 403, we note that its consideration would only serve to buttress the court's ultimate exclusion of the proffered experts.") "The waste-of-time ground for exclusion is particularly persuasive when detailed rebuttal testimony would be necessary to establish that the proffered evidence lacks probative worth." *In re Agent Orange Prod. Liab. Litig.,* 611 F.Supp. 1223, 1256 (E.D.N.Y. 1985), *aff'd,* 818 F.2d 187 (2d Cir.1987). In addition, such evidence would undoubtedly tend to confuse the issues and mislead the jury, and NPC would be unfairly prejudiced. Therefore, even if relevant, the evidence of non-statistically-significant epidemiologic studies must be excluded.

47. This does not mean that conclusive published epidemiologic studies are required in every case alleging cause and effect. In this case, however, other types of evidence upon which plaintiff might reasonably rely are equally absent. For example, as noted above, the *unpublished* human studies do not support plaintiff's experts' hypotheses. Further, plaintiff's experts admit that they do not understand and certainly have not articulated the purported mechanism by which bromocriptine allegedly causes the adverse effect at issue, *i.e.,* alleged cerebral vasoconstriction. Additionally, there is no animal evidence that even purports to show that bromocriptine (a) causes ICH; (b) causes any type of stroke; (c) causes generalized hypertension or vasoconstriction in intact animals; or (d) causes even peripheral vasoconstriction at doses relevant to therapeutic uses of Parlodel®. In these circumstances, epidemiologic evidence is even more important if a plaintiff is to make out a *prima facie* showing that her experts' medical causation opinions are scientifically reliable and more than speculation. *See* MANUAL at 125.

48. The Court also concludes that plaintiff's experts present a moving target regarding the requirement of epidemiologic evidence to justify placing and keeping something on a differential diagnosis as a possible cause of stroke. Despite their agreement that epidemiology is the best methodology for demonstrating that a particular drug causes a particular event, *see, e.g. Siharath,* 131 F.Supp.2d at 1357, plaintiff's experts disavow the need for epidemiologic evidence to place and keep Parlodel® on the differential diagnosis. More importantly, when confronted with other

potential alternative causes of stroke, plaintiff's experts demand solid epidemiologic evidence in the form of multiple studies before agreeing that something can be placed and kept on the differential. Such inherent inconsistency itself renders plaintiff's experts' methodology unreliable, regardless of the weight the case law generally affords epidemiology in evaluating general causation.

E. Conclusions of Law Regarding Plaintiff's Experts' Reliance on Anecdotal Case Reports

49. Plaintiff's experts rely heavily on anecdotal case reports to support their opinions on general causation. The Court of Appeals for the Third Circuit has cautioned against reliance upon information that is "purely anecdotal." *In re TMI Litig.,* 193 F.3d at 673 (affirming exclusion of expert testimony based on information that was "purely anecdotal"). Accordingly, with this caution in mind, the Court reviews the case law concerning the use of anecdotal case reports as support for general causation opinions and concludes that expert opinion based on ADEs and anecdotal case reports is not admissible, at least in the circumstances of this case, under Rules 702 and 703 of the Federal Rules of Evidence.

50. The Federal Rules of Evidence allow experts to testify only to "scientific... knowledge [to] assist the trier of fact to understand the evidence or to determine a fact in issue," Fed.R.Evid. 702, and further require that the "facts or data ... upon which an expert bases an opinion or inference ... [are] of a type reasonably relied upon by experts in the particular field in forming opinions or inferences upon the subject," Fed.R.Evid. 703. As explained by the Supreme Court in *Daubert,* the fundamental principle underlying the rules is that juries should not be asked to render decisions on scientific issues unless provided with evidence that is scientifically reliable or, in other words, is "based upon scientific validity." 509 U.S. at 590 n. 9, 113 S.Ct. 2786; *see also e.g.,* Fed.R.Evid. 702, 703. As demonstrated below, the great weight of authority—and the most current authority—squarely rejects the use of ADEs and case reports for the purpose of establishing general causation.

51. The Court notes at the outset that the case reports relied upon by plaintiff's experts do not themselves attribute causation to Parlodel ®, instead speaking only in terms of possibilities and uncertainties. Accordingly, because the case reports themselves say that causation has not been proven, reliance on the case reports is *per se* unscientific. *See, e.g., Reynard v. NEC Corp.,* 887 F.Supp. 1500, 1505 (M.D.Fla. 1995) (rejecting causation testimony where articles on which expert relied stated that hypothesis was uncertain).

52. More importantly, this Court is persuaded by the reasoning of the *Brumbaugh* Court, a Parlodel ® case in which the Court excluded a proffered expert opinion based in part upon ADEs and anecdotal case reports:

> Adverse drug events (ADEs) are temporal associations between a drug's administration and an unexpected physical reaction. In this case, Dr. Iffy admits that ADEs do not demonstrate a causal link but instead represent coincidence. Case reports and ADEs are compilations of occurrences, and have been rejected as reliable scientific evidence supporting expert opinion so as to meet the requirements set forth in *Daubert. Jones v. United States,* 933 F.Supp. 894, 899 (N.D.Cal.1996), *aff'd,* 127 F.3d 1154 (9th Cir.1997), *cert. denied* 524 U.S. 946, 118 S.Ct. 2359, 141 L.Ed.2d 728 (1998) (anecdotal case reports are not derived through the scientific method and "fall

short of the proven, cause and effect relationship that is necessary to satisfy the *Daubert* standard."). *See also Sanderson v. International Flavors,* 950 F.Supp. 981, 1000 (C.D.Cal.1996) (holding that temporal coincidence is not a "valid scientific connection" to satisfy *Daubert*); *Casey v. Ohio Medical Products,* 877 F.Supp. 1380, 1385–86 (N.D.Cal.1995) (case reports are not reliable scientific evidence of causation and not sufficiently based on scientific reliability and methodology to be admitted into evidence under Fed.R.Evid. 702 and 703).

Neither case reports nor adverse drug reaction reports contain scientific analysis with the safeguards of a controlled experiment. Their most significant analytical defect is that they don't isolate and investigate the effects of alternative causation agents. They are compilations of reported phenomena. Unlike epidemiological studies, they do not contain a testable and systemic inquiry into the mechanism of causation. As such, they reflect reported data, not scientific methodology. The *Daubert* court noted this phenomenon was the distinguishing characteristic of scientific evidence. *Daubert,* 509 U.S. at 593, 113 S.Ct. 2786, 125 L.Ed.2d 469.

Brumbaugh, 77 F.Supp.2d at 1156.

53. This Court also is persuaded by the reasoning of another Parlodel ® decision, *Revels v. Novartis Pharmaceuticals Corp.,* 1999 WL 644732, No. 03–98–00231–CV (Tex.App. Aug. 26 1999) (Aboussie, C.J.) (applying Texas *Daubert* analog), Ex. SN, *petition for review denied.* The *Revels* court rejected ADEs and case reports in general and those upon which plaintiff here attempts to rely in particular as a valid means for proving causation. The court held that case reports "contain 'uncontrolled' information," at *3, "are not 'scientifically reliable' evidence and should be rejected as a basis on which an expert may base his or her opinion," *id.* at *4. The *Revels* court also noted that the Parlodel ®-related case reports "do not purport to prove a causal relationship between the drug and the adverse event, but merely record the physician's observations of a particular patient." *Id.* at *3. The court further noted that the case reports were prepared in conjunction with Parlodel ® litigation, weighing against the admissibility of expert testimony based on such reports. *Id.* at *4–5. Moreover, the court rejected the lone "rechallenge" case report, relied upon by plaintiff in this case, as inadequate to prove causation, stating "[e]ven the Larrazet challenge/rechallenge experiment, appellant's strongest evidence of general causation, constitutes but one single, uncontrolled experiment." at *5; *see also id.* ("While the case reports illustrate an association between adverse drug experiences and Parlodel ®, the supreme court has clearly warned that such an association does not equate to causation. *See [Merrell Dow Pharm., Inc. v.] Havner,* 953 S.W.2d [706], 718, 724 [Tex. 1997], *cert. denied,* [523 U.S. 1119, 118 S.Ct. 1799, 140 L.Ed.2d 939] (1998).") [8]

8. This Court observes that, even under the *Frye* standard, case reports form an unreliable basis for expert opinion with respect to Parlodel®. *See, e.g., Kuhn v. Sandoz Pharms. Corp.,* No. 96 C 1930, Journal Entry Granting Defendants' Motions for Summary Judgment on Grounds of Failure to Plaintiffs' Medication Causation Proof, at 3–4 (18th Jud. Dist., Sedgwick County, Kan. Apr. 6, 1999) (excluding Dr. Iffy and three other medical doctors' proffered expert opinions; "The studies, literature and other evidence upon which plaintiffs' experts purport to rely for their general causation opinions concerning the alleged causal relationship between Parlodel® and serious injuries are not sufficient legally reliable support for such opinions....

54. Similarly, the Court of Appeals for the Third Circuit and district courts therein have held that adverse event reporting system data are not a legitimate basis for causation opinions involving pharmaceutical products. For example, in *DeLuca*, the district court found that "[ADEs] [and] DERs are not of a type of data that are reasonably relied upon by experts ... to make a determination of the causal relationship between a given substance and [the injury]," 791 F.Supp. at 1051. The basis for this finding was that "even if [ADE] or DER information was accurately reported, ADEs have inherent biases as they are second-or-third hand reports, are affected by medical or mass media attention, and are subject to other distortions." *Id.* at 1050. The *DeLuca* court concluded that "[ADE] or DER data ... produce[s] inaccurate and unreliable results because such data are unreliable for determining causation." *Id.* at 1057. Similarly, in *Wade–Greaux*, the court held that anecdotal reports, adverse reaction reports, and claims for injuries asserted in pharmaceutical products liability lawsuits should not be considered in determining causation; such data "represent anecdotal information of chance associations, do not purport to assess cause and effect and have no epidemiological significance." *Wade–Greaux*, 874 F.Supp. at 1481. The court concluded that, "by using anecdotal data as a basis [for a causation opinion], the methodologies of [the experts] are likely to produce inaccurate and unreliable results." *Id.* The Court adopts the reasoning of *DeLuca* and *Wade–Greaux*, which it concludes is consistent with the Court of Appeals for the Third Circuit's admonition against reliance on "purely anecdotal" information in *In re TMI Litigation*.

55. This Court notes that its conclusion is consistent as well with that of numerous other federal courts which have also rejected general causation opinions based on ADEs and case reports. *See, e.g., Allison v. McGhan Med. Corp.*, 184 F.3d 1300, 1316 (case reports held inadmissible; "while we acknowledge the importance of anecdotal studies for raising questions and comparing clinicians' findings, in the face of controlled, population-based epidemiological studies which find otherwise, these case studies pale in comparison.") [9]

56. The Court agrees with the opinion of the Court of Appeals for the Eighth Circuit in *Glastetter* that:

> Case reports make little attempt to screen out alternative causes for a patient's condition. They frequently lack analysis. And they often omit relevant facts about the patient's condition.

[but] are instead offered without proper foundation and are speculative.''), Ex. SM.

9. *Pick v. American Med. Sys.*, 958 F.Supp. 1151, 1161 (E.D.La.1997) (drug product case reports are ''subjective'' and ''susceptible to exaggeration and outright falsity,'' they present a real danger of bias in reporting from doctors who ''engage in litigation or otherwise have their livelihood dependent on it,'' and they are ''an insufficient basis to decide causation''); *Haggerty v. Upjohn Co.*, 950 F.Supp. 1160, 1164 (S.D.Fla.1996) (Spontaneous Reporting System (SRS) data is raw, unverified information, is not peer reviewed, has no known rate of error, is untested, and is generally unaccepted as the basis of causation opinions); *Hall v. Baxter Healthcare Corp.*, 947 F.Supp. 1387, 1411 (D.Or.1996) (''[c]ase reports and case studies are universally regarded as an insufficient basis for a conclusion regarding causation because case reports lack controls''); *Cartwright v. Home Depot U.S.A., Inc.*, 936 F.Supp. 900, 903 (M.D.Fla. 1996) (''case reports are no substitute for a scientific study [but][a]t best .. indicate possibilities that help inform productive paths for further research''); *Casey v. Ohio Med. Prods.*, 877 F.Supp. 1380, 1385 (N.D.Cal.1995) (anecdotal case reports are not reliable scientific evidence of causation regarding pharmaceutical products).

> Hence, causal attribution based on case studies must be regarded with caution.

Glastetter, 252 F.3d at 990–91 (quotation and citation omitted).

57. Plaintiff cites testimony of NPC's expert acknowledging unusual instances in which case reports can be a useful part of causation assessment. But the examples relate only to those events which are virtually never encountered unless caused by a drug and in which the exact causal mechanism, on a cellular level, is well understood. They do not relate to events which were otherwise expected at some rate in the general population (such as stroke generally or postpartum stroke specifically) or to events (such as the alleged cerebral vasoconstriction in this case) in which the purported mechanism is admittedly unknown.

58. The highly documented background incidence of stroke is significant, not negligible, so plaintiff's examples have no "fit" with her case. *See, e.g.,* Kittner (postpartum period itself increases the risk of cerebral infarction by a factor of 8.7 and ICH by a factor of more than 28 (statistically-significant), Ex. GA). Thus, even if this Court were to find—which it does not—that case reports could assist in forming a generally-reliable basis for expert opinion in the case of an exceedingly rare event, plaintiff has failed even to proffer how such a conclusion "fits" the facts and circumstances here.

59. Case reports and other anecdotal reports are unreliable because they do not take into account the known background risk of a disease. *See Glastetter*, 107 F.Supp.2d at 1031 (rejecting Dr. Kulig's and Dr. Petro's reliance on case reports because, *inter alia*, these reports do not take into account postpartum incidence of stroke); *Hollander*, 95 F.Supp.2d at 1237 (rejecting Dr. Kulig's reliance on case reports because, *inter alia*, these reports "fail to take into account the postpartum incidence of stroke and other factors"). A mere temporal association between exposure and an adverse occurrence can be due to chance or numerous other factors, which makes anecdotal reports of adverse events unreliable evidence for analyzing general causation issues. *See Glastetter*, 252 F.3d at 989–90 (temporal association demonstrated through case reports not scientifically valid proof of causation); *Glastetter*, 107 F.Supp.2d at 1030 ("case reports are not reliable, because normally, such reports record nothing more than a temporal association between an exposure and a particular occurrence" (internal quotation omitted)); *Hollander*, 95 F.Supp.2d at 1237 n. 19 ("Case study populations are frequently small, leaving open the real possibility that the findings are due to chance rather than to exposure to the suspected substance." *quoting Pick*, 958 F.Supp. at 1160–61); *Brumbaugh*, 77 F.Supp.2d at 1156 ("Neither case reports nor [ADEs] contain scientific analysis with the safeguards of a controlled experiment. Their most significant analytical defect is that they don't isolate and investigate the effects of alternative causation agents.... Unlike epidemiological studies, [case reports or ADEs] do not contain a testable and systematic inquiry into the mechanism of causation."); *see also Pappas v. Sony Elec., Inc.*, 136 F.Supp.2d, 413, 427 (W.D.Pa.2000) (would require leap grounded in guesswork to conclude that there was a defect in television solely on evidence that fire started in area where television was located).

60. To the extent that case reports could ever be reliable evidence of general causation, they are not in this case. As did the *Caraker* court, this Court concludes:

> In this case, ...we have a scant number of case reports indicating that Parlodel ®

> is temporally associated with all types of adverse events. There is not the volume of or specificity within these case reports to reliably show that Parlodel ® causes ICH.

Caraker, 172 F.Supp.2d at 1050 (citations omitted); *see also Siharath,* 131 F.Supp.2d at 1360–61 (Parlodel ® case reports lack the quantity, nature, and content to provide reliable information regarding causation).

61. Accordingly, this Court agrees with the conclusions reached by the courts in the Parlodel ® cases cited above—and by numerous other courts throughout the country—that case reports, ADEs and other anecdotal information based on temporal proximity between exposure to a substance and alleged injury simply do not constitute reliable support for plaintiff's experts' causation opinions. *In re: Diet Drugs,* 2001 WL 454586 at *15 (E.D.Pa. 2001) (case reports "are universally recognized as insufficient and unreliable evidence of causation"); *DeLuca,* 791 F.Supp. at 1050–51 (ADEs have inherent biases and are not the type of data reasonably relied upon by experts); *Wade–Greaux,* 874 F.Supp. at 1481 (ADEs and case reports "represent anecdotal information of chance associations" and "do not purport to assess cause and effect"); *see also Allison,* 184 F.3d at 1316 (affirming district court's rejection of expert's reliance on anecdotal case reports); *Muzzey v. Kerr–McGee Chem. Corp.,* 921 F.Supp. 511, 519 (N.D.Ill.1996) ("Anecdotal reports . . . are not reliable bases to form a scientific opinion about a causal link"); *In re Breast Implant Litig.,* 11 F.Supp.2d 1217, 1227–29 (D.Colo.1998) (case reports "suggest only potential, untested hypothesis"); *Pick,* 958 F.Supp. at 1161 (drug product case reports are "subjective" and "susceptible to exaggeration or outright falsity" and are "an insufficient basis to decide causation"); *Haggerty,* 950 F.Supp. at 1164 (ADEs are "raw information that has not been scientifically or otherwise verified as to cause and effect"); *Hall,* 947 F.Supp. at 1411 ("case reports and case studies are universally regarded as an insufficient basis for a conclusion regarding causation because case reports lack controls").

62. Even the Larrazet article about a "possible" bromocriptine-induced heart attack purportedly triggered by a "dechallenge/rechallenge" test—a piece of evidence upon which plaintiff's experts rely heavily to support their causation theory—is merely one anecdotal case report that does not provide reliable causation evidence. In addition to the other flaws that render this article unreliable and inapplicable in this case, this Court agrees with the *Revels* court's observation, when affirming the trial court's grant of summary judgment, that the Larrazet article "constitutes but one single, uncontrolled experiment." *Revels,* 1999 WL 644732 at *5. Therefore, even assuming *arguendo*—contrary to this Court's findings—that this article represents a valid application of the dechallenge/rechallenge method, this is still merely one isolated case report that is not reliable evidence to support plaintiff's experts' causation theory. *See id.* (rejecting plaintiffs' experts' reliance on Larrazet article.).

63. The "dechallenge/rechallenge" reports relied upon by plaintiff's experts lack controls, involve injuries other than ICH, are too scant in number, and "do not contain a testable and systematic inquiry into the mechanism of causation." *Caraker,* 172 F.Supp.2d at 1050; *see also Glastetter,* 107 F.Supp.2d at 1031 & n. 9 (rejecting plaintiffs' experts' reliance on dechallenge/rechallenge articles); *Hollander,* 95 F.Supp.2d at 1235 n. 10 (rejecting plaintiffs' experts' reliance on dechallenge/rechallenge articles because, *inter alia,* there

are "too few [such articles] for them to be consequential, [and] they present the problems inherent in the other case studies or adverse drug reaction reports relied upon by the plaintiffs' experts").

[16] 64. This Court concludes that plaintiff's experts' reliance on anecdotal case reports to support their causation opinions is contrary to both good scientific practice and the *Daubert* case law. Such testimony is not "scientific knowledge" and will not assist the trier of fact, and the data are not of a type reasonably relied on by experts in the field. *E.g., Havner,* 953 S.W.2d at 720 ("physicians following scientific methodology would not . . . rely on case reports to determine whether a substance is harmful") (*citing* David E. Bernstein, "The Admissibility of Scientific Evidence After *Daubert v. Merrell Dow Pharmaceuticals, Inc.*," 15 Cardozo L.Rev. 2139, 2148–49 (1994)).

[17] 65. The same problems that make case reports and ADEs unreliable for purposes of analyzing a medical causation issue also undermine plaintiff's experts' reliance on a few medical treatises. A second-hand statement in a treatise that merely recites anecdotal information from case reports can be no more reliable than the case reports themselves. Thus, plaintiff's experts' medical causation opinions are not bolstered by their reliance on a few treatise excerpts that have the same reliability problems as case reports. *See Glastetter,* 107 F.Supp.2d at 1035 n. 18 (rejecting plaintiffs' experts' reliance on medical treatises and journals because, *inter alia,* "[t]he 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"); *accord Caraker,* 172 F.Supp.2d at 1052; *Siharath,* 131 F.Supp.2d at 1370. *See also* In re: Diet Drugs, 2000 WL 962545 at *9 (E.D.Pa.2000) (rejecting expert's reliance on scientific literature that simply cited to same flawed studies already rejected by court).

66. In affirming the district court's opinion in *Glastetter,* the Court of Appeals for the Eighth Circuit summarized the unreliability of the medical texts on which plaintiff's experts rely:

> Each of these texts suffers from one or more infirmities that prevented the district court from accepting its conclusions. Some of the texts were largely grounded upon case reports and other anecdotal information. One text reported Parlodel's propensity to cause diseases *other* than ICH, such as coronary vasospasm and heart attack. Still other texts relied upon generic comparisons between bromocriptine and related chemical compounds. At least one text ventured a hesitant conclusion that Parlodel® causes vasoconstriction, but the explanation made clear that more research was needed before causation could be firmly established.

Glastetter, 252 F.3d at 990 (noting that court regarded claims of plaintiff's experts "with some suspicion since one leading treatise on medical toxicology concludes that bromocriptine has *no* vasoconstrictive properties") (emphasis in original) (citations omitted).

67. Plaintiff has referred the Court to regulatory proceedings of FDA and ADEs reported to FDA as somehow supportive of her position on medical causation. This Court concludes that FDA does not—and the scientific community cannot—utilize postmarketing surveillance in assessing causation. "[B]ecause of incomplete data and the uncertainty caused by the underlying illness, indication, or other drug exposures, adverse experience reports may be attributed to a drug or biological product

even though it may not necessarily have caused the adverse experience." Final Rule, Department of Health and Human Services, Food and Drug Administration, "Postmarketing Expedited Adverse Experience Reporting for Human Drug and Licensed Biological Products; Increased Frequency Reports," 62 Fed.Reg. 34166, 34167 (1997).

68. Nor do FDA regulations regarding reports of adverse events offer a methodology for proving causation. FDA's regulations specifically call for reports of adverse events following usage of drugs whether or not there is any belief that a causal relationship was at work. *See* 21 C.F.R. § 314.80(c).

69. Over a decade ago, FDA's Surveillance and Data Processing Branch of the Division of Epidemiology and Surveillance published a "Brief Description [of Adverse Reaction Reporting System ("ARRS")] with Caveats of [the] System." According to FDA, "[t]he primary purpose for maintaining the [ARRS] data base is to serve as an early warning or signaling system. . . ." Brief Description with Caveats of System, Surveillance and Data Processing Branch of the Division of Epidemiology and Surveillance, Dec. 1988, at p. 1 ("Dec. 1988 FDA Caveats"), Ex. RN; *see also* Nov. 1991 FDA Caveats, at p. 1 (Att.25).

70. These FDA Caveats further state that:

> for any given case report, *there is no certainty that the suspect drug caused the reaction.* This is because physicians are encouraged to report all suspected drug events, not just those that are known to have been caused by the drug. The event reported in a case report may have been related to an underlying disease for which the drug was given, to other drugs being taken concurrently, or may have occurred by chance at the same time the suspected drug was taken.

Dec.1988 FDA Caveats, at p. 1 ¶ 1, Ex. RN; *see also* Nov. 1991 FDA Caveats, at p. 1 ¶ 1 (Att.25). Thus, "[a]ccumulated case reports cannot be used to calculate incidence or estimates of drug risk. They must be carefully interpreted as reporting rates and not occurrence or incidence rates. Comparisons of drug safety cannot be made from these data." Dec.1988 FDA Caveats, at p. 2 ¶ 2, Ex. RN; *see also* Nov. 1991 FDA Caveats, at p. 2 ¶ 2 (Att.25).

71. This Court observes that FDA is a regulatory agency whose mandate is to control which drugs are marketed in the United States and how they are marketed. FDA ordinarily does not attempt to prove that the drug in fact causes a particular adverse effect. FDA has never concluded (and could not so conclude, given its own standards, even at the regulatory level) that Parlodel ® causes stroke, based upon ADEs or case reports or any other evidence.

72. The WARNINGS section of the current package labeling for Parlodel ® states that a causal relationship between Parlodel ® and the adverse events of stroke, seizure and hypertension *has not been established:*

> Symptomatic hypotension can occur in patients treated with Parlodel ® (bromocriptine mesylate) for any indication. In postpartum studies with Parlodel ® (bromocriptine mesylate), decreases in supine systolic and diastolic pressures of greater than 20 mm and 10 mm Hg, respectively, have been observed in almost 30% of patients receiving Parlodel ® (bromocriptine mesylate). On occasion, the drop in supine systolic pressure was as much as 50–59 mm of Hg. **While hypotension during the start of therapy with Parlodel ® (bromocriptine mesylate) occurs in**

some patients, in postmarketing experience in the U.S. in postpartum patients 89 cases of hypertension have been reported, sometimes at the initiation of therapy, but often developing in the second week of therapy; seizures have been reported in 72 cases (including 4 cases of status epilepticus), both with and without the prior development of hypertension; 30 cases of stroke have been reported mostly in postpartum patients whose prenatal and obstetric courses have been uncomplicated. Many of these patients experiencing seizures and/or strokes reported developing a constant and often progressively severe headache hours to days prior to the acute event. Some cases of strokes and seizures were also preceded by visual disturbances (blurred vision, and transient cortical blindness). Nine cases of acute myocardial infarction have been reported.

Although a causal relationship between Parlodel ® (bromocriptine mesylate) administration and hypertension, seizures, strokes, and myocardial infarction in postpartum women has not been established, use of the drug for prevention of physiological lactation, or in patients with uncontrolled hypertension is not recommended.

Physicians' Desk Reference, Aug. 1, 1998 (bold emphasis in original), Ex. RB.

73. In the sub-section entitled "Adverse Events Observed in Other Conditions, *Postpartum Patients*" of the ADVERSE REACTIONS section, the current package labeling further states:

> In postmarketing experience in the U.S. serious adverse reactions reported include 72 cases of seizures (including 4 cases of status epilepticus), 30 cases of stroke, and 9 cases of myocardial infarction among postpartum patients. Seizure cases were not necessarily accompanied by the development of hypertension. An unremitting and often progressively severe headache, sometimes accompanied by visual disturbance, often preceded by hours to days many cases of seizure and/or stroke. Most patients had shown no evidence of any of the hypertensive disorders of pregnancy including eclampsia, preeclampsia or pregnancy induced hypertension.... **The relationship of these adverse reactions to Parlodel ® (bromocriptine mesylate) administration has not been established.**

Physicians' Desk Reference, Aug. 1, 1998, Ex. RB (emphasis added).

74. This FDA-approved labeling for Parlodel ®—first approved in March 1995 (Att.19), just two months after the Federal Register action confirming withdrawal of the PPL indication, and in effect since then—demonstrates FDA's acknowledgment that no causal relationship has been established between Parlodel ® and hypertension, seizures, strokes, or myocardial infarction. If FDA believed otherwise, FDA would not have approved this quoted language that has now appeared in the Physicians' Desk Reference and in every package insert for Parlodel ® for over five years.

[18] 75. Thus, the Court holds that the *Daubert* reliability requirement precludes plaintiff's experts from basing their causation opinions on FDA actions with respect to Parlodel ®. *See Glastetter*, 107 F.Supp.2d at 1035–36 (holding that FDA actions regarding Parlodel ® do not establish reliability of plaintiffs' experts' causation opinions); *Hollander*, 95 F.Supp.2d at 1234 n. 9 (holding that "the plaintiffs' reliance on the position taken by the Food and Drug Administration with respect to Parlodel ® is misplaced").

F. Conclusions of Law on DMC causality assessments

[19] 76. As noted above, plaintiff asks this Court to accept the methodology she says is endorsed by Sandoz Ltd. or Sandoz Pharma Ltd. as part of the DMC's "causality assessments" for ADEs. The Court concludes that plaintiff has failed to demonstrate that the methodology—adopted for foreign regulatory purposes—meets any of the *Daubert* criteria, nor has plaintiff shown any other indicia of reliability. Accordingly, reliance by plaintiff's experts on these DMC "causality assessments" is precluded under Federal Rule of Evidence 702.

77. As further support for its conclusions, the Court notes that Dr. Kulig has conceded that such "causality assessments" could not be published in a peer-reviewed publication because the methodology for making "causality assessments" is not adequately described therein. Kulig/*Hollander* Dep. at 115–16 (Att.3). Where the methodology is unknown, the opinion is inadmissible. See *Mitchell v. Gencorp Inc.,* 165 F.3d 778, 781 (10th Cir. 1999) (expert testimony must, at a minimum, include a description of methodology used and scientific data supporting the determination).

[20] 78. The Court agrees with the *Glastetter* court that plaintiff's experts' reliance on phrases plucked from corporate documents also does not provide scientific evidence of causation:

> [Plaintiff] argues that Novartis's internal documents admit that Parlodel causes hypertension and strokes. She points to three or four statements excerpted from company memoranda.... [Plaintiff] lifted these statements out of context from longer memoranda between Novartis doctors. Placed in proper context, it is apparent that Novartis doctors simply expressed a desire to perform further testing to determine whether Parlodel might be associated with certain types of seizures and strokes. These statements do not "admit" that Parlodel can cause an ICH.

Glastetter, 252 F.3d at 991 (internal citation omitted); *accord Caraker,* 172 F.Supp.2d at 1052.

[21] 79. In the instant case, plaintiff has referred to "causality assessments" showing that the DMC attributed "probable causation" in certain case reports of digital vasospasm to Parlodel®. No such "causality assessments" showed the DMC attributing "probable causation" in a case of ICH to Parlodel®. *See* 11/15 Tr. at 51 (concession by Dr. Petro that digital vasospasm is not the same as ICH); 11/17 Tr. at 47–48 (unchallenged testimony of Dr. Green that "it is well-known in medicine and science that the body has different vascular beds[;] [and that] [t]here are different sorts of receptors, populations of receptors on the peripheral vasculature that serves our fingers and toes than there are for major vessels, such as coronary arteries or cerebral arteries"). Accordingly, the evidence of the DMC "causality assessments" does not fit the issues in this case and is therefore not relevant under Federal Rule of Evidence 401 or, if relevant, is entitled to exceedingly little weight in the Court's review of the methodology of plaintiff's experts.

80. Further, plaintiff has not shown that the DMC had adequate medical records of the patients referred to in the "causality assessments." 11/9 Tr. at 66 (admission by Dr. Kulig that he did not know how "causality assessments" were done at DMC and, in particular, whether DMC had "received everything" at the time DMC made such assessments). Among other things, incomplete medical records would preclude DMC from ade-

quately considering whether there were confounding factors in the patients addressed by the "causality assessments," *e.g.,* concomitant use of other drugs. *Id.* at 67 ("causality assessments" may not take into account confounding factors). Again, if such "causality assessments" are even admissible under Rule 401 (and the Court concludes they are not), they would be entitled to exceedingly little weight in the Court's review of the methodology of plaintiff's experts.

81. In any event, the issue before this Court is whether the methodology *employed by plaintiff's experts* is scientifically valid. *Daubert,* 509 U.S. at 592–93, 113 S.Ct. 2786. For the reasons stated in this opinion, the Court concludes that their methodology is not valid in the circumstances of this case.

[22] 82. Finally, the Court concludes independently that it would exclude the "causality assessments" and plaintiff's experts' reliance thereon under Fed.R.Evid. 403. These "causality assessments," prepared for entirely different purposes than the scientific determination of causation in controlled settings, would be grossly misleading to a finder of fact, and the likelihood of misleading the finder of fact would greatly outweigh any probative value.

G. Conclusions of Law Regarding Plaintiff's Proposed Use of Animal Studies Evidence

[23] 83. To ensure that the expert's conclusion based on animal studies is reliable, there must be "a scientifically valid link"—such as supporting human data—"between the sources or studies consulted and the conclusion reached." *Cavallo v. Star Enterprise,* 892 F.Supp. 756, 762 (E.D.Va.1995), *aff'd in part, rev'd in part on other grounds,* 100 F.3d 1150 (4th Cir. 1996).

84. This Court observes that studies of laboratory animals are routinely excluded as irrelevant and unreliable when proffered as a basis for medical causation testimony. For example, in *Joiner,* the Supreme Court found that the district court did not abuse its discretion when it determined that the animal studies involving infant mice that had massive doses of PCBs injected directly into their peritoneums or stomachs were so dissimilar to the plaintiff's situation that they were unreliable as a basis for expert opinion on causation. *Joiner,* 522 U.S. at 144, 118 S.Ct. 512. In *Joiner,* "massive doses of PCBs [in a highly concentrated form] were injected into [infant mice]." *Id.* In contrast, "Joiner was an adult human being whose alleged exposure to PCBs was far less than the exposure in the animal studies." *Id.* The district court had concluded that "[t]he analytical gap between the evidence presented and the inferences to be drawn on the ultimate issue of human birth defects is too wide. Under such circumstances, a jury should not be asked to speculate on the issue of causation." *Joiner v. General Elec. Co.,* 864 F.Supp. 1310, 1323 (N.D.Ga.1994).

85. In *Wade–Greaux v. Whitehall Laboratories, Inc.,* 874 F.Supp. 1441 (D.Vi.), *aff'd without op.,* 46 F.3d 1120 (3d Cir. 1994), the court granted summary judgment on the claim that skeletal birth defects were caused by the mother's use of over-the-counter asthma medications Primatene® Tablets and Primatene® Mist. The court rejected plaintiffs' experts' methodologies which relied, *inter alia,* on extrapolation from experimental animal studies without supportive positive human studies. *Wade–Greaux,* 874 F.Supp. at 1480 (court "conclud[ing] that the theory of plaintiff's expert witnesses that they can directly extrapolate from experimental animal studies without supportive positive human studies to opine as to causation in

humans is one that has an extraordinarily high rate of error").

86. *See also Allison,* 184 F.3d at 1313–14 (affirming district court ruling that plaintiffs' expert failed to draw a sufficient connection between animal studies and the disease in issue); *Ruffin v. Shaw Indus.,* 149 F.3d 294, 297 (4th Cir.1998) (affirming the district court's exclusion of causation testimony where animal studies allegedly showed that the product at issue caused adverse effects in mice, but results could not be replicated); *Allen v. Pennsylvania Eng'g Corp.,* 102 F.3d 194, 195 (5th Cir. 1996) ("Where, as here, no epidemiological study has found a statistically-significant link between EtO exposure and human brain cancer; the results of animal studies are inconclusive at best; and there was no evidence of the level of [plaintiff's] exposure to EtO, the expert testimony does not exhibit the level of reliability necessary to comport with the Federal Rules of Evidence 702 and 703, ... *Daubert* ... and this court's authorities"); *Daubert II,* 43 F.3d at 1319–20 (rejecting experts' opinions which relied on animal studies, chemical structure analyses, and epidemiological data when experts failed to clearly demonstrate scientific methodology); *Conde v. Velsicol Chem. Corp.,* 24 F.3d 809, 814 (6th Cir.1994) (finding animal studies inadequate for showing causation of disease in humans with chlordane exposure); *Renaud v. Martin Marietta Corp., Inc.,* 972 F.2d 304, 307 (10th Cir.1992) ("The etiological evidence proffered by the plaintiff was not sufficiently reliable, being drawn from tests on non-human subjects without confirmatory epidemiological data."); *Richardson v. Richardson–Merrell, Inc.,* 857 F.2d 823, 830–32 (D.C.Cir.1988) (animal studies unreliable), *cert. denied,* 493 U.S. 882, 110 S.Ct. 218, 107 L.Ed.2d 171 (1989).

[24] 87. Here, plaintiff's experts' failure to take into account critical differences between animal data and human experience—including but not limited to extrapolations in dosing—renders their methodology scientifically invalid and unreliable. *See, e.g., Cartwright v. Home Depot, U.S.A.,* 936 F.Supp. 900, 906 (M.D.Fla. 1996) ("the question for causation purposes is ... [a]t what levels of exposure do what kinds of harm occur?"); *Chikovsky v. Ortho Pharm. Corp.,* 832 F.Supp. 341, 345–46 (S.D.Fla.1993) (excluding testimony where expert failed to perform comparisons between the dose of the drug relevant to plaintiff and dose used in studies on which he relied).

88. As in *Joiner,* evidence from the animal studies relied upon by plaintiff's experts to support their hypothesis is not sufficiently tied to the facts at issue here, *i.e.,* a live human being with an intact nervous system who ingested no more than two 2.5 mg doses of Parlodel ® per day and who had a stroke. Because "[t]he analytical gap between the evidence presented and the inferences to be drawn on the ultimate issue ... is too wide," this evidence must be excluded as scientifically unreliable. *Joiner,* 864 F.Supp. at 1323.

89. In the present case, plaintiff's experts attempted to base their causation opinions in part on animal studies in which animals that were treated with bromocriptine allegedly had adverse vasoconstrictive effects. The Court concludes that these animal studies do not present a scientifically-reliable basis for the causation opinion of plaintiff's experts because: (a) plaintiff's experts did not attempt to correlate the doses used in such studies to the dose of bromocriptine arising from the use of Parlodel ® for the prevention of lactation; (b) plaintiff's experts did not demonstrate, or attempt to demonstrate, that the dose of a drug is an unimportant factor in the types of reactions that may be caused by that drug; (c) plaintiff's experts in fact con-

ceded that the concept of "dose-response" is a fundamental premise of toxicology; (d) plaintiff's experts did not demonstrate that the dog or the rat, *i.e.,* the species in which these studies were performed, were sufficiently similar to a human being with regard to vasoconstrictive reactions to make reliance on such studies reasonable; and (e) plaintiff's experts did not demonstrate that the observed effects of "tail necrosis" and "ear tip necrosis" were sufficiently similar to the cerebral vasoconstriction that they allege occurred in this case such as to make reliance on such studies reasonable. Additionally, for the above-stated reasons, plaintiff did not demonstrate an adequate "fit" between the testimony of her experts based on such animal studies and the issue to be determined in this case, *i.e.,* whether bromocriptine can cause cerebral vasoconstriction in human beings using Parlodel ® to prevent lactation.

H. Conclusions of Law Regarding Plaintiff's Proposed Use of Other Ergot Alkaloid Evidence

90. This Court finds that plaintiff's experts rely upon data on drugs *other* than bromocriptine to support their hypotheses. Although they concede that bromocriptine is pharmacologically shown to cause vasodilation, *see, e.g.,* Iffy Dep. at 60 (a large body of literature states that Parlodel ® is vasodilatory) (Att.18), they nevertheless argue that—in an otherwise unidentifiable subset of women that happens to include plaintiff—bromocriptine somehow causes the opposite effect, vasoconstriction, because, they claim, it is structurally similar to other ergot-derived drugs, some of which have vasoconstrictive properties. That explanation does not "fit" the facts of this case where bromocriptine, not another drug, is at issue.

91. The Court of Appeals for the Third Circuit and its district courts have held that evidence concerning the effect of allegedly "similar" chemicals on the body cannot substitute for direct evidence about the drug in question. For example, in *DeLuca,* the court addressed claims by the plaintiff's expert that Bendectin was chemically similar to antihistamines generally, that antihistamines were associated with birth defects, and that therefore Bendectin caused birth defects. *DeLuca,* 791 F.Supp. at 1054. Noting that small differences in chemical structure could cause "very different human effects," the court rejected this type of analysis and excluded the testimony under Rule 702. *Id.*

92. In *Hoffman v. Sterling Drug, Inc.,* 374 F.Supp. 850 (M.D.Pa.1974), a retrial of a product liability action regarding the drug Aralen, the plaintiff sought to introduce evidence of "chemically related" drugs. After discussing "[t]he dubious value of such evidence," the court followed its prior holding which "denied permission at the first trial to introduce evidence on the known side effects of drugs allegedly chemically related to Aralen." *Hoffman,* 374 F.Supp. at 862.

93. The Court of Appeals for the Third Circuit's decision in *Kannankeril v. Terminix International, Inc.,* 128 F.3d 802 (3d Cir.1997), is not contrary to the Court's conclusions here. In *Kannankeril,* the Court did note that "the toxic effects of organophosphates on humans are well recognized by the scientific community." *Id.* at 809. However, the proposition that chlorpyrifos—the active ingredient of Dursban at issue in *Kannankeril*—acts like other organophosphates was apparently not challenged by defendant there. Rather, the issue in *Kannankeril* appears to have been, not whether general causation could be established, but whether plaintiff in fact was sufficiently exposed to chlorpyrifos. In the instant case, by contrast, NPC *does* contest general causation

and plaintiff's theory that bromocriptine acts like other ergots vis-a-vis causing vasoconstriction at therapeutic doses. Moreover, whereas in *Kannankeril* the precise mechanism of chlorpyrifos toxicity was well understood (chlorpyrifos "inhibit[s] the normal breakdown of acetylcholine, which functions as a neurotransmitter in . . . human beings," 128 F.3d at 805), in the instant case there is no scientific knowledge whatsoever concerning how bromocriptine allegedly causes vasoconstriction. Accordingly, *Kannankeril* is not on point.

94. Particularly because plaintiff's experts admit they do not know the mechanism by which Parlodel ® allegedly causes vasoconstriction, this Court is persuaded by the reasoning of the decision in *Brumbaugh* which excluded plaintiff's expert's opinion based, among other things, on plaintiff's inability to establish a causal association through evidence of compounds structurally "similar" to bromocriptine:

> [Dr. Iffy's] hypothesis is that drugs similar to Parlodel ® are vasoconstrictors and not vasodilators, and some women "cannot distinguish" between them. No study of this lack of discrimination is put forward. Testimony extending general conclusions about similar drugs does not meet Daubert's requirement of reliability. *Schudel v. General Electric Co.,* 120 F.3d 991, 996–97 (9th Cir.1997). The *Schudel* court recognized that "small differences in molecular structure often have significant consequences." *Id.*

Brumbaugh v. Sandoz Pharm. Corp., 77 F.Supp.2d at 1157.

95. Other federal courts facing proffered expert testimony based on the effects of allegedly similar chemicals have reached the same conclusion and rejected such contentions; these courts have found that consideration of the effects of *other* drugs can only lead away from the truth. *See, e.g., Mitchell v. Gencorp, Inc.,* 165 F.3d 778, 782 (10th Cir.1999) (excluding testimony based on similarities between benzene and defendant's products); *Schudel,* 120 F.3d at 997 (excluding opinions extrapolating from studies of organic solvents allegedly similar to the chemicals in question); *Thomas v. Hoffman–LaRoche, Inc.,* 949 F.2d 806, 814 n. 36 (5th Cir.1992) (actual side effects experienced by patients taking Accutane were a "much better indication of the risks associated with Accutane" than side effects of Vitamin A); *Chikovsky,* 832 F.Supp. at 345–46 (proposed analogy between Accutane and Vitamin A was "wanting"); *see also Havner,* 953 S.W.2d at 730 (evidence that an antihistamine *other* than doxylamine succinate had a similar structure and allegedly caused some adverse effect did not support the opinions of plaintiffs' expert and "could not legitimately form the basis for a jury verdict").

96. This Court's conclusion on this issue is further supported by the other Parlodel ® cases in which courts have uniformly rejected as unreliable plaintiff's experts' attempts to base their opinions on evidence concerning other ergots. *See Glastetter,* 252 F.3d at 990 (Dr. Kulig's and Dr. Petro's "generic assumption that bromocriptine behaves like other ergot alkaloids carries little scientific value"); *Caraker,* 172 F.Supp.2d at 1051–52 (rejecting plaintiff's experts' "guilt by association" ergot theory as scientifically unreliable); *Siharath,* 131 F.Supp.2d at 1363–64 (plaintiff's experts' reliance on general conclusions about family of ergot drugs does not meet *Daubert* reliability standards); *Glastetter,* 107 F.Supp.2d at 1034 (rejecting Dr. Kulig's and Dr. Petro's reliance on other ergots evidence); *Hollander,* 95 F.Supp.2d at 1238 (rejecting Dr. Kulig's reliance on other ergots evidence); *Brumbaugh,* 77 F.Supp.2d at 1157 ("Testimony extending

general conclusions about . . . drugs [similar to bromocriptine] does not meet *Daubert's* requirement of reliability.") (*citing Schudel,* 120 F.3d at 996–97).

[25] 97. In the present case, plaintiff is not alleging exposure to any ergot alkaloid other than bromocriptine. In the absence of a particularized showing of how and why this group of compounds must have pharmacologically identical modes of action, evidence regarding other ergot alkaloids is not reliable or relevant and must be excluded, Fed.R.Evid. 401, 402, 403 and 702, nor can plaintiff's expert witnesses properly base their opinions on such evidence.

I. Conclusions of Law Regarding Plaintiff's Proposed Use of Evidence of Other Injuries and Other Parlodel ® Indications Not Alleged Or Raised in Plaintiff's Complaint

98. Proffered evidence must be relevant under Federal Rule of Evidence 401 to be admissible; the evidence must have a "tendency to make the existence of any fact that is of consequence to the determination of the action more probable or less probable than it would be without the evidence." Fed.R.Evid. 401; *see, e.g., Michetti v. Linde Baker Material Handling Corp.,* 969 F.Supp. 286, 287–88 (E.D.Pa. 1997). Evidence that is not relevant is not admissible. Fed.R.Evid. 402.

99. The Court of Appeals for the Third Circuit has repeatedly held that evidence of other injuries is not admissible unless the circumstances of the other occurrences are "substantially similar" to those in the case at bar. *See, e.g., Barker v. Deere and Co.,* 60 F.3d 158, 162 (3d Cir.1995) (noting "substantially similar" standard is held by all other federal courts of appeal); *Wolf v. Procter & Gamble Co.,* 555 F.Supp. 613 (D.N.J.1982).

[26] 100. That the evidence of other injuries allegedly involves the same product "is not enough to make the [evidence] admissible even under the liberal standard of admissibility of Fed.R.Evid. 401." *Gumbs v. International Harvester, Inc.,* 718 F.2d 88, 98 (3d Cir.1983) (reversing district court's admission of allegedly similar prior accidents involving U-bolts on loadstar trucks).

101. The Court concludes that evidence of other uses of Parlodel ® must be substantially similar to the circumstances in which plaintiff used Parlodel ®. Unless there is a sufficient connection, the mere fact that the alleged other incidents involve the same product "is not enough to make the [evidence] admissible even under the liberal standard of admissibility of Fed.R.Evid. 401." *Gumbs,* 718 F.2d at 98 (excluding evidence of other injuries allegedly due to same product).

[27] 102. Here, where plaintiff alleges that her ICH was caused by cerebral vasoconstriction, plaintiff must also prove that the prior events had also been caused by cerebral vasoconstriction. This is especially true given that plaintiff cannot articulate a mechanism by which Parlodel ® causes cerebral vasoconstriction in the first place. Plaintiff has not met her burden; the causal basis of the other events upon which plaintiff's expert witnesses rely is a matter of hypothesis that has not been "established" for purposes of Rule 401 and *Gumbs.*

[28] 103. Plaintiff's expert witnesses may not rely on evidence of other injuries and other indications because such reliance would be "likely to lead to jury misdecision based on inflamed passions, confusion of issues or the like." *Corrigan v. Methodist Hospital,* 874 F.Supp. 657, 658 (E.D.Pa. 1995); Fed.R.Evid. 403 (evidence should be excluded if "its probative value is sub-

stantially outweighed by the danger of unfair prejudice, confusion of the issues, or misleading the jury, or by considerations of undue delay, waste of time, or needless presentation of cumulative evidence"); *Wolf,* 555 F.Supp. at 622 ("the tendency would be for the jury to consider the evidence as proof of product defect, negligence, or causation. . . .").

J. Conclusions of Law Concerning Plaintiff's Experts' Purported Application of Differential Diagnosis as a Methodology in Reaching Opinions Concerning Specific Causation

[29] 104. Plaintiff's experts contend that they applied the methodology of differential diagnosis to reach the opinion that Parlodel ® caused plaintiff's ICH. The Court of Appeals for the Third Circuit recognizes the application of differential diagnosis for the purposes of determining specific medical causation. *Heller,* 167 F.3d at 154. However, as *Heller* also demonstrates, the mere statement by an expert that he or she applied differential diagnosis in determining causation does not *ipso facto* make that application scientifically reliable or admissible. In *Heller* itself, the Court affirmed the district court's *exclusion* of causation opinions based on the purported use of differential diagnosis.

105. In *Heller,* the Court of Appeals for the Third Circuit noted that differential diagnosis would sustain a specific causation opinion if it was "thorough," if it "ruled out other possible causes," and if it was based on "a valid and strong temporal relationship." 167 F.3d at 154. The importance of the temporal relationship depends "on the strength of that relationship." *Id.* But even an exact temporal relationship and a "proper differential diagnosis" by a "well-qualified physician" would not serve as the foundation for an admissible causation opinion regardless of the circumstances. *Id.* Accordingly, the Court pointed out that it would "not necessarily [be] error to exclude [the expert's] conclusion as unreliable if [the expert] relied on no scientific studies and the remaining foundation for his conclusion was shaky." *Id.* at 156. As shown below, this Court concludes that the differential diagnoses offered by plaintiff's experts were "shaky" at best and, in fact, not valid or reliable differential diagnoses.

106. *Heller* ruled that, in determining whether a particular differential diagnosis was sufficiently reliable to be admitted, a district court should not demand that the expert rule out "*all* alternative possible causes." 167 F.3d at 156. Accordingly, this Court does not require plaintiff's experts to show that they have adequately ruled out all alternative possible causes. However, the Court of Appeals for the Third Circuit does require that "obvious alternative causes" be ruled out. *Id.* As that Court reminded us in *Heller,* "where a defendant points to a plausible alternative cause and the doctor offers *no* explanation for why he or she has concluded that was not the sole cause, the doctor's methodology is unreliable." 167 F.3d at 156 (*quoting Paoli II,* 35 F.3d at 759 n. 27). Accordingly, this Court must explore the alternative hypotheses posited by defendant's experts and plaintiff's experts' response thereto. If the alternative hypotheses are "plausible," then plaintiff's experts must show that they have been reliably ruled out.

107. *Heller* provides specific guidance concerning what it means to reliably rule out a plausible alternative hypothesis:

> As we concluded in *Paoli [II],* a physician need not conduct *every* possible test to rule out all possible causes of a patient's illness, "*so long as he or she employed sufficient diagnostic tech-*

niques to have good grounds for his or her conclusion."

167 F.3d at 156 (*quoting Paoli II,* 35 F.3d at 761) (emphasis added). Accordingly, this Court will consider the sufficiency of the diagnostic techniques, if any, that plaintiff's experts employed or relied upon in the formation of their opinions via differential diagnosis. Before the Court focuses on such techniques, however, the Court reviews the primary alternative causal hypotheses put forward by NPC to determine if such hypotheses are "plausible." Because the Court concludes that plaintiff's experts did not adequately rule out these primary alternative causes, the Court need not consider other alternative causes that NPC raised at the *Daubert* hearing, including, *inter alia,* plaintiff's smoking history and the admitted stress under which plaintiff found herself in the weeks prior to her stroke.

108. NPC puts forward essentially three primary alternative causal hypotheses. First, NPC asserts that the postpartum period itself is a known risk factor for stroke in general and ICH in particular. *See, e.g.,* 11/15 Tr. at 168–76 (Buchholz). Accordingly, NPC contends not only that the risk of the postpartum period itself is a plausible alternative hypothesis, but that it is in fact the most likely cause of plaintiff's stroke. Second, NPC asserts that (a) because plaintiff contends she suffered an event of cerebral vasoconstriction leading to the ICH, and (b) because plaintiff admittedly was found to have what was initially characterized as a "large amount" of some type of sympathomimetic compound in her blood at the time of her stroke, then such sympathomimetic compounds are also a plausible alternative cause. Third, NPC asserts that (a) because plaintiff contends she suffered an event of cerebral vasoconstriction leading to the ICH, and (b) because all human beings have endogenous vasoconstrictive substances in their blood at all times, including vasoconstrictors much stronger than bromocriptine, then such endogenous vasoconstrictive substances are also a plausible alternative cause. The Court reviews these arguments *seriatim.*

[30] 109. NPC's argument that the postpartum period itself is a plausible alternative cause of plaintiff's ICH is supported in large measure by the Kittner Study and published in the New England Journal of Medicine. Dr. Buchholz, a co-author of that study, testified at the *Daubert* hearing. The Kittner Study concluded that the relative risk of ICH in the postpartum period was a statistically-significant 28.3, *i.e.,* that postpartum women are more than 28 times more likely to have ICH than other, similarly-aged women who are not postpartum. Plaintiff's main criticism of this study is that it was conducted at a time when Parlodel ® was available for the prevention of lactation and that the investigators, not having ascertained the drugs, if any, used by the women in the study, cannot exclude the possibility that some of the observed strokes occurred in women using Parlodel ®.

110. The Court concludes that, notwithstanding plaintiff's criticisms of the Kittner Study, the risk of the postpartum period itself still constitutes a plausible alternative hypothesis that plaintiff's experts must rule out if they are to conduct a valid differential diagnosis. First, plaintiff's criticism is based on an assumption that Parlodel ® was in fact in use at the hospitals involved in the Kittner Study during the two years of that study. They did not present any evidence to support such an assumption, however. Dr. Kulig testified, for example, that in his own hospital, Parlodel ® was taken off the preprinted standing orders during the time

frame of the Kittner Study. 11/8 Tr. at 32 (Kulig); Ex. 615. It is equally likely, at least in the absence of contrary evidence, that regular Parlodel ® usage had terminated at the hospitals in the Kittner Study as well. Second, plaintiff's criticism is based on the further assumption that some or all of the women identified in the Kittner Study with postpartum stroke had been (a) bottle-feeding and (b) using a drug to suppress lactation. Again, there is no evidence to support such assumptions. Third, Dr. Kittner engaged in a subsequent case-control study, examining the potential risk factors for ischemic stroke in the same geographic area. 11/15 Tr. at 179–80 (Buchholz); Ex. GB. As Dr. Buchholz testified—and as plaintiff did not contradict—the case-control study *did* seek information concerning drug use within one month of an incident stroke, and none of the seven postpartum women who had stroke in that study indicated usage of Parlodel ®. These facts were set forth in a letter from Dr. Kittner published in the New England Journal of Medicine and support an inference that Parlodel ® may not have been available in the hospitals covered by the study. Accordingly, the Court concludes that plaintiff did not provide any evidence to support her argument that the postpartum strokes noted in the Kittner Study may have been in women who were taking Parlodel ® at the time.

111. Quite apart from the conclusions of the Kittner Study itself, the Court notes that plaintiff's expert, Dr. Petro, admitted that postpartum strokes "have been known about since the beginning of recorded medical history." 11/10 Tr. at 213–14 (Petro). Recent peer-reviewed, published papers that reflect the background risk of stroke in the postpartum period include papers by Lanska, *et al.* 11/15 Tr. at 168–69 (Buchholz); Ex. GU. Additionally, plaintiff's experts Drs. George Macones and Leslie Iffy both admitted at depositions that the postpartum period is itself a risk factor for stroke.

112. Additionally, NPC has presented evidence, uncontested by plaintiff, that there are various physiologic changes that occur in the postpartum period in all women that create, in and of themselves, an increased risk of stroke. Thus, for example, Dr. Buchholz testified that:

> There are a number of physiological changes that occur in the transformation from pregnancy back to the non-pregnant state. These take place in what's known as the postpartum period, which is defined as the first six weeks postdelivery. During that time there's a major decrease in blood volume; there are hormonal changes, as the woman shifts from the hormonal state of pregnancy to non-pregnancy; there are changes in coagulation of the blood that are thought to create a hypercoagulable state, that is a state in which blood clots more easily in some women in this period. Those are some of the mechanisms that have been put forth to account for the rise in stroke in the postpartum period.

11/15 Tr. at 170 (Buchholz). The Court concludes that such unchallenged testimony, in and of itself, is sufficient to establish the postpartum period itself as a plausible alternative cause of plaintiff's stroke. Therefore, any valid differential diagnosis must use scientifically-reliable means, *i.e.,* "sufficient diagnostic techniques," to exclude the risk of the postpartum period itself as the sole cause of plaintiff's stroke.

113. The Court concludes that plaintiff's experts did not use any methodology, let alone "sufficient diagnostic techniques," to rule out the postpartum period itself as the sole cause of plaintiff's stroke.

114. Even if there is no increased risk of stroke arising from the postpartum pe-

riod itself, plaintiff's experts admitted that there is a background risk of stroke that occurs in human beings independent of any drug use. The Court concludes that plaintiff's experts did not demonstrate any valid diagnostic methodology—any "sufficient diagnostic technique"—for excluding the background risk of stroke as the sole cause of plaintiff's stroke.

115. NPC's argument that some, unidentified over-the-counter sympathomimetic drug ingested by plaintiff must be ruled out as the sole cause of her ICH similarly presents an alternative causation scenario that the Court concludes is "plausible" within the meaning of *Heller* and *Paoli II*. First, it is clear that plaintiff's theory of causation is that bromocriptine was capable of causing, and did cause, plaintiff's cerebral hemorrhage because it is a "vasoconstrictive" compound. *See, e.g.,* 11/8 Tr. at 12 (opening statement of plaintiff's counsel Kristal); *id.* at 59, 85–86, 113, 127, 129, 136–38, 140–42, 156 (Kulig) [10] ; 11/10 Tr. at 38, 51, 54, 67 (Petro). Indeed, Dr. Petro, on direct examination, set forth plaintiff's position about the significance of a compound's ability to cause vasoconstriction quite succinctly:

> Q. Do you have an opinion to a reasonable degree of medical certainty whether vasoconstriction can cause an intracerebral hemorrhage?
>
> A. Yes.
>
> Q. What is your opinion?
>
> A. My opinion is that in fact vasoconstriction is a cause for intracerebral hemorrhage.

11/10 Tr. at 67 (Petro).

116. Second, the evidence unequivocally showed that, in two drug screens performed on samples of plaintiff's urine at or around the time of her stroke, a sympathomimetic substance was found. The first of these, obviously taken closer in time to plaintiff's ICH, showed a "large amount" present. Plaintiff does not dispute the fact that sympathomimetic substances are uniformly vasoconstrictive. *See, e.g.,* 11/8 Tr. at 90 (Kulig); 11/15 Tr. at 23 (Petro).

117. Although Dr. Kulig opined that the "large amount" present could still have been consistent with a therapeutic dose of a drug such as Contac—and the Court does not take issue with that testimony for the purposes of this opinion—the exact level of sympathomimetic substance present is not material for the purposes of determining what might be a "plausible" alternative hypothesis. This is so for at least two reasons. First, plaintiff's experts admitted that cases of stroke have been recorded in young people who have had no other obvious risk factor than the use of therapeutic amounts of over-the-counter ("OTC") drugs containing a sympathomimetic ingredient. 11/15 Tr. at 17 (Petro); *see also* 11/16 Tr. at 71 (testimony of Dr. Cohan that "the use of sympathomimetic compounds . . . ha[s] been reported in association with cerebral hemorrhage"), 81–83 (same). Because plaintiff's methodology relies upon case reports of stroke in patients using Parlodel ® as evidence that Parlodel ® causes stroke, the case reports of stroke in patients using therapeutic amounts of OTC drugs containing sympathomimetics likewise establishes such OTC drugs as a "plausible" alternative cause that must be included on a valid differential diagnosis. Stated otherwise, it would be decidedly *unscientific* and *unreliable* to allow certain drugs to appear on a differential diagnosis on the basis of case reports, *e.g.,* Parlodel ®, but to exclude from that differential other

10. Dr. Kulig testified that "vasoconstriction without actually causing hypertension [can] lead to hemorrhagic stroke just by itself." 11/8 Tr. at 156 (Kulig).

drugs for which comparable case reports exist, *e.g.,* OTC sympathomimetic drugs. Second, the causation opinions of plaintiff's experts concerning Parlodel ® do not depend upon any particular level of bromocriptine allegedly existing in plaintiff's blood. Indeed, there is no objective record at all of any particular level of bromocriptine in plaintiff's blood at the time of her stroke. Accordingly, plaintiff's experts cannot validly resist inclusion of sympathomimetic substances on their differentials merely because high levels of such substances were not proven to exist in plaintiff's blood.

118. The Court concludes that the presence of sympathomimetic substances in plaintiff's blood, in and of itself, is sufficient to establish such sympathomimetic substances as a plausible alternative cause of her stroke. Therefore, any valid differential diagnosis must use scientifically-reliable means, *i.e.,* "sufficient diagnostic techniques," to exclude the possibility that the stroke was caused solely by such substances.

119. The Court concludes that plaintiff's experts did not use any methodology, let alone "sufficient diagnostic techniques," to rule out such sympathomimetic substances as the sole cause of plaintiff's stroke.

120. NPC's argument that endogenous vasoconstrictive substances are also a plausible alternative cause of plaintiff's ICH is based on the testimony of Dr. Petro, plaintiff's neurologist, and Dr. Engelman, NPC's expert in internal medicine. Dr. Petro testified as follows:

> Q. By the way, norepinephrine is a neurosympathomimetic compound?
>
> A. Yes.
>
> Q. It's one the human body itself manufactures, correct?
>
> A. Correct.
>
> Q. In fact, the human body is constantly manufacturing norepinephrine and other vasoconstrictive substances, isn't that right?
>
> A. Yes.
>
> Q. To list just some of them, that would include serotonin?
>
> A. Yes.
>
> Q. It would include angiotensin?
>
> A. Yes.
>
> . . .
>
> Q. In your research related to this case, did you do any research to determine the comparative vasoconstrictive effects of norepinephrine to the alleged vasoconstrictive effect of bromocriptine?
>
> A. No.
>
> Q. Did you make that comparison or attempt to do such a comparison with any of the endogenous vasoconstrictors, such as serotonin or angiotensin?
>
> A. No.

11/15 Tr. at 24–25 (Petro). Although Dr. Petro did not attempt to make any comparison between the vasoconstrictive potency of the endogenous vasoconstrictors (*e.g.,* norepinephrine and serotonin), compared to bromocriptine, the "superficial hand vein" study, *i.e.,* a study by Sandoz's Dr. Aellig, Ex. 1410, which Dr. Kulig relied upon, 11/9 Tr. at 113, demonstrated that the vasoconstrictive strength of the endogenous vasoconstrictors is greater than that of bromocriptine. 11/16 Tr. at 149–50 (Engelman). According to Dr. Engelman, the naturally-occurring vasoconstrictors norepinephrine and serotonin are "the most potent vasoconstrictors," even when compared to bromocriptine as they were in this study. *Id.*

121. The Court concludes that the endogenous vasoconstrictors are themselves a plausible alternative cause of plaintiff's stroke. Therefore, any valid differential diagnosis must use scientifically-reliable

means, *i.e.,* "sufficient diagnostic techniques," to exclude the possibility that the stroke was caused solely by such endogenous vasoconstrictors.

122. The Court concludes that plaintiff's experts did not use any methodology, let alone "sufficient diagnostic techniques," to rule out endogenous vasoconstrictors as the sole cause of plaintiff's stroke.

[31] 123. In addition, the Court concludes that, quite apart from plaintiff's experts' failure to demonstrate sufficient diagnostic techniques by which they could rule out the postpartum period itself, sympathomimetic substances, and/or endogenous vasoconstrictors as sole causes of plaintiff's stroke (individually or acting with each other), the differential diagnoses attempted by plaintiff's experts were not based on "a valid and strong temporal relationship" as required by *Heller.* 167 F.3d at 154. As noted above, plaintiff can rely only on her own testimony—uncertain on its face—as to when she last took Parlodel ®. If she last took Parlodel ® as much as 60 hours prior to her stroke, a possibility recognized by her experts, *see* 11/15 Tr. at 57 (Petro), and if the half-life of Parlodel ® in the blood is as short as three hours, again a possibility recognized by her experts, *see id.* at 58 (Petro), then her blood levels of bromocriptine would be reduced by a factor of 2 20 from their initial, therapeutic level, *i.e.,* would be less than one two-millionth of their starting levels.[11] On the other hand, if plaintiff took Parlodel ® only 24 hours before her stroke, and if the half-life is as high as 100 hours, a situation postulated by her experts, *see id.,* at 58 (Petro), then her blood levels at the time of the stroke would be only barely lower than they were when last at therapeutic levels. Accordingly, given the uncertainties in the timing of plaintiff's last dose and uncertainties with respect to the half-life of bromocriptine articulated by plaintiff's experts, the level of bromocriptine in plaintiff's blood would vary from the therapeutic level at one extreme to 1/2,000,000th of the therapeutic level at the other extreme. The Court concludes, therefore, that plaintiff has not shown a "valid and strong temporal relationship." Stated otherwise, in the language of *Heller,* plaintiff's temporal relationship is too "shaky" to constitute a valid basis for inclusion of Parlodel ® on the differential diagnosis.

124. Accordingly, even if plaintiff's experts were not required to demonstrate "sufficient diagnostic techniques" for excluding the postpartum period, sympathomimetic drugs, and endogenous vasoconstrictors (or any combination thereof), or if plaintiff's experts had in fact appropriately used such techniques, the Court concludes that Parlodel ® cannot be placed *on* the differential diagnosis at all.

[32] 125. The Court concludes, independently, that plaintiff's experts' proposed differential diagnoses fail for lack of scientific reliability as a result of plaintiff's experts' failure to demonstrate adequate evidence that plaintiff's ICH was caused by vasospasm. The angiogram performed on plaintiff did not mention vasospasm or vasoconstriction. Although the word "arthritis" appears, which the Court accepts as a typographical error for "arteritis," the angiogram report explains that the possibility of arteritis was raised by evidence of ectasia in plaintiff's arteries. Uncontradicted testimony at the hearing shows that "ectasia" is a medical term for dilation, the opposite of constriction. Accordingly, the angiogram report directly contradicts plaintiff's causal theory.

11. If the half-life is three hours, than a 60–hour period contains 20 half-lives. Two raised to the twentieth power is more than 2,000,000.

126. In addition to the angiogram report, experts on both sides discussed other diagnostic techniques utilized with respect to plaintiff. These include pathologic examination of a specimen taken during the craniotomy that plaintiff underwent as well as examination by the neurosurgeon during that operation. Neither the pathologic reports nor the neurosurgeon's reports mention vasospasm or vasoconstriction or suggest its existence.

127. Plaintiff's experts contend that vasospasm or vasoconstriction could still have existed at the time of plaintiff's ICH, but then disappeared by the time of the angiogram and other diagnostic measures. However, at the same time, they also rely heavily on the angiogram and the other diagnostic measures to rule out certain alternative causes of ICH, *e.g.,* arteriovenous malformation ("AVM") or aneurysm. Thus, plaintiff's experts take the inconsistent position that negative results on these tests are *capable* of disproving alternative causes of ICH, but are *incapable* of disproving vasospasm or vasoconstriction as a cause of ICH. This inconsistency is the hallmark of a decidedly *unscientific* approach.

128. Accordingly, the Court concludes that plaintiff has failed to demonstrate with scientifically-reliable methodology that the cause of her ICH was vasospasm or vasoconstriction.

K. Conclusions of Law on Sufficiency of Evidence

129. Even if plaintiff's experts' opinions concerning medical causation are admissible, the Court must also determine whether they are sufficient as a matter of law to provide a basis for a jury finding on this element of plaintiff's case. *See Daubert,* 509 U.S. at 596, 113 S.Ct. 2786 ("in the event the trial court concludes that the scintilla of evidence presented supporting a position is insufficient to allow a reasonable juror to conclude that the position more likely than not is true, the court remains free to ... grant summary judgment") (*citing Turpin v. Merrell Dow Pharm., Inc.,* 959 F.2d 1349 (6th Cir.) (holding that scientific evidence that provided foundation for expert testimony, viewed in the light most favorable to plaintiffs, was not sufficient to allow a jury to find it more probable than not that defendant caused plaintiff's injury), *cert. denied,* 506 U.S. 826, 113 S.Ct. 84, 121 L.Ed.2d 47 (1992); *Brock v. Merrell Dow Pharm., Inc.,* 874 F.2d 307 (5th Cir.1989) (reversing judgment entered on jury verdict for plaintiffs because evidence regarding causation was insufficient), *modified,* 884 F.2d 166 (5th Cir.1989), *cert. denied,* 494 U.S. 1046, 110 S.Ct. 1511, 108 L.Ed.2d 646 (1990)).

[33] 130. Here, the Court concludes that, even if plaintiff's experts' testimony on medical causation were admissible under Rules 401–03, 702 and 703, such evidence provides but a scintilla of support for plaintiff's position and would not be sufficient to allow a reasonable jury to find that plaintiff's ICH had been caused by Parlodel ®.

L. Plaintiff Has Failed to Demonstrate General Causation

[34] 131. The Court concludes that the methodology employed by plaintiff's experts fails all three of the Rule 702 prongs and is thus inadmissible. Plaintiff's experts' opinions are merely "educated guesses dressed in evening clothes." *Siharath,* 131 F.Supp.2d at 1373.

(i) The Insufficiency of the Evidence

132. The first prong of Rule 702 requires the Court to determine whether the proffered expert testimony "is based on sufficient facts or data." Fed.R.Evid. 702.

133. In evaluating the admissibility of plaintiff's experts' testimony and the usefulness of the conclusions drawn in Dr. Flockhart's Rule 706 report, the Court must consider whether these opinions are adequately grounded in an objectively sufficient quantum and type of data. *See id.; see also In re: Canvas Specialty, Inc.*, 261 B.R. 12, 20 (Bankr.C.D.Cal.2001) (first criterion of Rule 702 requires sufficient quantum of right kinds of data).

134. The Court concludes, as did Dr. Powers and Dr. Savitz, that the existing data regarding Parlodel ® and stroke are simply insufficient both in terms of quantity and type to reliably support the testimony of Drs. Kulig and Petro.

135. Although the Court recognizes that courts in other Parlodel ® cases have been willing to lower the bar of sufficiency to conform to the lack of informative data, *see, e.g., Globetti v. Sandoz Pharm. Corp.*, 111 F.Supp.2d 1174, 1179 (N.D.Ala.2000) (allowing testimony of Drs. Kulig and Petro because they made best use of *available* evidence), this Court concludes that adoption of such a shifting standard would strip Rule 702 and *Daubert* of their objective anchors by lowering the admissibility standard to meet whatever evidence happens to be available, regardless of its scientific unreliability. *See Siharath*, 131 F.Supp.2d at 1373 (disagreeing with *Globetti* holding and stating that *Daubert* does not establish a " 'best efforts' test").

136. Dr. Flockhart relies upon a similar, standardless approach in concluding that plaintiff's experts' testimony is grounded in reliable methodology. Dr. Flockhart's approach, which would allow plaintiff's experts to draw conclusions simply because NPC allegedly did not conduct sufficient studies to prove those conclusions wrong, would turn Rule 702 and *Daubert* on their heads by allowing the *absence* of reliable testing and data to support a causation opinion. Such an approach would also flip the relevant burdens—it is plaintiff who has the burden of proving causation and the reliability of her experts' testimony.

137. This Court concludes that lowering Rule 702's objective requirements to meet the available evidence would result in an infinite error rate. Although plaintiff's experts may honestly believe that they have done the best analysis they could with the data available and that defendant should have conducted additional scientific studies, those beliefs do not enhance the reliability of their testimony. *See Total Containment, Inc. v. Dayco Prods., Inc.*, 2001 WL 1167506 at *7 (E.D.Pa.2001) (if enough relevant data to support methodology are simply unavailable, methodology will have infinite error rate); *In re: Diet Drugs*, 2001 WL 454586 at *13 (excluding expert testimony of scientist who failed to conduct blinded test, because fact that it was conduct of adverse party which prevented blinding does not make testimony any more reliable); *Pappas*, 136 F.Supp.2d at 426 (excluding testimony of expert pursuant to *Daubert*, although expert carefully examined available evidence and although fire destroyed large portion of evidence needed to prove fire's cause); *see also Siharath*, 131 F.Supp.2d at 1372 (*Daubert* does not establish a "best efforts" test; Drs. Kulig and Petro could not express an opinion based upon a reliable scientific methodology given the current state of the scientific data regarding Parlodel ® and stroke).

(ii) Plaintiff's Experts Have Failed to Present Reliable Evidence That Parlodel ® Can Cause Intracerebral Hemorrhage

138. The second prong of Rule 702 requires the Court to focus on whether an expert's opinion is reliable, *i.e.*, whether it

consists of valid scientific knowledge. *See* Fed.R.Evid. 702.

139. As used in Rule 702, "the adjective 'scientific' implies a grounding in the methods and procedures of science," and "[t]he word 'knowledge' connotes more than subjective belief or unsupported speculation." *Daubert,* 509 U.S. at 589–90, 113 S.Ct. 2786; *accord.*

140. The factors the Court may consider in assessing the admissibility of proffered expert testimony include, but are not limited to: "(a) whether a method consists of a testable hypothesis; (2) whether the method has been subjected to peer review; (3) the known or potential rate of error; (4) the existence and maintenance of standards controlling the technique's operation; (5) whether the method is generally accepted; (6) the relationship of the technique to methods which have been established to be reliable; (7) the qualifications of the expert witness testifying based on the methodology; and (8) the non-judicial uses to which the method has been put." *Oddi,* 234 F.3d at 145 (*quoting Paoli II,* 35 F.3d at 742 n. 8).

141. The hallmark of *Daubert's* reliability prong is the scientific method—namely, the generation of testable hypotheses that are then subjected to the real world crucible of experimentation, falsification/validation, and replication. *See Daubert,* 509 U.S. at 593, 113 S.Ct. 2786; *Oddi,* 234 F.3d at 156 (excluding expert testimony that failed key requirement of testing); *Elcock,* 233 F.3d at 747 (excluding expert testimony that failed to articulate methodology with objective standards and reproducible results).

[35] 142. As explained in *Elcock,* an expert's testimony should be excluded if testing his methodology does not generate consistent results. Inconsistency of results demonstrates the method is "unreliable because it is subjective and unreproducible." *Elcock,* 233 F.3d at 747. Similarly in *Oddi,* the Court of Appeals for the Third Circuit held that expert testimony based on training and experience as opposed to adequate testing was properly excluded. *Oddi,* 234 F.3d at 157 (*Daubert* requires more than "haphazard, intuitive inquiry"); *see also In re: TMI,* 193 F.3d at 675, 703 n. 144 ("*Daubert* recognized that science is an empirical endeavor in which testing plays a crucial role"; "it is impossible to test a hypothesis generated by a subjective methodology") (internal quotations omitted); *Chester Valley Coach Works v. Fisher–Price, Inc.,* 2001 WL 1160012 at *4 (E.D.Pa.2001) (excluding opinion based on experience and training as opposed to testing); *Booth,* 166 F.Supp.2d at 220–21 (excluding testimony based on training and experience as opposed to testing; although method was intuitively appealing, it was not based on objective anchor of testing); *In re: Diet Drugs,* 2001 WL 454586 at *10, *13 (expert testimony excluded where methodology was overly subjective and not reproducible); *Pappas,* 136 F.Supp.2d at 425 (expert opinion based on years of experience and appeal to common sense excluded in absence of testing).

143. Thus, although the Court imposes no requirement that plaintiff's experts point to "definitive published studies," *Heller,* 167 F.3d at 154, in order for their methodology to be reliable, some reliable evidence of adequate testing of their hypothesis that Parlodel ® causes ICH is required. *See Elcock,* 233 F.3d at 747; *Oddi,* 234 F.3d at 156. As discussed below, the Court concludes, as did Dr. Powers and Dr. Savitz, that plaintiff's experts have failed to show that their hypothesis has been tested, and consistently and reliably demonstrates that Parlodel ® causes ICH. Nor have plaintiff's experts come forward with any other reliable evidence to

create a solid foundation for their hypotheses and conclusions. *See Heller,* 167 F.3d at 156 (exclusion of expert testimony appropriate where expert "relied on no scientific studies and the remaining foundation for his conclusion was shaky").

(1) Plaintiff's Experts Fail to Faithfully Apply Their Own Scientific Standards

144. In analyzing the reliability of plaintiff's experts' opinions, it is appropriate for the Court to consider whether the testimony they intend to give faithfully complies with their own views of what standards constitute the scientific method. Although *Daubert* and Rule 702 focus on "scientific knowledge," the Court agrees that "something doesn't become 'scientific knowledge' just because it's uttered by a scientist; nor can an expert's self-serving assertion that his conclusions were 'derived by the scientific method' be deemed conclusive." *Daubert II,* 43 F.3d at 1315–16.

145. The reliability of plaintiff's experts' opinions is significantly undermined by the fact that they abandon the method that they themselves have defined. For example, Dr. Petro acknowledges that the scientific method requires the formulation and testing of hypotheses, and he explained how one would test the hypothesis that a particular drug causes a specific adverse event. But when Dr. Petro was asked whether his causation hypothesis in this case had ever been tested in this manner, he admitted that it had not. Moreover, Dr. Petro has also conceded that his methodology in this case—concluding causation in the absence of human studies—is "more subjective than scientific methodology."

146. The reliability of Dr. Kulig's opinions in this case is likewise undermined by his failure to follow his own standards. During a *Daubert* hearing in another Parlodel ® case, he agreed that the scientific method includes, *inter alia,* "test[ing] the hypothesis." Dr. Kulig has conceded that to test the hypothesis that Parlodel ® can cause stroke, one needs an experimental method. Dr. Kulig has also conceded—while testifying as a defense expert witness in a breast implant lawsuit—that the scientific method for establishing causation cannot be based on case reports and differential diagnosis, but must instead be based on the demonstration of an association through a controlled study. Although he has confirmed that the methodology he would use to assess causation in this case is "exactly the same" as the methodology he used in the breast implant litigation, Dr. Kulig admits (like Dr. Petro) that the testing of hypotheses required by the scientific method has *not* been done with respect to Parlodel ® and stroke. *See also Glastetter,* 107 F.Supp.2d at 1042–44 (stating that Dr. Kulig could not point to any statistically-significant study demonstrating an association between Parlodel ® and stroke).

147. Notwithstanding the significant concessions discussed above, Dr. Petro and Dr. Kulig are still being offered to give general causation opinions in this case. However, the Court concludes that their significant departures from their own standards render their methodology scientifically unreliable.

148. Moreover, the opinions of Dr. Kulig and Dr. Petro are inconsistent with the opinion of plaintiff's expert in epidemiology and obstetrics/gynecology, Dr. Macones. He "can't say either way" whether Parlodel ® can cause stroke.

149. The Court further concludes that Dr. Kulig and Dr. Petro apply different standards in evaluating whether other plausible causes of plaintiff's stroke should be placed and kept on the differential diag-

nosis than they do in making the same assessments regarding Parlodel®. For example, plaintiff's experts demand multiple solid epidemiology studies before they will agree to place certain other plausible causes of plaintiff's stroke on the differential diagnosis, but abandon that standard when it comes to Parlodel®. *See, e.g., Glastetter,* 107 F.Supp.2d at 1024–25.

150. Dr. Flockhart's report evinces a similar tendency to apply a double standard when it comes to ruling possibilities in or out of the differential diagnosis. For example, Dr. Flockhart rules out caffeine, a substance he knows is a known vasoconstrictor, as a potential cause of plaintiff's stroke because he says there is no credible evidence it causes stroke. However, when he goes through what should be the same analysis regarding Parlodel®, he leaps to the conclusion that if Parlodel® can allegedly cause vasoconstriction in dogs' ears it can also cause ICH in humans. Such inconsistent application of methodology renders any conclusions scientifically unreliable.

151. Because consistency is a hallmark of the scientific method, plaintiff's experts must be required to satisfy their own standards of reliability. *See Lust v. Merrell Dow Pharm., Inc.,* 89 F.3d 594, 598 (9th Cir.1996) ("the district court should be wary that the [expert's] method has not been faithfully applied"); *O'Conner v. Commonwealth Edison Co.,* 13 F.3d 1090, 1106–07 (7th Cir.1994) (excluding opinion where expert did not follow his own expressed methodology for establishing causation); *Hall v. Baxter Healthcare Corp.,* 947 F.Supp. 1387, 1400 (D.Or.1996). In any event, the Court independently concludes that plaintiff's experts have failed to satisfy the Court of Appeals for the Third Circuit's standards of reliability.

(2) No Known Biological Mechanism

152. An important aspect of the *Daubert* reliability analysis is determining whether an expert's causation opinion is supported by an explanation of the biological and/or pathological mechanism at work. "The underlying predicates of any cause-and-effect medical testimony are that medical science understands the physiological process by which a particular disease or syndrome develops and knows what factors causes the process to occur." *Black v. Food Lion, Inc.,* 171 F.3d 308, 314 (5th Cir.1999); *see also Brumbaugh,* 77 F.Supp.2d at 1157 (excluding plaintiff's expert's testimony regarding Parlodel® because, *inter alia* no proof was presented to support his "causal mechanism theory"); *Reference Manual on Scientific Evidence* at 422 (2d ed.2000) ("it is difficult to accept an association between a [chemical] compound and a health effect when no mechanism can be identified by which the chemical exposure leads to a putative effect").

153. Neither Dr. Flockhart nor plaintiff's experts can explain to the requisite reasonable degree of medical certainty the biological and/or pathological mechanism by which Parlodel® allegedly causes stroke or other adverse reactions in humans. *See also Glastetter,* 107 F.Supp.2d at 1032 (excluding Dr. Kulig's testimony and stating that he "does not know the mechanism by which bromocriptine causes seizure"); *Hollander,* 95 F.Supp.2d at 1235 (excluding Dr. Kulig's testimony and stating that he "could only list 'possible' mechanisms for Parlodel® causing hypertension") (footnote omitted).

154. Nor can plaintiff's experts explain the biological or pathological mechanism by which Parlodel® allegedly causes vasoconstriction (which they contend led to plaintiff's stroke).

155. Indeed, plaintiff's experts have not even reliably demonstrated that cerebral vasoconstriction causes ICH.

156. While *Daubert* does not require absolute precision in identifying the medical mechanism of injury, there still must be "sufficiently compelling proof that the agent must have caused the damage somehow." *Brumbaugh*, 77 F.Supp.2d at 1157 (citation omitted). Dr. Flockhart's statement that the lack of understanding regarding the mechanism by which Parlodel ® allegedly causes vasoconstriction should not detract from a conclusion that Parlodel ® can cause vasoconstriction if "the preponderance of the evidence makes it clear it can do so," is irrelevant because there is no such preponderance of reliable evidence in this case. Without requiring undue precision in this regard, the Court nevertheless concludes that the lack of evidence regarding a medical mechanism to explain plaintiff's experts' causation theory further undermines the reliability of their opinions. *See, e.g., In Re: Diet Drugs,* 2000 WL 962545 at *6 (lack of knowledge regarding biological mechanism cited as undermining reliability of expert medical causation opinion).

M. The Evidence Relied Upon by Plaintiff's Experts Does Not "Fit" the Facts of This Case

[36] 157. The third Rule 702 prong requires the Court to determine whether there is an adequate "fit" between an expert's opinions and the facts at issue in this lawsuit. *See Daubert*, 509 U.S. at 591, 113 S.Ct. 2786. Under *Daubert*, scientific testimony does not assist the trier of fact unless it has a valid scientific connection to the pertinent inquiry. *See id.; Heller*, 167 F.3d at 152; *Paoli II*, 35 F.3d at 742–43. Expert testimony based on false assumptions and fictional or random data is inadmissible. *Elcock*, 233 F.3d at 756 n. 13.

158. As noted by the Supreme Court in *Joiner*, "conclusions and methodology are not entirely distinct from one another." *Joiner*, 522 U.S. at 146, 118 S.Ct. 512. "A court 'must examine the expert's conclusions in order to determine whether they could reliably flow from the facts known to the expert and the methodology used.' " *Oddi*, 234 F.3d at 146 (*quoting Heller*, 167 F.3d at 153). "A court may conclude that there is simply too great an analytical gap between the data and the opinion proffered." *Joiner*, 522 U.S. at 146, 118 S.Ct. 512; *see also Oddi*, 234 F.3d at 146; *In re: TMI*, 193 F.3d at 666.

159. The Court agrees with the *Caraker* court that:

> The most glaring problem with the opinions of Drs. Kulig and Petro is that their "ruling in" decision requires too many extrapolations from dissimilar data, too many analytical leaps, and involves a loose application of purportedly objective scientific causation standards. For these and other reasons, the data these experts used to extrapolate their conclusions is suspect, and their opinions are more like personal opinions than products of any scientific methodology rigorously applied.

Caraker, 172 F.Supp.2d at 1049; *see also Siharath*, 131 F.Supp.2d at 1371 (concluding that plaintiff's experts do not provide "good grounds" at each step of causal chain) (*citing Paoli II*, 35 F.3d at 745).

(i) The Theory That Parlodel ® is a Vasoconstrictor

160. Even if this Court were to accept as scientifically reliable plaintiff's experts' conclusion that Parlodel ® acts as a vasconstrictor, these experts have not demonstrated that this alleged vasoconstriction can cause the specific injury at issue here: ICH in humans. Plaintiff's experts' opinions are based largely on purported evi-

dence that Parlodel ® can cause peripheral vasoconstriction or digital vasospasm—*i.e.,* vasoconstriction in the fingers, toes, tips of the nose and ears. But there is no evidence such peripheral vasoconstriction either indicates the presence of cerebral vasoconstriction or leads to hemorrhagic strokes of the type experienced by plaintiff. *See In re: Diet Drugs,* 2000 WL 962545 at *10 (rejecting expert's attempts to rely on results measuring brain serotonin and extrapolating from them to draw conclusions regarding serotonin in the periphery).

161. In other words, plaintiff seeks to have her experts testify that Parlodel ® causes constriction of the cerebral arteries based on an extrapolation from evidence concerning peripheral vasoconstriction. However, the bald assertion of these experts that this extrapolation is justified does not make it so: Trained experts commonly extrapolate from existing data. But nothing in either *Daubert* or the Federal Rules of Evidence requires a district court to admit opinion evidence that is connected to existing data only by the *ipse dixit* of the expert." *Joiner,* 522 U.S. at 146, 118 S.Ct. 512. This Court "is not required to simply 'tak[e] the expert's word for it.' " *Caraker,* 172 F.Supp.2d at 1047 (*quoting* Advisory Committee Notes to 2000 Amendments to Rule 702); *accord In re: TMI Litig.,* 193 F.3d at 687. This Court concludes, as contemplated by the Supreme Court in *Joiner* and the Court of Appeals for the Third Circuit in *Paoli II,* that in this case "there is simply too great an analytical gap between the data and the opinion proffered" by plaintiff's experts. *Joiner,* 522 U.S. at 146, 118 S.Ct. 512. By failing to present reliable scientific evidence linking the peripheral vasoconstriction premise to their ICH-causation conclusion, plaintiff's experts have run afoul of the fit requirement. Therefore, the testimony that Parlodel ® is a vasoconstrictor must be excluded. See *In re: Diet Drugs,* 2000 WL 962545 at *10 (excluding expert opinion relying on extrapolation from brain to periphery); *Barker v. Deere and Co.,* 60 F.3d 158, 162 (3d Cir.1995) (evidence of other injuries not admissible unless circumstances of other occurrences are "substantially similar"); *Wolf v. Procter & Gamble,* 555 F.Supp. 613, 621 (D.N.J.1982) (same); *see also Allison,* 184 F.3d at 1314 (affirming exclusion of expert's causation testimony in silicone breast implant case based on human retinal studies due to expert's failure to establish adequate connection between such studies and plaintiff's complaints of disease; "[e]ven assuming gel bleed, a finding that silicone *oil* emulsifies the eye indicates that silicone gel similarly emulsifies in breast tissue and causes systemic disease is quite a leap.") (emphasis omitted).

162. Along similar lines, even if this Court were to accept plaintiff's experts' conclusion that Parlodel ® is a *cerebral* vasoconstrictor (a conclusion that they have not established by reliable, scientifically valid evidence), plaintiff's experts have failed to demonstrate that this alleged cerebral vasoconstriction can cause ICH, the injury at issue in this case. There is no scientifically reliable evidence that cerebral vasoconstriction causes hemorrhagic strokes in the type experienced by plaintiff.

[37] 163. In sum, the testimony offered by plaintiff's experts that Parlodel ® acts as a cerebral vasoconstrictor does not "fit" the facts of the case, and does not assist the trier of fact in evaluating the evidence. Therefore, under *Daubert* and Rule 702, this testimony is inadmissible. *See, e.g., In re: Diet Drugs,* 2000 WL 962545 at *8 (evidence that drug could cause increase in platelet serotonin unreliable to prove drug causes adverse event

where there was no reliable evidence that an increase in platelet serotonin actually causes adverse event).

(ii) The Theory That Parlodel ® Causes Other Kinds of Strokes

164. Plaintiff's experts have also testified that Parlodel ® causes strokes different from the kind that plaintiff experienced, namely, *inter alia,* ischemic strokes. But her experts and treating physicians agree that plaintiff experienced an ICH. Plaintiff's experts have not presented any reliable evidence establishing a valid scientific connection between their contention that Parlodel ® causes ischemic strokes and their conclusion that it also causes ICH. *See Siharath,* 131 F.Supp.2d at 1365. In other words, there has been no effort to demonstrate generally that whatever causes an ischemic stroke ("dry" stroke) also causes hemorrhagic stroke ("wet" stroke).

[38] 165. Therefore, plaintiff's experts' testimony that Parlodel ® causes non-ICH stroke does not fit the facts of this case. Because such testimony would not "assist . . . the trier of fact," Rule 702, it is inadmissible under *Daubert* and its progeny. *See, e.g., In re: Diet Drugs,* 2000 WL 962545 at *8 (excluding testimony relying on evidence that drug caused increase in platelet serotonin to prove drug caused increase in plasma serotonin); *Barker,* 60 F.3d at 162 (evidence of other injuries not admissible unless circumstances of other occurrences are "substantially similar"); *Wolf,* 555 F.Supp. at 613 (same).

(iii) The Generic Ergot Theory

166. Plaintiff's experts have testified that some ergots have been known to cause vasoconstriction, and hypothesize that it would not be unlikely if Parlodel ®, a member of the ergot family, acts like other ergots.

167. The Court agrees with the conclusions of the *Caraker* court that:

> . . . using this 'guilt by association' inference in their methodology is of questionable scientific reliability, inasmuch as (1) a structural difference between bromocriptine and other Ergots is the addition of a bromine atom . . ., and (2) even small structural changes at the molecular level can radically change a particular substance's properties.

Caraker, 172 F.Supp.2d at 1051 (internal citation omitted). Such assumptions are particularly suspect here, where it is alleged that Parlodel ® causes both vasoconstriction and vasodilation, and "[n]o evidence exists that other ergot alkaloids cause such peculiar effects." *Siharath,* 131 F.Supp.2d at 1364.

[39] 168. Plaintiff's experts have not presented reliable scientific evidence supporting their speculation that all ergots act alike in producing vasoconstriction, much less ICH. Therefore, plaintiff's experts' testimony that Parlodel ® causes vasoconstriction and ICH because it is a member of the ergot family is too great a leap and is inadmissible. *See Caraker,* 172 F.Supp.2d at 1051 (ergot family guilt by association theory too great a leap to be reliable); *Siharath,* 131 F.Supp.2d at 1363 (plaintiff's experts' reliance on generalized ergot inference "raises serious questions of 'fit' "); *Hollander,* 95 F.Supp.2d at 1238 (no reliable evidence that "bromocriptine and the other Ergots have sufficiently similar physiological effects to warrant comparison"); *see also In Re: Diet Drugs,* 2000 WL 962545 at *8 (conclusions based on actions of drug in same chemical family did not reliably follow); *DeLuca,* 791 F.Supp. at 1054 (rejecting analogy to chemically similar compounds).

[40] 169. Plaintiff's experts rely upon evidence of animal and other laboratory studies to support their opinion that Parlodel ® causes ICH in humans. As the Court has found, however, these animal studies differ from the facts of this case in several important respects, including: (1) use of significantly higher doses of bromocriptine than the doses plaintiff consumed; (2) injection of bromocriptine into animals whose nervous systems had previously been destroyed and who were not in the postpartum period; (3) injection of bromocriptine into preparations involving strips of arteries that had been removed from animals; (4) analysis of animal body parts that may have different receptors than the cerebral arteries of the same animal—and different receptors than human cerebral arteries; and (5) injection of Parlodel ® into a human hand vein that has been physically isolated from the rest of the body's blood system. Plaintiff's experts have not presented reliable evidence that there is a valid scientific connection between the data derived from these studies and the completely different factual scenario presented in this lawsuit.

[41] 170. The differences between the hand vein study and the facts of this case—large disparities in dosage; direct injection of a bromocriptine bolus (avoiding the metabolic breakdown of the drug) versus oral ingestion of the drug (with a resulting metabolic effect); the venous effect in a hand as opposed to the arterial effect in the brain; and the differences between a blood vessel isolated from or connected to the body's entire blood system—are so significant that the hand vein study does not have a valid scientific connection to the facts of this case. As with the animal studies, evidence of (and opinions based) on the hand vein study do not satisfy the *Daubert* "fit" requirement.

N. Plaintiff Fails to Reliably Demonstrate Specific Causation

171. Although this Court's conclusion that plaintiff's experts' general causation evidence is inadmissible disposes of NPC's *Daubert* challenge, *see, e.g., Brumbaugh,* 77 F.Supp.2d at 1155 n. 1 ("The issue of specific causation is material, however, only if plaintiff can demonstrate general causation between Parlodel ® and her injury."), the Court will nevertheless also address—in the alternative—whether the specific causation opinions proffered by plaintiff's experts satisfy *Daubert.*

172. Plaintiff's experts utilize the differential diagnosis, which, when reliably applied, has been recognized as an appropriate methodology for assessing specific causation in the Third Circuit. However, the mere statement by an expert that he applied a differential diagnosis in determining specific causation does not *ipso facto* make that application scientifically reliable or admissible. *See Heller,* 167 F.3d at 154 (affirming exclusion of causation opinions based on purported use of differential diagnosis).

173. For the reasons set forth below, the Court holds that Dr. Kulig's and Dr. Petro's specific causation opinions are inadmissible under *Daubert* because: (a) even assuming their general causation methodology was reliable (and the Court has already concluded it was not), they do not—and cannot—rule out, in a reliable, scientifically valid manner, alternative possible causes of plaintiff's ICH that they would be required to consider if they had applied their own methodology in a fair and consistent manner; and (b) they do not apply the differential diagnosis methodology properly in a manner that fits the facts of this lawsuit.

(i) The Insufficiency of the Evidence

174. As with plaintiff's general causation evidence, the Court concludes that

there is insufficient data to support plaintiff's experts' specific causation opinions.

175. The Court concludes that the lack of reliable evidence with respect to general causation leads ineluctably to the conclusion that there is insufficient evidence of specific causation.

176. Even if there were sufficient reliable evidence of general causation, plaintiff's experts are unable to point to reliable evidence in plaintiff's medical records indicative of vasoconstriction, "ergotism," or alleged Parlodel ®-induced ICH. There are simply insufficient data in the case of plaintiff to support plaintiff's experts' conclusions regarding specific causation.

177. Nor did plaintiff's experts rely on sufficient evidence or data in ruling out various plausible alternative causes of plaintiff's ICH.

(ii) Plaintiff's Experts Have Failed to Present Reliable Evidence That Parlodel ® Caused Plaintiff's ICH

178. Women in the postpartum period are at a particularly high risk for stroke. It is well-established that they have an approximately *2800 percent* increased risk of having an ICH—the injury that plaintiff experienced—as compared to women in similar ages who are not postpartum.

179. Therefore, this Court concludes that, for a differential diagnosis of the cause of plaintiff's postpartum ICH to be scientifically valid, it must include as a potential cause the background incidence of postpartum ICH. *See Glastetter,* 107 F.Supp.2d at 1045 n. 29 (holding that plaintiff's experts' conclusions regarding specific causation were inadmissible because they were "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 [plaintiff]"); *Hollander,* 95 F.Supp.2d at 1239 n. 27 (holding that plaintiffs' specific causation evidence was inadmissible because "plaintiffs' experts fail to factor into their analyses, among other possible causes for Mrs. Hollander's stroke, the increased risk of stroke during the postpartum period"); *In re: Paoli,* 2000 WL 1279922 at *5 (specific causation testimony excluded where expert failed to eliminate other possible diagnoses); *In re: Paoli,* 2000 WL 274262 at *7 (excluding testimony due to failure to offer reasonable explanation for ruling out alternative causes of plaintiff's injuries); *Turbe,* 1999 WL 1087026 at *6 (differential diagnosis must "rule out obvious alternative causes"); *see also Chester Valley,* 2001 WL 1160012 at *10 (failure to rule out alternative causes of fire through investigation and testing as opposed to experience and education required exclusion of opinion).

180. In this case, neither Dr. Kulig nor Dr. Petro has provided any reasonable explanation or sufficient diagnostic techniques to rule out the substantial background risk of ICH that exists during the postpartum period. Moreover, they do not have any reliable, reasonable explanation or sufficient diagnostic techniques to rule out other possible causes of plaintiff's ICH, such as sympathomimetic amines, AVM, caffeine, smoking, blood abnormalities, stress, hormones, endogenous vasoconstrictors, or idiopathic causes. Although NPC did not argue that each of these other possible causes has been proven by scientifically reliable evidence to cause stroke, the low threshold that plaintiff's experts applied to place Parlodel ® on their differential diagnosis would require that these alternatives be considered and reasonably ruled out using "sufficient diagnostic techniques." *Heller,* 167 F.3d at 156 (internal citation omitted). If case reports and other indirect evidence are insufficient to place these alternative potential causes on the differential diagnosis, then they

would not be sufficient to place Parlodel ® on the differential diagnosis either. In any event, plaintiff's experts themselves stated that many of these possibilities must be included on any reliable differential diagnosis.

181. Although Dr. Kulig and Dr. Petro claim to have utilized the methodology of differential diagnosis to rule out other possible causes of plaintiff's ICH, the Court's scrutiny of their "methodology" refutes their claim. These witnesses have actually turned the process inside out and leaped to an unreliable, unscientific causation conclusion: namely, because plaintiff took Parlodel ®, all other possible causes of her ICH can be automatically excluded. *See* Kulig/*Glastetter* Dep. at 613–14 ("I've excluded [other causes] as being the likely explanation, taking into consideration the fact that she was taking a drug known to cause this."). This is a fundamental flaw in their differential diagnosis/specific causation analysis. *See Chester Valley,* 2001 WL 1160012 at *4 (expert should not approach investigation with preconceived notions of results); *In re: Diet Drugs,* 2001 WL 454586 at *14 (starting with assumption that drug causes adverse event and then attempting to confirm assumption inverts scientific method); *Caraker,* 172 F.Supp.2d at 1049, n. 5 ("Justifying a conclusion after the fact by applying a methodology does not generally lead to reliable scientific knowledge.").

[42] 182. When an expert fails to conduct a differential diagnosis in a proper manner, the expert's specific causation opinions must be rejected as unsound and scientifically unreliable. *See Heller,* 167 F.3d at 156–57 (affirming exclusion of causation opinion purportedly applying differential diagnosis); *In re: Paoli,* 2000 WL 1279922 at *6 (excluding inadequate differential diagnosis); *In re: Paoli,* 2000 WL 274262 at *7 (same). This Court agrees with the *Glastetter* court's conclusion that Dr. Kulig's and Dr. Petro's differential diagnosis opinions are unreliable and constitute an "improper use of differential diagnosis." *Glastetter,* 107 F.Supp.2d at 1045 n. 29.

(iii) The Evidence Relied Upon by Plaintiff's Experts Does Not "Fit" the Facts of this Case

183. In addition to failing the reliability prong, plaintiff's experts' reliance on their differential diagnosis also does not satisfy the *Daubert* "fit" requirement. Plaintiff's experts failed to identify any reliable evidence from plaintiff's medical records indicative of vasoconstriction, ergotism, or alleged Parlodel ®-induced stroke. Plaintiff's experts' opinions with respect to specific causation are thus unsubstantiated leaps that have no "fit" with the facts of this case.

184. Plaintiff's experts' differential diagnosis also does not reliably rule out reasonable alternative causes of ICH (such as the postpartum period) or idiopathic causes. As a result, there is no valid scientific connection between their opinions and the facts at issue in this lawsuit.

185. Accordingly, this Court concludes that plaintiff's experts' failure to include all relevant circumstances in their differential diagnosis of plaintiff's ICH that are plausibly relevant through consistent application of their methodology, renders their specific causation opinions inadmissible. These opinions do not fit the facts of this case and therefore do not assist the trier of fact within the meaning of *Daubert* and Rule 702. *See Elcock,* 233 F.3d at 756 n. 13 (where methodology depends on false assumptions, it cannot assist trier of fact).

O. Conclusions of Law Regarding Plaintiff's Expert Dr. Kenneth Kulig

[43] 186. In addition to the conclusions of law set forth above, and for the

independent reasons set forth below, the Court concludes that Dr. Kulig's opinions concerning general causation and the methodologies upon which they are based are not scientifically reliable. The Court also concludes that such opinions—as they are based on other ergots, animal models, and adverse events in human beings that are *not* ICH—do not have an adequate "fit" with the issues in this case under Federal Rule of Evidence 702. Accordingly, the Court rules that Dr. Kulig's opinions on general causation are not admissible.

(i) Federal Rule of Evidence 702

187. Before being permitted to give opinion testimony on a particular subject, a witness must be "qualified" as an expert on that subject. *See* Fed.R.Evid. 702 (requiring witness to be "qualified as an expert by knowledge, skill, experience, training, or education"). Here, plaintiff does not proffer Dr. Kulig as an expert in the fields of epidemiology, statistics, neurology, neuropathology, or obstetrics/gynecology. Therefore, the Court holds that he is not qualified as an expert in those fields and is barred by Rule 702 from giving expert testimony as to subjects within those medical/scientific specialties. *See In re: Diet Drugs,* 2001 WL 454586 at *7 ("a party cannot qualify as an expert generally by showing that the expert has specialized knowledge or training which would qualify him or her to opine on some other issue"); *In re: Diet Drugs,* 2000 WL 962545 at *3 (testimony outside expert's area of expertise should be excluded) (citing cases).

188. The Court also concludes that the other requirements of Rule 702, as interpreted by *Daubert* and its progeny, require that Dr. Kulig's opinions be excluded in their entirety. For the reasons set forth throughout the Court's Findings of Fact and Conclusions of Law, Dr. Kulig's opinions fail all three Rule 702 prongs. His testimony is not reliably derived from sufficient data or scientific principles. Nor does his testimony have a valid scientific connection to the facts at issue in this lawsuit so as to assist the fact finder in evaluating the evidence.

189. Moreover, Dr. Kulig's testimony also fails to satisfy the eight, non-exclusive factors that *Daubert* and the Third Circuit law have identified for courts to consider in deciding whether expert testimony is admissible. *See Daubert,* 509 U.S. at 592–94, 113 S.Ct. 2786; *Oddi,* 234 F.3d at 145; *see also Siharath,* 131 F.Supp.2d at 1355 (noting failure of Dr. Kulig's and Dr. Petro's testimony to satisfy *Daubert* factors).

190. First, his opinions—that Parlodel® can cause ICH and did so in this case—have not been validated by testing in accordance with the "[s]cientific methodology ... [of] generating hypotheses and testing them to see if they can be falsified." *Daubert,* 509 U.S. at 593, 113 S.Ct. 2786 (internal quotation marks omitted); *see also Glastetter,* 107 F.Supp.2d at 1045 n. 28 ("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."); *Siharath,* 131 F.Supp.2d at 1358 (same).

191. Second, except for anecdotal information from unreliable case reports, Dr. Kulig's opinions have never been articulated in peer-reviewed publications. They have not appeared in the form of epidemiologic or other scientifically reliable studies. *See Glastetter,* 107 F.Supp.2d at 1045 n. 28 (stating that plaintiff's experts' causation theory has been subjected to peer review and publication "only in the form of unreliable case reports" and that "no peer reviewed epidemiological study or publication conclud[es] that Parlodel® causes ICH"); *Siharath,* 131 F.Supp.2d at 1358 (same). Moreover, even in his single anec-

dotal publication, Dr. Kulig goes no further than to say that a causal association is possible.

192. Third, because Dr. Kulig's opinions are not based on a valid scientific methodology, neither the Court nor anyone else can reliably determine the "known or potential rate of error," *Daubert*, 509 U.S. at 594, 113 S.Ct. 2786, applicable to his opinions. *See Glastetter*, 107 F.Supp.2d at 1045 n. 28 ("the Court has no data available to ascertain whether [plaintiff's experts'] theory has a known rate of error"); *accord Siharath*, 131 F.Supp.2d at 1355. However, on the basis of the Court's detailed findings and conclusions set forth above regarding the significant flaws in Dr. Kulig's opinions, the Court holds that the potential error rate is unacceptably high, if not completely unknown or unknowable, and thus unacceptable for that reason.

193. Fourth, Dr. Kulig's opinions are not generally accepted in the relevant scientific community. *See Daubert*, 509 U.S. at 594 ("Widespread acceptance can be an important factor in ruling particular evidence admissible, and a known technique which has been able to attract only minimal support within the [relevant scientific] community may properly be viewed with skepticism.") (internal quotations omitted); *Glastetter*, 107 F.Supp.2d at 1045 n. 28 ("it does not appear that the theory that Parlodel ® causes ICH in humans is generally accepted in the relevant scientific community"); *accord Siharath*, 131 F.Supp.2d at 1355.

194. To shore up his general causation opinion, Dr. Kulig has relied extensively on the Bradford–Hill criteria, which, according to Dr. Kulig, he has been trained to use. However, the Court concludes that the Bradford–Hill criteria were developed for the purposes of determining whether, when an association between an exposure and a disease has already been demonstrated, that association is causal or not. Review of the criteria themselves, as set forth in the seminal remarks of Dr. Bradford–Hill, shows that an epidemiologic foundation is a prerequisite for application of his criteria. "The Bradford–Hill criteria start with an association demonstrated by epidemiology and then apply such criteria as the temporal sequence of events, the strength of the association, the consistency of the observed association, the dose-response relationship, and the biologic plausibility of the observed association." *In re Breast Implant Litig.*, 11 F.Supp.2d at 1233 n. 5. Accordingly, because plaintiff's experts have not demonstrated any statistically-significant epidemiologic study showing an increased risk of postpartum stroke in women using Parlodel ®, application of the Bradford–Hill criteria is unwarranted. *See also Havner*, 953 S.W.2d at 718–19 (Bradford–Hill criteria are to be used by epidemiologists).

195. Contrary to the position of Dr. Kulig, the Bradford–Hill criteria are not factors for evaluating anecdotal case reports. *Pick*, 958 F.Supp. at 1160 n. 31 ("Dr. Campbell argues that case studies can fulfill the so-called Hill criteria.... [T]his Court agrees with AMS that [the Hill criteria are factors for evaluating epidemiological findings, not anecdotal case studies]."). Plaintiff here failed to demonstrate to the Court that the general toxicologic or medical communities apply the Bradford–Hill criteria in the absence of an association demonstrated by epidemiology, *e.g.*, to mere anecdotal case reports.

196. Dr. Kulig concedes that no epidemiologic study in the peer-reviewed medical literature shows a statistically-significant association between Parlodel ® and stroke. This Court concludes that Dr. Kulig's misapplication of the Bradford–Hill criteria weighs against the admissibility of

his proffered expert opinion under *Daubert.*

197. Additionally, Dr. Kulig cannot explain the mechanism by which bromocriptine allegedly causes cerebral vasoconstriction. He offers no valid or even probable mechanism to support his causal hypothesis. As explained by the Federal Judicial Center, "[i]n the absence of an understanding of the biological and pathological mechanisms by which disease develops, epidemiological evidence is the most valid type of scientific evidence of toxic causation." [12] REFERENCE MANUAL ON SCIENTIFIC EVIDENCE at 126. As noted above, there is no statistically-significant epidemiologic evidence showing that Parlodel ® increases the risk of postpartum stroke, nor is there anything but uncontrolled, anecdotal case reports to suggest that bromocriptine can cause cerebral vasoconstriction.

198. Further, this Court concludes that Dr. Kulig cannot define or defend a rate of error in his methodology concerning general causation. The failure of Dr. Kulig even to address this major *Daubert* factor counsels strongly against admissibility of his opinions.

199. This Court concludes that Dr. Kulig's reliance on dissimilar animal and other models does not "fit" as required by *Daubert* and its progeny in the Third Circuit.

200. This Court also concludes that Dr. Kulig's reliance on allegedly similar compounds, not bromocriptine, fails to comply with the "fit" requirement.

201. This Court thus finds that Dr. Kulig had no scientifically-valid basis to include Parlodel ® on the differential. Further, Dr. Kulig testified previously that differential diagnosis is *not* an acceptable methodology for determining general medical causation. *See* 11/8 Tr. at 180 (Kulig), and excerpts from Dr. Kulig's testimony at hearing in *Brusca,* a New York State case involving breast implants in which Dr. Kulig testified for the defense. As Dr. Kulig has testified that both general and specific causation must be proven, his failure to support general causation in a sound scientific way requires exclusion of his testimony.

202. This Court concludes that Dr. Kulig has no scientifically-reliable means of excluding plausible alternative causes of plaintiff's stroke—the risks inherent in the postpartum period, the sympathomimetic drug in her blood at the time of her stroke, and endogenous vasoconstrictors. To the extent Dr. Kulig simply disregards conclusions about postpartum risks as published in widely accepted and peer-reviewed journals, he is not qualified to do so, *i.e.,* he is not an expert in maternal-fetal medicine or even in obstetrics, and in any event, he has proffered no scientifically sound basis to do so.

203. Thus, for all the reasons set forth above, the Court concludes that Dr. Kulig's methodology and opinions are inadmissible under Federal Rule of Evidence 702 and *Daubert.*

(ii) Federal Rule of Evidence 703

204. The *Daubert* Court directed judges assessing proffers of expert testimony under Fed.R.Evid. 702 to "also be mindful of other applicable rules," including Federal Rule of Evidence 703. *Daubert,* 509 U.S. at 595, 113 S.Ct. 2786; *see also Paoli II,* 35 F.3d at 748 (opinion resting on data so lacking in reliability no

12. In *Rosen v. Ciba–Geigy Corp.,* 78 F.3d 316, 319–20 (7th Cir.1996), the court rejected expert testimony in large part because no theory was offered on the crucial issue of mechanism, or *how* the injury (heart attack) could be caused by the product (a nicotine patch).

reasonable expert would base opinion on them must be excluded); *In re: Diet Drugs*, 2001 WL 454586 at *7 (recognizing that *Daubert* inquiry does not obviate need for district courts to also analyze proffered scientific evidence under Rule 703); *In re: Diet Drugs*, 2000 WL 962545 at *4 (same). Rule 703 requires that "[t]he facts or data . . . upon which an expert bases an opinion or inference" must be "of a type reasonably relied upon by experts in the particular field in forming opinions or inferences upon the subject." Fed.R.Evid. 703.

P. Conclusion of Law Regarding Plaintiff's Expert Dr. Denis Petro

205. This Court concludes that Dr. Petro's opinion derives from the same sources as that of Dr. Kulig, including non-statistically-significant epidemiologic studies, ADEs and anecdotal case reports, extrapolation from animal studies, and use of evidence of other drugs, not bromocriptine.

(i) Federal Rule of Evidence 702

206. Much of the foregoing analysis applies as well to Dr. Petro. He is not proffered as an expert in the fields of epidemiology, statistics, or obstetrics/gynecology. Therefore, the Court concludes that he is not qualified as an expert in those fields and that Fed.R.Evid. 702 precludes him from giving expert testimony as to subjects within those medical/scientific specialties. *See In re: Diet Drugs*, 2001 WL 454586 at *7 ("a party cannot qualify as an expert generally by showing that the expert has specialized knowledge or training which would qualify him or her to opine on some other issue"); *In re: Diet Drugs*, 2000 WL 962545 at *3 (testimony outside expert's area of expertise should be excluded) (citing cases).

207. The Court also holds that the other requirements of Fed.R.Evid. 702, as interpreted by *Daubert* and its progeny, require that Dr. Petro's opinions be excluded in their entirety. For the reasons set forth throughout the Court's Findings of Fact and Conclusions of Law, his opinions fail all three prongs of Fed.R.Evid. 702. His testimony is not reliably derived from sufficient data or scientific principles. Nor does his testimony have a valid scientific connection to the facts at issue in this lawsuit so as to assist the fact finder in evaluating the evidence.

208. Like Dr. Kulig's testimony, Dr. Petro's testimony does not satisfy the eight, non-exclusive factors that *Daubert* and the Court of Appeals for the Third Circuit have identified for courts to consider in deciding whether expert testimony is admissible. *See Daubert*, 509 U.S. at 592–94; *Oddi*, 234 F.3d at 145; *see also Siharath*, 131 F.Supp.2d at 1355. (i) His opinions have not been validated by testing through a scientifically acceptable methodology. *See Glastetter*, 107 F.Supp.2d at 1045 n. 28; *Siharath*, 131 F.Supp.2d at 1355. (ii) Although certain of Dr. Petro's opinions have been addressed in a few case reports published in peer-reviewed publications, the anecdotal information in these case reports is scientifically unreliable and not supported by any epidemiologic or other scientifically reliable studies. *See Glastetter*, 107 F.Supp.2d at 1045 n. 28; *Siharath*, 131 F.Supp.2d at 1355. (iii) The potential rate of error for Dr. Petro's opinions is unacceptably high, if not completely unknown and unknowable. *See Glastetter*, 107 F.Supp.2d at 1045 n. 28; *Siharath*, 131 F.Supp.2d at 1355. (iv) Finally, his opinions have not been generally accepted in the relevant scientific community. *See Glastetter*, 107 F.Supp.2d at 1045 n. 28; *Siharath*, 131 F.Supp.2d at 1355.

209. Dr. Petro cannot explain the mechanism by which Parlodel® allegedly causes stroke. He offers no valid or even

probable mechanism—*i.e.,* a testable biologic explanation—to support his causal hypothesis.

210. This Court concludes that Dr. Petro's inability to show a mechanism, which is important to the Court's review of scientific reliability, demonstrates a faulty methodology that is not scientifically valid. As explained by the Federal Judicial Center, "[i]n the absence of an understanding of the biological and pathological mechanisms by which disease develops, epidemiological evidence is the most valid type of scientific evidence of toxic causation." REFERENCE MANUAL ON SCIENTIFIC EVIDENCE at 126.

211. Anecdotal case reports and temporal proximity do not constitute a scientifically reliable basis for Dr. Petro's opinions on general medical causation.

212. Dr. Petro has not exposed his opinions and methodology to his peers and does not rely on any peer-reviewed literature by third parties that makes the statement that bromocriptine causes stroke. Analysis that has not been "subjected to normal scientific scrutiny through peer review and publication" is suspect under *Daubert. Daubert II,* 43 F.3d at 1318; *see also, e.g., Haggerty,* 950 F.Supp. at 1164.

213. Expert opinions generated as the result of litigation are given less credibility than opinions generated as the result of academic research or other forms of "pure" research. *E.g., Daubert,* 509 U.S. at 593, 113 S.Ct. 2786 (one factor to consider is whether opinion was generated to further litigation or was subject to peer review); *Wade–Greaux,* 874 F.Supp. at 1465, 1476. In this case, Dr. Petro's opinions are expressed only in the litigation arena.

214. This Court concludes that Dr. Petro's reliance on dissimilar animal and other models does not "fit."

215. This Court also concludes that Dr. Petro's reliance on allegedly similar compounds, not bromocriptine, fails to comply with the "fit" requirement.

216. This Court concludes that Dr. Petro has no scientifically reliable means of excluding plausible alternative causes of plaintiff's stroke—the risks inherent in the postpartum period, the sympathomimetic drug in her blood at the time of her stroke, and endogenous vasoconstrictors. To the extent Dr. Petro simply disregards conclusions about postpartum risks as published in widely accepted and peer-reviewed journals, he is not qualified to do so, *i.e.,* he is not an expert in maternal-fetal medicine or even an expert in obstetrics, and in any event, he has proffered no scientifically sound basis to do so.

217. Thus, for all the reasons set forth above, the Court concludes that Dr. Petro's methodology and opinions are inadmissible under Federal Rule of Evidence 702 and *Daubert.*

(ii) Federal Rule of Evidence 703

218. In the alternative, the Court has also considered whether Dr. Petro's opinions pass muster under Fed.R.Evid. 703. *See Daubert,* 509 U.S. at 595, 113 S.Ct. 2786; *Paoli II,* 35 F.3d at 748; *In re: Diet Drugs,* 2001 WL 454586 at *7.

[44] 219. The Court holds that the facts and data upon which Dr. Petro relies to support his opinions do not satisfy the requirements of Fed.R.Evid. 703. They are not the kind of information reasonably relied upon by experts forming medical causation opinions in the applicable medical and/or scientific fields of epidemiology, pharmacology, neurology, neuropathology, statistics, or obstetrics/gynecology. Therefore, Fed.R.Evid. 703 also requires that Dr. Petro's opinions be excluded. *See Hamilton,* 133 F.Supp.2d at 372 (expert

opinion based only on his own authority violates Fed.R.Evid. 703).

Q. While plaintiff did not call Dr. George Macones, an epidemiologist, to testify at the *Daubert* hearing, Dr. Macones' opinion is relevant to plaintiff's other causation experts and must be considered.

220. Dr. George Macones is an expert in epidemiology and obstetrics. Although he was named as a witness for the *Daubert* hearing, he was never called by plaintiff.

221. Based on the deposition testimony of Dr. Macones, the Court concludes that there is a background incidence of postpartum stroke completely independent of drug usage. Accordingly, any appropriate differential diagnosis must include, as a plausible alternative cause, the background incidence of postpartum stroke.

222. Based on the deposition testimony of Dr. Macones, the Court concludes that the postpartum period is a particularly high-risk period for postpartum stroke and that postpartum women are roughly 28 times more likely to incur ICH than similarly-aged women who are not postpartum. Accordingly, any appropriate differential diagnosis must include, as a plausible alternative cause, the background incidence of postpartum stroke.

223. Based on the deposition testimony of Dr. Macones, the Court concludes that the human body independently manufactures vasoconstrictive substances, including norepinephrine, angiotensin II, and renin. Because it is plaintiff's experts' hypothesis in this case that a vasoconstrictive substance manufactured by NPC caused her ICH, any appropriate differential diagnosis must include, as a plausible alternative cause, the vasoconstrictive substances produced by the human body itself.

224. Dr. Macones cannot testify to a reasonable degree of medical certainty that Parlodel ® increases the risk of stroke in postpartum women or in any group of patients using Parlodel ®.

225. Based on Dr. Macones' deposition testimony, there is no evidence that Parlodel ® increases the risk of postpartum stroke.

226. In other words, no one has shown as a matter of scientific knowledge, as required by *Daubert*, that Parlodel ® use is a risk factor for postpartum stroke.

227. Dr. Macones has attempted in deposition testimony and in affidavits submitted to the Court to suggest that if certain studies, such as the ERI study, were performed differently, or were larger, then a positive association between Parlodel ® use and postpartum stroke would have emerged with greater clarity. However, such testimony is entirely speculative and is not based on reliable science. In any event, criticisms of the epidemiologic studies upon which NPC relies cannot substitute for positive evidence upon which plaintiff can rely. *See, e.g., Brumbaugh*, 77 F.Supp.2d at 1156; *Conde*, 24 F.3d at 814.

R. Conclusions of Law Regarding Plaintiff's Expert Dr. Leslie Iffy

228. While plaintiff did not call Dr. Iffy to testify at the *Daubert* hearing, Dr. Iffy's opinion is relevant to plaintiff's other causation experts and must be considered. Other courts in the Third Circuit have considered the "withdrawn" testimony on the question of the admissibility of all of plaintiff's experts' testimony. For example, in *Wade–Greaux*,; the federal district court considered the "withdrawn" expert's testimony in its decision whether to exclude the testimony of plaintiff's other experts. 874 F.Supp. at 1448, 1465 ("Plaintiff withdrew Alan K. Done, M.D. as an

expert witness following defendants' cross-examination of the witness [at the evidentiary *Daubert* (*Downing*) hearing]. However, the court refused to exclude the testimony already received from him. . . . [T]he court determined that his testimony would remain of record for consideration of all issues pertinent to the *Downing* hearing."). Moreover, the court spent nearly five pages of its opinion specifically addressing the testimony of the "withdrawn" expert and excluding his proffered expert opinion as inadmissible under *Daubert*. *Id.* at 1465–69. Thus, this Court may consider Dr. Iffy's opinion directly and as part of its determination whether to exclude the testimony of plaintiff's other experts.

229. Dr. Iffy has been excluded from numerous Parlodel®-related cases on the ground that his theories that Parlodel® causes stroke, seizure, and other cardiovascular injury were not scientifically reliable and did not meet the standards required by *Daubert*. *See, e.g., Brumbaugh,* 77 F.Supp.2d at 1157; *Revels v. Sandoz Pharm. Corp.,* No. 95–11076, Orders of Mar. 13 and Apr. 1, 1998 (201st Jud. Dist., Travis County, Tex.) (excluding general causation evidence in similar Parlodel® case as "not sufficiently scientifically reliable or relevant" and granting summary judgment) (Att.40), *aff'd* 1999 WL 644732, (Tex.App.–Austin 1999) (Aboussie, C.J.), *petition for review denied.*

230. This Court concludes that Dr. Iffy's opinion derives from the same sources as that of Dr. Kulig, including non-statistically-significant epidemiologic studies, ADEs and anecdotal case reports, and use of evidence of other drugs, not bromocriptine.

231. A key factor inherent in the "scientific method" is whether a hypothesis generated by an expert is "testable" and whether it has been successfully tested and the results replicated. *Daubert,* 509 U.S. at 593, 113 S.Ct. 2786; *Heller,* 167 F.3d at 154–55; *Paoli II,* 35 F.3d at 742 n. 8. This Court concludes that Dr. Iffy's methodology is not founded upon the scientific method.

232. Dr. Iffy cannot explain the mechanism by which Parlodel® allegedly causes stroke. He offers no valid or even probable mechanism—*i.e.,* a testable biologic explanation—to support his causal hypothesis.

233. This Court concludes that Dr. Iffy's inability to show a mechanism, which is important to the Court's review of scientific reliability, demonstrates a faulty methodology that is not scientifically valid. As explained by the Federal Judicial Center, "[i]n the absence of an understanding of the biological and pathological mechanisms by which disease develops, epidemiological evidence is the most valid type of scientific evidence of toxic causation." REFERENCE MANUAL ON SCIENTIFIC EVIDENCE at 126.

234. Anecdotal case reports and temporal proximity do not constitute a scientifically reliable basis for Dr. Iffy's opinions on general medical causation. Indeed, Dr. Iffy's own Parlodel®-related case reports do not themselves profess to opine to a reasonable degree of medical certainty that Parlodel® caused the symptoms and injuries reported.

235. Expert opinions generated as the result of litigation are given less credibility than opinions generated as the result of academic research or other forms of "pure" research. *E.g., Daubert,* 509 U.S. at 593, 113 S.Ct. 2786 (one factor to consider is whether opinion was generated to further litigation or was subject to peer review); *Wade–Greaux,* 874 F.Supp. at 1465, 1476. All of Dr. Iffy's opinions and case reports have been generated in the litigation arena.

236. This Court concludes that Dr. Iffy cannot define or defend a rate of error in his methods. The failure of Dr. Iffy even to address this *Daubert* factor counsels against admissibility of his opinions or of comparably-based opinions.

237. This Court further concludes—and Dr. Iffy admits—that Dr. Iffy's methodology and opinions are not generally accepted in the scientific community. Deposition of Dr. Leslie Iffy in *Revels* at 211–12 ("medical community looks at any medicolegal proceeding with suspicion because of the adversary nature of the legal process") (Att.26); Iffy, et al, *The Role of Medical Legal Reviews in Medical Research* at 402 ("[t]he adversary nature of legal proceedings, understandably, has generated doubt in the minds of members of the medical profession about the validity of observations and conclusions deriving from malpractice reviews") (Att.27).

238. This Court also concludes that Dr. Iffy's reliance on allegedly similar compounds, not bromocriptine, fails to comply with the "fit" requirement.

239. This Court concludes that Dr. Iffy has no scientifically-reliable means of excluding plausible alternative causes of plaintiff's stroke—the risks inherent in the postpartum period, the sympathomimetic drug in her blood at the time of her stroke, and endogenous vasoconstrictors. To the extent Dr. Iffy simply disregards conclusions about postpartum risks as published in widely accepted and peer-reviewed journals, he has proffered no scientifically-sound basis to do so.

240. Thus, for all the reasons set forth above, the Court concludes that Dr. Iffy's Methodology and opinions are inadmissible under Federal Rule of Evidence 702 and *Daubert*.

S. Judicial Estoppel

[45] 241. In its recent decision, *Montrose Medical Group Participating Savings Plan v. Bulger*, 243 F.3d 773, 777, 778, 780, 781 (3d Cir.2001), the Court of Appeals for the Third Circuit delineated the circumstances which permit a district court to apply judicial estoppel. It held that in order for a district court to properly apply judicial estoppel, it must determine if three requirements have been met: "(i) the party to be estopped must have taken two positions that are irreconcilably inconsistent; (ii) judicial estoppel is unwarranted unless the party changed his or her position in bad faith—*i.e.*, with intent to play fast and loose with the court; and (iii) a district court may not employ judicial estoppel unless it is tailored to address the harm identified" and no lesser sanction would adequately remedy the damage done by the litigant's misconduct." *Id.*, at 779–80 (citations omitted).

242. Further, in elaborating on the issue, the Court of Appeals for the Third Circuit observed:

> Inconsistencies are not sanctionable unless a litigant has taken one or both positions "in bad faith—i.e., with intent to play fast and loose with the court." *Ryan Operations G.P. v. Santiam–Midwest Lumber Co.*, 81 F.3d 355, 361 (3d Cir.1996). A finding of bad faith "must be based on more than" the existence of an inconsistency, *Klein v. Stahl GMBH & Co. Maschinefabrik*, 185 F.3d 98, 111 (3d Cir.1999) (emphasis added); indeed, a litigant has not acted in "bad faith" for judicial estoppel purposes unless two requirements are met. First, he or she must have behaved in a manner that is somehow culpable. *See Ryan Operations*, 81 F.3d at 362 (stating that judicial estoppel may not be employed unless " 'intentional self contradiction is . . . used as a means of obtaining *unfair*

advantage' " (quoting *Scarano v. Central R. Co. of N.J.,* 203 F.2d 510, 513 (3d Cir.1953) (emphasis added))); *id.* ("An inconsistent argument sufficient to invoke judicial estoppel must be attributable to intentional *wrongdoing.*" (emphasis added)); *see also In re Chambers Dev. Co. Inc.,* 148 F.3d 214, 229 (3d Cir.1998) (quoting this language from *Ryan Operations*).

Second, a litigant may not be estopped unless he or she has engaged in culpable behavior *vis-a-vis* the court. As we have stressed time and time again, judicial estoppel is concerned with the relationship between litigants and the legal system, and not with the way that adversaries treat each other. *See, e.g., Ryan Operations,* 81 F.3d at 360 ("Judicial estoppel 'is intended to protect the courts rather than the litigants.' " (quoting *Fleck v. KDI Sylvan Pools, Inc.,* 981 F.2d 107, 121–22 (3d Cir.1992))); *Delgrosso v. Spang & Co.,* 903 F.2d 234, 241 (3d Cir.1990) (same). Accordingly, judicial estoppel may not be employed unless a litigant's culpable conduct has assaulted the dignity or authority of the court.

Id., 780, 781.[13]

[46] 243. Given that the three appointed medical experts recognize the need for plaintiff's medical experts to rule out PPA or other amphetamine-type drugs in arriving at their differential diagnosis, and in view of the admission of the plaintiff's experts for the most part, that PPA or other amphetamine-type drugs can cause stroke or in the least, can cause vasospasm or vasoconstriction, the Court concludes that the issue raised by plaintiff is essentially a medical issue rather than a legal issue, and it would not be appropriate for the Court to apply judicial estoppel on the issue of the scientific reliability of the methodology of plaintiff's medical experts.

244. Moreover, based on the record, the Court cannot conclude that NPC has acted in bad faith in asserting that a proper differential diagnosis requires including and ruling out these alternatives as a cause of plaintiff's ICH.

245. Moreover, the Court cannot and does not conclude that NPC, by the position that it has asserted with regard to the plaintiff's differential diagnosis, has assaulted the dignity or authority of this Court.

246. Under the totality of the circumstances, the Court declines to invoke the doctrine of judicial estoppel in determining whether plaintiff's medical testimony and evidence is admissible under *Daubert.*

T. Conclusions of Law Regarding Plaintiff's Failure to Prove Elements Necessary to Sustain Her Pharmaceutical Products Liability Action Under Pennsylvania Law

247. Incorporating all of its previous findings and conclusions, the Court concludes that plaintiff has not met her burden of demonstrating that any of her experts renders a scientifically-reliable expert opinion that would assist the trier of fact in resolving whether Parlodel ® can cause postpartum stroke or, if so, whether it did so in this case. *Daubert II,* 43 F.3d at 1322. Thus, plaintiff's proffered experts may not testify regarding either general or specific causation.

248. In the absence of expert testimony, plaintiff has failed to demonstrate that

13. *Cf. Bendet v. Sandoz Pharmaceuticals Corp.,* 308 F.3d 907 (8th Cir.2002) (Plaintiff, who allegedly suffered an ischemic stroke as a result of Parlodel ® was not judicially estopped from arguing that the Court of Appeals' analysis in *Glastetter v. Novartis Pharm. Corp.,* 252 F.3d 986 (8th Cir.2001) (*per curium*) was not fatal to her case.)

Parlodel® can and did cause her ICH. Given her failure to produce competent evidence in support of an element she would be required to prove at trial, summary judgment must therefore be granted to NPC. *See Celotex*, 477 U.S. at 322–323, 106 S.Ct. 2548; *Zimmerman*, 168 F.3d at 684.

U. Conclusion

249. The ICH suffered by Ms. Soldo and her ensuing disabilities therefrom are truly tragic, and the Court has the utmost sympathy for Ms. Soldo and her family. However, the opinions proffered by Drs. Kulig and Petro do not satisfy the *Daubert* /Fed.R.Evid. 702 requirements of being scientifically reliable and having a valid scientific connection to the facts of this lawsuit. Nor do these opinions satisfy the requirements of Fed.R.Evid. 703. Accordingly, this Court holds that these experts' opinions are inadmissible in their entirety and that NPC's motion to exclude their testimony and for summary judgment must be granted.

250. This Court has applied no particular litmus test or absolute requirements in this case other than sufficiency, reliability and relevance. *See Caraker*, 172 F.Supp.2d at 1049 n. 6.

251. This Court analyzed the evidence on which Dr. Kulig and Dr. Petro have relied both as individual items of proof as well as in the aggregate. However, plaintiff's experts "cannot lump together lots of hollow evidence" and reach a reliable conclusion. *Siharath*, 131 F.Supp.2d at 1371; *see also Glastetter*, 252 F.3d at 992 (neither individual elements nor aggregate of evidence provide reliable scientific basis for conclusions of Dr. Petro and Dr. Kulig); *accord Caraker*, 172 F.Supp.2d at 1053; *Hollander*, 95 F.Supp.2d at 1230; *Brumbaugh*, 77 F.Supp.2d at 1153.

ORDER OF COURT

AND NOW, this 13th day of January, 2003, it is hereby

ORDERED that defendant's **Motion for Summary Judgment on Issues of Medical Causation** (Document No. 77) is **GRANTED**;

IT IS FURTHER ORDERED that the following motions are **DENIED AS MOOT**:

(i) **Novartis Pharmaceuticals Corporation's Motion for Partial Summary Judgment on Fraud and Negligent Misrepresentation Claims** (Document No. 55); and

(ii) **Novartis Pharmaceuticals Corporation's Motion for Partial Summary Judgment on Warning Claims** (Document No. 58);

IT IS FURTHER ORDERED that judgment is entered for the defendant and against the plaintiff.

Shade POPOOLA

v.

MD–INDIVIDUAL PRACTICE ASSOCIATION, INC., et al.

No. CIV.A. DKC 2000–2946.

United States District Court,
D. Maryland.

Feb. 4, 2003.

Insured brought state-court class action against health maintenance organiza-