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IN THE CIRCUIT COURT OF KANAWHA COUTY, WEST VIRGINIA

IN RE: ZOLOFT LITIGATION **Civil Action No. 14-C-7000**

THIS DOCUMENT APPLIES TO:

J.C., a minor by and through his mother and next friend Michelle C	Civil Action No. 12-C-146 WNE
I.H., a minor by and through her mother and next friend Angela H	Civil Action No. 13-C-229 WNE

ORDER REGARDING DEFENDANTS' MOTION TO EXCLUDE THE OPINIONS OF PLAINTIFFS' EXPERTS, JOHN MACGREGOR, MD, RA-ID ABDULLA, MD, AND ROBERT M. CABRERA, PH.D.

The Court has reviewed and maturely considered *Defendants' Motion to Exclude the Opinions of Plaintiffs' Experts, John MacGregor, MD, Ra-Id Abdulla, MD, and Robert M. Cabrera, Ph.D.* (Transaction ID 59426170) ("Motion"), the accompanying Memorandum of Law, all responsive briefing and filings of the parties.[1] Having conferred with one another to insure uniformity of their decision, as contemplated by Rule 26.07(a) of the West Virginia Trial Court Rules, the Presiding Judges unanimously find that Defendant's Motion should be and is **GRANTED** in part and **DENIED** in part.

Defendants' motion to exclude the specific causation opinions of Robert M. Cabrera, Ph.D. in the above-referenced cases is **GRANTED** for the reasons stated in the Court's *Order Regarding Motion to Exclude Causation Opinions of Plaintiffs' Expert Robert M. Cabrera, Ph.D., and Motion for Summary Judgment* (Transaction ID 59655574) filed in *D.B., a minor, by and through his mother and next friend Nina E v. Pfizer, Inc., et al.*, Civil Action No. 12-C-164 WNE ("*Brumfield*"). For all of the reasons stated in this Order, Defendants' Motion is otherwise **DENIED.** Accordingly, Dr. MacGregor, Dr. Abdulla, and Dr. Cabrera's general

[1] The Parties waived oral arguments and agreed to submit the motion for decision on the basis of their briefs.

causation opinions, and Dr. MacGregor, and Dr. Abdulla's specific causation opinions are admissible.

The Court makes the following Findings of Fact and Conclusions of Law. To the extent any Finding of Fact constitutes a Conclusion of Law, the Court adopts it as such. To the extent any Conclusion of Law constitutes a Finding of Fact, the Court also adopts it as such.

Procedural Background

1. Plaintiffs have collectively designated three experts to offer general and specific causation opinions in these cases: Dr. Robert M. Cabrera, Ph.D., a teratologist who studies the causes of birth defects; Dr. Ra-Id Abdulla, M.D., a board-certified pediatric cardiologist whose practice includes the diagnosis and treatment of congenital heart defects; and Dr. John MacGregor, M.D., Ph.D., a physician and medical scientist who has board certifications in both Cardiovascular Diseases and Interventional Cardiology.

2. Defendants filed their Motion, seeking to exclude the general and specific causation opinions of all three of Plaintiffs' experts, on August 15, 2016. Defendants' Motion does not challenge Plaintiffs' experts' qualifications to offer general causation opinions, and does not challenge Dr. Abdulla or Dr. MacGregor's qualifications to offer specific causation opinions. Rather, the Motion challenges Dr. Cabrera's qualifications to offer specific causation opinions and contends that all three of Plaintiffs' experts' opinions are based on "unscientific, unreliable" methods and should be excluded under West Virginia Rule of Evidence 702, as interpreted in *Wilt v. Buracker,* 191 W. Va. 39, 443 S.E.2d 196 (1993) and its progeny.

3. Plaintiffs filed a response in opposition to Defendants' Motion (the "Response") on August 29, 2016 (Transaction ID 59487637).

Findings of Fact

4. Minor Plaintiff I.H. was born with patent ductus arteriosus ("PDA"), a congenital heart defect.

5. Minor Plaintiff J.C. was both born with coarctation of the aorta, a congenital heart defect.

6. Dr. Cabrera is a Ph.D. teratologist who studies the causes of birth defects. He is a research scientist for the Dell Pediatric Research Institute at The University of Texas at Austin Dell Medical School and also serves as a lecturer in the Department of Nutritional Sciences at The University of Texas at Austin. Dr. Cabrera received his Ph.D. in Medical Sciences from Texas A&M University, where he focused his studies on genetics and pharmaceutically induced congenital anomalies in experimental animal models and humans. Plaintiffs designated Dr. Cabrera to offer his opinions that Zoloft is causally associated with cardiac birth defects generally (general causation) and that Zoloft was a cause in fact of Plaintiffs' injuries specifically (specific causation).[2]

7. Dr. Abdulla is a licensed medical doctor with board certifications in cardiology and pediatric cardiology. He is a Professor of Pediatrics (Pediatric Cardiology) at Rush University in Chicago and senior attending of Pediatric Cardiology at Rush University Medical Center. He is the Director of the Section of Pediatric Cardiology in the Department of Pediatrics and a member of the Pediatric Congenital Heart Disease Program at Rush University. Dr. Abdulla has been Editor-in-Chief of *Pediatric Cardiology*, a peer-review medical journal, since

[2] Dr. Cabrera's qualifications to provide a specific causation opinion in these cases is addressed in the Court's *Order Regarding Motion to Exclude Causation Opinions of Plaintiffs' Expert Robert M. Cabrera, Ph.D., and Motion for Summary Judgment* (Transaction ID 59655574) filed in *Brumfield*, which is incorporated by reference as if fully set forth herein.

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2000. Plaintiffs have designated Dr. Abdulla to offer his general causation opinion and a specific causation opinion in the *Cook* case.

8. Dr. MacGregor is a Professor of Medicine at the University of California San Francisco and the Director of the Cardiac Catheterization Laboratory and Interventional Cardiology at San Francisco General Hospital. Dr. MacGregor is board-certified both in Cardiovascular Diseases and in Interventional Cardiology. As part of his practice, Dr. MacGregor diagnoses and treats patients with congenital heart disease. In addition to his medical degree, Dr. MacGregor has a Ph.D. in biochemistry. Dr. MacGregor has been designated to offer his general causation opinion and a specific causation opinion in the *H* case.

9. Each of Plaintiffs' experts has based his opinions on the application of generally accepted methodologies, including the Bradford Hill criteria, and his review of the available epidemiological and other scientific literature, including *in vivo* and *in vitro* studies. These methodologies are widely used in the scientific community, are generally accepted, and are the same methodologies used both by Defendants' experts and by Pfizer's in-house scientists.

10. Epidemiological research into the possible connection between *in utero* Zoloft exposure and birth defects, particularly cardiac birth defects, has reported, and continues to report, many positive associations between the exposure and such defects, including multiple statistically significant positive associations.

11. The opinions of Plaintiffs' experts raise a factual issue about the ultimate cause of the Plaintiffs' birth defects that must be answered by the jury.

Conclusions of Law

12. Dr. Cabrera's, Dr. MacGregor's, and Dr. Abdulla's general causation opinions, and Dr. MacGregor's and Dr. Abdulla's specific causation opinions, are admissible under West Virginia law.

13. Rule 702 of the West Virginia Rules of Evidence provides:

> 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. . . . [E]xpert testimony based on a novel scientific theory, principle, methodology, or procedure is admissible only if: (1) the testimony is based on sufficient facts or data; (2) the testimony is the product of reliable principles and methods; and (3) the expert has reliably applied the principles and methods to the facts of the case.

14. "Rule 702 reflects an attempt to liberalize the rules governing the admissibility of expert testimony." *Harris v. CSX Transp., Inc.*, 232 W. Va. 617, 621, 753 S.E.2d 275, 279 (2013).

15. The Supreme Court of Appeals of West Virginia has explained that the circuit courts "must conduct a two-part inquiry under Rule 702 and ask: (1) is the witness [qualified as] an expert; and, if so, (2) is the expert's testimony relevant and reliable?" *Id*. at 621.

16. The meaning of "reliable" in West Virginia jurisprudence "does not mean an assessment of whether the testimony is persuasive, convincing, or well-founded." *In re Flood Litig. Coal River Watershed*, 222 W. Va. 574, 582, 668 S.E.2d 203, 211 (2008). Rather, "reliability" means that "the testimony is to a reasonable degree based on the use of knowledge and procedures that have been arrived at using the methods of science—rather than being based on irrational and intuitive feelings, guesses, or speculation." *Id*. More specifically, "[t]he problem is not to decide whether the proffered evidence is right, but whether the science is valid

enough to be reliable." *Gentry v. Mangum*, 195 W. Va. 512, 523, 466 S.E.2d 171, 182 (1995) (emphasis in original).

17. Under West Virginia law, "deciding which expert opinion to believe" is the "exclusive role" of the jury. *CSX Transp., Inc.*, 232 W. Va. at 622. Defendant's Motion asks the Court to usurp this role and make its own determination of which party's experts are correct in their analysis.

18. Defendants' Motion also improperly asks the Court to parse the epidemiological literature and reach detailed conclusions about, for example, which of two possible causes is the more likely cause of Plaintiffs' congenital heart defects, or whether certain research results were or were not properly attributable to confounding. Answering such questions is incompatible with the narrowly limited role of the trial court in determining admissibility of expert testimony under West Virginia law. See *CSX Transp., Inc.*, 232 W. Va. 617; *In re Flood Litig. Coal River Watershed*, 222 W. Va. at 586; *State ex rel. Wiseman*, 212 W.Va. 128; *Gentry*, 195 W. Va. at 523.

19. The Court finds that the general causation opinions of Plaintiffs' experts are relevant and reliable. Plaintiffs' experts rely on epidemiological and other scientific literature, including *in vivo* and *in vitro* studies, and application of the Bradford Hill criteria. These methods have been recognized as scientific and reliable by the Supreme Court of Appeals of West Virginia.

20. Plaintiffs' experts rely on numerous epidemiological studies reporting positive associations between exposure to Zoloft and other selective serotonin reuptake inhibitors ("SSRIs") and congenital heart defects, including repeated, statistically significant findings.

21. Defendants' Motion contends that, despite the findings between heart defects and Zoloft/SSRIs, "more recent studies" have shown that those results were the product of confounding. The only confounder suggested in Defendants' Motion is "confounding by indication," the potential that indications for which Zoloft is prescribed (e.g., depression) themselves create an increased risk of congenital heart disease. But Defendants' confounding-by-indication theory is an unproven hypothesis, not scientific fact, and it does not provide a basis for excluding Plaintiffs' experts' contrary conclusions.

22. Plaintiffs' experts have considered the studies that Defendants put forth and concluded that there is no evidence that maternal depression causes congenital heart defects. The authors of one study of depression during pregnancy noted, "We could identify no studies that link maternal depression to congenital anomalies in their infants."[3] Plaintiffs have cited studies that have either rejected the confounding-by-indication hypothesis or concluded that it is in need of further study.[4] As Plaintiffs point out, if confounding by indication was the explanation of the reported associations between SSRIs and heart defects, non-SSRI drugs for the same indication, depression, should also reflect an increased risk for birth defects. But across multiple studies, no such increase was apparent.

23. Defendants' Motion contends that Dr. MacGregor improperly "ruled out" smoking as the cause of I.H.'s patent ductus arteriosus ("PDA"). Dr. MacGregor properly considered smoking as a potential cause, reviewed applicable epidemiological literature, and

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[3] Yonkers et al., *The management of depression during pregnancy: a report from the American Psychiatric Association and the American College of Obstetricians and Gynecologists*, Obstetrics & Gynecology (2009) (reaffirmed 2014),

[4] Kornum et al., *Use of selective serotonin-reuptake inhibitors during early pregnancy and risk of congenital malformations: updated analysis.* Clin Epidemiol, 29-36 (2010); Jimenez-Solem et al., *Exposure to selective serotonin reuptake inhibitors and the risk of congenital malformation: a nationwide cohort study*, BMJ (2012); Wemakor et al., *Selective serotonin reuptake inhibitor antidepressant use in first trimester pregnancy and risk of specific congenital anomalies: a European register-based study*, Eur. J. Epidemiol (2015).

determined that smoking was not a likely cause of I.H.'s PDA. Dr. MacGregor determined that the available epidemiological evidence does not report a strong or persistent correlation between maternal smoking and PDA, or between maternal smoking and congenital heart defects considered as a group. Dr. MacGregor followed a generally accepted methodology in ruling out smoking as the most likely cause of I.H.'s PDA.

24. Dr. MacGregor's opinion is supported by proper scientific methodology. Defendants point to two studies reporting a positive correlation between maternal smoking and PDA—*Lee* (2013)[5] and *Kallen* (1999).[6] Both studies reported comparatively small correlations indicating that even among exposed cases, the background risk accounts for far more of the incidence of PDA than does maternal smoking. Moreover, *Lee* does not truly replicate the findings in *Kallen* because *Lee* is a metaanalysis, not an original study, and it includes the *Lee* data set in its analysis. Finally, neither *Kallen* nor *Lee* take steps to control for the positive correlation between smoking and SSRI use among pregnant women. Failing to control for the potential confounding effects of SSRI use among smoking mothers means that results reported in *Kallen* and *Lee* may have been skewed toward showing a correlation that does not exist.

25. Dr. MacGregor relies on a more recent case-control study, *Sullivan* (2015),[7] which included far more cases than *Kallen* and actually reported a *negative* correlation between maternal smoking and PDA. Sullivan included 2,352 cases of PDA compared with only 458 in Kallen and a total of only 684 (including the 458 Kallen cases) in *Lee*'s metaanalysis. The negative correlation reported by Sullivan implies a *protective* effect of an exposure on the studied outcome. Dr. MacGregor did not suggest that maternal smoking actually protects against

[5] Lee et al., *Maternal Smoking During Pregnancy and the Risk of Congenital Heart Defects in Offspring: A Systematic Review and Metaanalysis*, Pediatr. Cardiol. (2013).
[6] Kallen, *Maternal smoking and congenital heart defects*, Eur. J. Epidem. (1999).
[7] Sullivan et al., *Risk of Congenital Heart Defects in the Offspring of Smoking Mothers: A Population-Based Study*, J. Pediatrics (2015).

PDA, but a negative correlation of the unadjusted and adjusted odds ratios in such a large case-control study is strong evidence against a real, positive correlation, and substantially undermines any hypothesis that smoking *causes* PDA.

26. Defendant attempts to criticize Dr. MacGregor for not reviewing the *Kallen* study prior to his deposition and for misreading one of the line items in the *Kallen* data tables when Defendant's counsel asked him to give an interpretation of the paper on the spot. These criticisms are not grounds for exclusion. In forming his initial causation opinion, Dr. MacGregor determined that he needed to consider the possible effects of smoking, then located and reviewed the two most recent epidemiological papers on the subject—*Sullivan* (2015) and *Lee* (2013). His ultimate exclusion of smoking as a potential cause was "based on the use of knowledge and procedures that have been arrived at using the methods of science—rather than being based on irrational and intuitive feelings, guesses, or speculation" and his opinion is therefore reliable and admissible. *In re Flood Litig. Coal River Watershed*, 222 W. Va. 574, 582, 668 S.E.2d 203, 211 (2008).

27. Defendant accuses Dr. MacGregor of applying different standards to the evidence of dose-response effects in smoking and SSRI exposure. Defendants argue that Dr. MacGregor cites the absence of a dose-response effect as a reason to rule out smoking but overlooks the absence of a dose-response effect with respect to SSRI exposure. We disagree. In his deposition, Defendants' counsel asked Dr. MacGregor to consider the findings of a study attempting to evaluate a dose-response relationship between SSRI exposure and congenital defects, *Jimenez-Solem* (2012). Dr. MacGregor observed that the low-dose results, though less extreme than the high-dose results, still reported a statistically significant positive association between SSRI exposure and congenital defects indicated a true correlation between SSRI use and

congenital defects each of the dose-based results reported in the study showed. Because even the low-dose results attained statistical significance, Dr. MacGregor reasoned that the results supported a conclusion that SSRIs are toxic even at low doses. By contrast, the dose-response results reported with respect to maternal smoking did not reach statistical significance at any dose level. Defendant's suggestion that Dr. MacGregor applied a different standard to his consideration of the dose-response data for SSRIs and cigarettes is unsupported by the record.

28. Similarly, Defendants allege that Dr. MacGregor gave greater importance to statistical significance in the context of smoking than in the context of SSRI use. We again disagree. In both contexts, Dr. MacGregor correctly maintained that from his point of view as a clinician, the .05 significance threshold should not be given disproportionate weight—a result just short of significance has comparable, though not equal, weight to a result just above the .05 cutoff. Dr. MacGregor considered statistically non-significant results along with statistically significant results when reaching his conclusions about the cause of I.H.'s PDA. He agreed that a result approaching, but short of, significance for smoking could very well constitute a trend if a similar positive correlation was reported in additional research findings. But Defendant has not pointed to any set of nonsignificant positive findings that might be considered a trend for maternal smoking and PDA.

29. Defendants argue that Dr. Cabrera and Dr. Abdulla failed to properly "rule in" Zoloft as a potential cause of J.C.'s coarctation of the aorta. This argument is a reformulation of Defendants' general causation argument: establishing that Zoloft causes cardiac defects in general is sufficient to rule Zoloft in as a potential cause of these specific Plaintiffs' heart defects. As demonstrated above, Dr. Cabrera and Dr. Abdulla have used reliable, scientific methodologies to conclude that Zoloft does indeed cause congenital heart defects.

30. In support of its contention that Plaintiffs' experts improperly "ruled in" Zoloft as a potential cause of J.C.'s coarctation of the aorta, Defendant argues that Drs. Abdulla and Cabrera contradicted each other in their deposition testimony. We disagree with Defendants' reading of the record. Both experts agree that it is important to consider all available evidence, including defect-specific evidence and evidence relating to cardiac defects generally, in reaching their ultimate conclusions. They also both agree that single agents can and do cause multiple types of birth defects. More importantly, even if there was a disagreement between two of Plaintiffs' experts on a particular point, it might provide fodder for cross-examination, but would not be grounds for exclusion for their testimony. *Cf. Watson*, 209 W. Va. at 244 (noting that a party "should address its criticisms of [opponent's expert's] testimony at trial through traditional methods such as vigorous cross-examination, rebuttal testimony by its own expert, and instructions on [the] burden of proof").

Conclusion

For the reasons stated in the Panel's separate *Order Regarding Motion to Exclude Causation Opinions of Plaintiffs' Expert Robert M. Cabrera, Ph.D., and Motion for Summary Judgment* (Transaction ID 59655574) filed in *Brumfield*, Defendants' motion to exclude the specific causation opinions of Robert M. Cabrera, Ph.D. is **GRANTED**. For all of the reasons stated herein, Defendants' Motion to Exclude the Opinions of Plaintiffs' Experts, John MacGregor, MD, Ra-Id Abdulla, MD, and Robert M. Cabrera, Ph.D. is otherwise **DENIED**. Accordingly, Dr. MacGregor, Dr. Abdulla, and Dr. Cabrera's general causation opinions, and Dr. MacGregor and Dr. Abdulla's specific causation opinions are admissible. Any exceptions or objections are noted and preserved for the record.

A copy of this Order shall be electronically served on all counsel of record via File & Serve*Xpress*.

It is so ORDERED.

ENTERED: October 5, 2016.

/s/ James P. Mazzone
Lead Presiding Judge
Zoloft Litigation