IN THE UNITED STATES COURT OF APPEALS
FOR THE THIRD CIRCUIT

No. 16-2247

In re Zoloft (Sertraline Hydrochloride) Products Liability Litigation

JENNIFER ADAMS, et al.,
Plaintiffs-Appellants,

v.

WOLTERS KLUWER HEALTH INC., et al.,
Defendants-Appellees.

On Appeal from the United States District Court
for the Eastern District of Pennsylvania, No. 2:12-cv-02342

BRIEF OF AMICI CURIAE AMERICAN TORT REFORM ASSOCIATION AND PHARMACEUTICAL RESEARCH AND MANUFACTURERS OF AMERICA SUPPORTING DEFENDANTS-APPELLEES AND URGING AFFIRMANCE

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CORPORATE DISCLOSURE STATEMENT

Amici curiae the American Tort Reform Association ("ATRA") and the Pharmaceutical Research and Manufacturers of America ("PhRMA") do not have any parent corporations and are not publicly traded entities. ATRA and PhRMA are represented in this matter by Joe G. Hollingsworth, a partner in the law firm Hollingsworth LLP.

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Interest of *Amici Curiae*

Founded in 1986, the American Tort Reform Association ("ATRA") is a broad-based coalition of businesses, corporations, municipalities, associations, and professional firms that have pooled their resources to promote reform of the civil justice system with the goal of ensuring fairness, balance, and predictability in civil litigation. Since that time, ATRA has been working to bring greater fairness, predictability and efficiency to America's civil justice system. Those efforts have resulted in the enactment of state and federal laws that make the system fairer for everyone. Among other things, ATRA has striven to ensure that all aspects of an expert's opinion are tested for reliability before admitted in court through application of the *Daubert* standard, which expects district court judges to act as gatekeepers over the reliability of expert testimony, carefully evaluating whether such testimony is based on sound scientific principles or is simply bought-and-paid for "junk science." For over two decades, ATRA has filed *amicus* briefs in appellate cases that have addressed important liability issues.

The Pharmaceutical Research and Manufacturers of America ("PhRMA") is a voluntary nonprofit association representing the nation's leading research-based pharmaceutical and biotechnology companies, which are devoted to discovering and developing medicines that enable patients to live longer, healthier, and more productive lives. PhRMA's mission is to conduct effective advocacy for public

policies that encourage discovery of important new medicines for patients by pharmaceutical and biotechnology research companies.

ATRA and PhRMA, on behalf of themselves and their membership, respectfully submit this *amici curiae* brief in support of the Appellees to provide the Court with further guidance regarding the district court's proper exercising of its gatekeeping responsibility to exclude scientifically unreliable expert testimony.[1] As Justice Breyer explained in *Joiner*, "modern life, including good health as well as economic well-being, depends upon the use of artificial or manufactured substances," and the gatekeeping role bestowed on district courts in *Daubert* is needed to assure that "the powerful engine of tort liability, which can generate strong financial incentives to reduce, or to eliminate, production, points toward the right substances and does not destroy the wrong ones." *Gen. Elec. Co. v. Joiner*, 522 U.S. 136, 148-49 (1997) (Breyer, J., concurring).

"The *Daubert* trilogy, in shifting the focus to the kind of empirically supported, rationally explained reasoning required in science, has greatly improved the quality of the evidence upon which juries base their verdicts." *Rider v. Sandoz Pharm. Corp.*, 295 F. 3d 1194, 1197 (11th Cir. 2002). The district court's ruling below reflects this proper understanding of scientific methodology and prevents

[1] No entities other than the identified *amici curiae* have contributed to the funding of this *amicus* brief, which was drafted by counsel for *amici* identified herein. All of the parties in this matter have consented to the filing of this brief.

the very type of hypothesizing and post hoc reasoning that *Daubert* and Federal Rule of Evidence 702 guard against.

Amici urge the Court to affirm the district court's *Daubert* and summary judgment rulings.

ARGUMENT

The district court conducted a thorough and appropriate analysis of the flawed methodologies of the appellants' causation expert. *Amici* will not recapitulate that entire analysis here but will focus on two scientific assertions at the heart of appellants' appeal: **first**, that an expert may opine that a substance is capable of causing an adverse event without replicated statistically-significant findings and when the larger body of epidemiological studies fails to find any such association, and **second**, that an expert can massage the data with after-the-fact analyses to create associations that were not found by the statistical methodologies originally selected by the scientists who performed the study. Scientists call the first cherry-picking and the second P-hacking. As the District Court correctly recognized, neither is a scientifically reliable methodology.

A. Overview Of Epidemiology And How It Is Used By Scientists

"Epidemiology, a field that concerns itself with finding the causal nexus between external factors and disease, is generally considered to be the best evidence of causation in toxic tort actions." *Rider v. Sandoz Pharm. Corp.*, 295

F.3d 1194, 1198 (11th Cir. 2002).[2] Epidemiological studies can be especially important in cases where the drug or substance at issue is widely used or where there is a measurable background rate of the alleged injury regardless of exposure. While the absence of epidemiology may not be fatal to a plaintiff's case, numerous courts have held that a plaintiff seeking to establish causation without such evidence will face a high evidentiary hurdle.[3]

This is also the case where, as here, a plaintiffs' expert proffers a causation opinion that contradicts a solid body of epidemiological evidence failing to find an association between the drug and the outcome at issue. "[W]hile an expert's conclusions reached on the basis of other studies could be sufficiently reliable where no epidemiological studies have been conducted, no reliable scientific

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[2] *See, e.g., Soldo v. Sandoz Pharm. Corp.*, 244 F. Supp. 2d 434, 532 (W.D. Pa. 2003) (epidemiology is "the primary generally accepted methodology for demonstrating a causal relation between a chemical compound and a set of symptoms or a disease" (quoting *Conde v. Velsicol Chem. Corp.*, 804 F. Supp. 972, 1025-26 (S.D. Ohio 1992), *aff'd*, 24 F.3d 809 (6th Cir. 1994))); *Hollander v. Sandoz Pharm. Corp.*, 95 F. Supp. 2d 1230, 1235, n.14 (W.D. Okla. 2000) ("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"), *aff'd*, 289 F.3d 1193 (10th Cir. 2002); *In re Breast Implant Litig.*, 11 F. Supp. 2d 1217, 1224-25 (D. Colo. 1998) (same, citing cases).

[3] *See, e.g., Siharath v. Sandoz Pharm. Corp.*, 131 F. Supp. 2d 1347, 1358 (N.D. Ga. 2001), *aff'd sub. nom Rider v. Sandoz Pharm. Corp.*, 295 F.3d 1194 (11th Cir. 2002).

approach can simply ignore the epidemiology that exists."[4] *See In re: Zoloft (Sertraline Hydrocloride) Prods. Liab. Litig.*, MDL No. 2342, 2015 WL 7776911, at *9 (E.D. Pa. Dec. 2, 2015) (discussing the numerous recent studies that "have uniformly failed to replicate the associations noted in early studies, and the study authors have concluded that the reported association between Zoloft and cardiac birth defects may have been the result of chance, confounding by indication, or other confounders"). Experts cannot ignore or dismiss the existing epidemiology simply because it conflicts with their conclusions.[5]

There are two categories of epidemiological studies: experimental studies and observational studies. The "gold standard" in experimental epidemiology is the double-blind, randomized controlled clinical trial ("RCT"), the type of experimental study that FDA requires before approving a drug as safe and effective.[6] In an RCT, scientists test a predetermined hypothesized association by exposing a group of randomly-assigned individuals in a clinical setting either to the

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[4] *Perry v. Novartis Pharm. Corp.*, 564 F. Supp. 2d 452, 465 (E.D. Pa. 2008); *see also, e.g., Norris v. Baxter Healthcare Corp.*, 397 F.3d 878, 881-87 (10th Cir. 2005).

[5] *See Perry*, 564 F. Supp. 2d at 465.

[6] *See* Michael D. Green *et al.*, *Reference Guide on Epidemiology*, *in Reference Manual on Scientific Evidence* 549, 555 (3d ed. 2011) ("Such a study design is often used to evaluate new drugs or medical treatments and is the best way to ensure that any observed difference in outcome between the two groups is likely to be the result of exposure to the drug or medical treatment.").

studied treatment or a placebo and then following them prospectively without knowledge of the group in which the individuals belong and measuring any differences in the outcome at interest. While RCTs are the most scientifically reliable method for reaching a causation opinion, the requirement that a subject be intentionally exposed to a drug or chemical limits the circumstances in which the study design may be used. As the district court correctly noted, "such studies may not ethically be conducted on pregnant women." *In re: Zoloft*, 2015 WL 7776911, at *2.

In the absence of RCTs, the most scientifically reliable evidence of causation in humans comes from observational epidemiology. In observational studies, scientists seek to infer associations from exposures that occur in non-controlled settings, either by comparing the incidence of disease among individuals exposed to an agent with an unexposed group ("cohort studies") or by comparing the frequency of prior exposures in individuals who have a disease as compared to a group of individuals who do not have the disease ("case control studies").[7] These are the types of epidemiological studies at issue here.

In both cohort and case-control studies, scientists compare two populations to determine if there is an association between an exposure and a disease. In a

[7] *See Magistrini v. One Hour Martinizing Dry Cleaning*, 180 F. Supp. 2d 584, 590-91 (D.N.J. 2002), *aff'd*, 68 Fed. Appx. 356 (3d Cir. 2003).

cohort study, scientists compare individuals with an exposure to individuals without an exposure. If a greater percentage of individuals with an exposure subsequently develop a disease than do those without the exposure, the study will report a positive association. Likewise, a case-control study will report a positive association, if a greater percentage of individuals with a disease (cases) report a given exposure in their past than do healthy individuals (controls). In both types of studies, a positive association will be reported as a risk ratio greater than 1.0. A risk ratio of 1.0, reflecting an identical percentage in both comparator groups and thus no increased risk, is referred to as the "null" hypothesis.[8]

The finding in any one epidemiological study of an *association* between a substance and an injury is not equivalent to finding *causation*.[9] There are three reasons that a positive association may be observed in an epidemiological study: (1) chance, (2) bias, and (3) real effect.[10] As the United States Supreme Court has explained, epidemiological research cannot provide a scientifically reliable basis for an affirmative causation opinion if it is statistically insignificant or

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[8] *See Turpin v. Merrell Dow Pharms., Inc.*, 959 F.2d 1349, 1353 n.1 (6th Cir. 1992).

[9] *See* Green *et al.*, *Reference Guide on Epidemiology*, *supra* note 6, at 552.

[10] *See Magistrini*, 180 F. Supp. 2d at 591; *Caraker v. Sandoz Pharm. Corp.*, 188 F. Supp. 2d 1026, 1032 (S.D. Ill 2001); *see also* Eddy A. Bresnitz, *Principles of Research Design*, *in* Goldfrank's Toxicologic Emergencies 1827-28 (Goldfrank *et al.* eds., 6th ed. 1998).

inadequately controlled for bias.[11]

Epidemiologists attempt to account for the possibility of chance by calculating 95% "confidence intervals" around the reported association. An epidemiological study is considered to show a statistically significant association if the confidence interval of upper and lower bound estimates of risk excludes the "null" hypothesis of no increased risk. If an epidemiological study is not statistically significant, that is, if the confidence interval includes the "null" hypothesis 1.0, it cannot provide scientifically reliable evidence of an association, let alone causation.[12]

While tests for statistical significance can limit the likelihood that a reported finding was due to chance, they do not address the separate issue of bias. Bias in epidemiology is any systematic error that makes the two groups being compared

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[11] *See General Electric Co. v. Joiner*, 522 U.S. 136, 145-46 (1997).

[12] *See id.* at 145; *In re TMI Litig.*, 193 F.3d 613, 711 n.165 (3d Cir. 1999) ("'Where the confidence interval contains a relative risk of 1.0, the results of the study are not statistically significant.'" (quoting Federal Judicial Center, Reference Manual on Scientific Evidence 173 (1994))); *see also Dunn v. Sandoz Pharm. Corp.*, 275 F. Supp. 2d 672, 681 (M.D.N.C. 2003) ("statistically insignificant results do not constitute proof" of causation); *Soldo*, 244 F. Supp. 2d at 533 ("Courts have emphasized that epidemiologic proof must be statistically significant.") (citing cases); *Caraker*, 188 F. Supp. 2d at 1034 (rejecting experts' causation opinions "inasmuch as they rely on selective use of statistically insignificant data from epidemiological studies").

different in more ways than just the exposure being studied.[13] Common sources of bias include confounding factors (other factors associated with the studied exposure that might account for a perceived increased risk), selection bias (uncontrolled differences between the studied populations that distort the data used to make the comparison), and information bias (systematic error in measuring data that results in differential accuracy of information).[14] A court must consider each of these sources of bias in interpreting an epidemiological study because bias can produce an erroneous association.[15] Thus, for example, courts have excluded expert causation testimony based on purported statistically significant epidemiologic evidence where the study failed to account for other confounding exposures that could have accounted for the apparent association.[16]

Even when investigators attempt to control for chance and bias, a finding of

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[13] *See Magistrini*, 180 F. Supp. 2d at 592.

[14] *See Merrell Dow Pharm. v. Havner*, 953 S.W.2d 706, 719 (Tex. 1997); *see also* Bresnitz, *supra* note 10, at 1831-32; Green *et al.*, *Reference Guide on Epidemiology*, *supra* note 6, at 583-97 (discussing sources of bias); David A. Grimes & Kenneth F. Schulz, *Bias and Causal Associations in Observational Research*, 359 The Lancet 248 (Jan. 19, 2002) (same, including real world examples of confounding errors).

[15] *Magistrini*, 180 F. Supp. 2d at 591; *Caraker*, 188 F. Supp. 2d at 1032; *see also Havner*, 953 S.W.2d at 719 ("Bias can dramatically affect the scientific reliability of an epidemiological study.").

[16] *See, e.g.*, *Nelson v. Tennessee Gas Pipeline Co.*, 243 F.3d 244, 252-54 (6th Cir. 2001) (expert's failure to account for confounding factors in cohort study of alleged PCB exposures rendered his opinion unreliable).

a small increased risk of 2.0 or 3.0 in an individual observational epidemiologic study does not provide reliable evidence of causation.[17] The scientific literature is replete with examples of associations in observational studies that were refuted by subsequent research. For example, "[b]y the late 1980s, epidemiologists had noted contradictory findings in published case-control studies on 56 different topics. More recently, researchers identified 12 randomized controlled trials that tested 52 claims from observational studies. None of the claims could be corroborated and, ironically, for five of the 52 claims, the treatment effect was statistically significant in the opposite direction."[18]

Reliable scientists accordingly pay close attention to whether the results of an epidemiologic study have been replicated. As explained in the Reference Manual on Scientific Evidence: "Rarely, if ever does a single study persuasively demonstrate a cause-effect relationship. It is important that a study be replicated in different populations and by different investigators before a causal relationship is

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[17] *See* David A. Grimes & Kenneth F. Schulz, *False Alarms and Pseudo-Epidemics: The Limitations of Observational Epidemiology*, 120 Obstetrics & Gynecology 920, 920 (2012).

[18] *Id.* (citations omitted); *see also* S. Stanley Young & Alan Karr, *Deming, Data and Observational Studies: A Process Out of Control and Needing Fixing*, Significance 116 (2011) ("There is now enough evidence to say what many have long thought: that any claim coming from an observational study is most likely to be wrong – wrong in the sense that it will not replicate if tested rigorously.").

accepted by epidemiologists and other scientists."[19] "Consistency in these findings is an important factor in making a judgment about causation."[20] In the present case, the consistent findings of multiple epidemiologic studies fail to reliably support causation.

Finally, scientists in the outside world do not base causation opinions on criticisms of contrary epidemiology. While such criticisms can play an important role in raising new hypotheses or pointing to the need for additional research, they do not provide any affirmative evidence in support of causation.[21]

Here, as discussed below, appellants' expert seeks to rely on epidemiology studies that have subsequently been contradicted by more recent and more comprehensive studies that do *not* report a statistically significant increased association between Zoloft and cardiac birth defects. Moreover, Dr. Jewell attempts to manipulate statistically insignificant results in order to provide epidemiologic evidence of such an association in order to turn to the Bradford Hill criteria. Accordingly, scientists outside the courtroom would recognize that the necessary precondition for the Bradford Hill criteria has not been met, and Dr.

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[19] Green *et al.*, *Reference Guide on Epidemiology*, *supra* note 6, at 604 (citations omitted).

[20] *Id.*

[21] *See Siharath*, 131 F. Supp. 2d at 1358 ("Plaintiffs' well-taken criticisms of the epidemiological studies does not satisfy their burden of proof.").

Jewell cannot rely on either the epidemiology he cites or the Bradford Hill methodology as support for his causation opinion in this case.

B. Cherry-Picking Studies To Support One's Conclusions Without A Consistent Scientific Basis Is Not A Scientific Methodology

Appellants contend that Dr. Jewell's analysis of – and ignoring of – certain peer-reviewed epidemiological studies constitutes good science and that the district court abused its discretion in excluding his testimony. They assert that causation conclusions can be reached without *any* epidemiology at all, *see* Appellants' Br. at 34, and that a causation analysis is appropriate following a single association in any study, *see id.* at 31. Neither claim is correct.

The first proposition arises only in some courts and only in contexts where no epidemiology exists. *See* Green *et al., Reference Guide on Epidemiology, supra* note 6, at 599 n.141 ("In a number of cases, experts attempted to use these [Bradford Hill] guidelines to support the existence of causation in the absence of any epidemiologic studies finding an association. . . . There may be some logic to that effort, but it does not reflect accepted epidemiologic methodology."); *Frischhertz v. SmithKline Beecham Corp.*, No. 10-2125, 2012 WL 6697124, at *3 (E.D. La. Dec. 21, 2012) (excluding expert testimony that purported to rely on Bradford Hill methodology without epidemiologic data showing a statistically significant association). Here, there is a well-developed body of epidemiology, and it must be accounted for.

The second proposition is somewhat more complicated, as it involves the appropriate threshold for a scientist to proceed to a causation analysis. Appellants seek to support their expert's causation opinion by arguing that he relied upon an accepted methodology known as the Bradford Hill criteria. However, an expert cannot invoke Bradford Hill as a basis for admissibility of his opinion unless he can show that he has faithfully applied that methodology to the facts in the case. *See Soldo v. Sandoz Pharm. Corp.*, 244 F. Supp. 2d 434, 561 (W.D. Pa. 2003) (in assessing the reliability of expert testimony, a court "should be wary that the [expert's] method has not been faithfully applied" (quoting *Lust v. Merrell Dow Pharm., Inc.*, 89 F.3d 594, 598 (9th Cir. 1996)).

As appellants recognize, a threshold requirement for a scientist to venture upon a Bradford Hill analysis is that there be a clear-cut association between the two variables under examination (Zoloft and cardiac birth defects, in this case) demonstrated by epidemiology. *See, e.g.*, Appellants' Br. at 19. "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." *Soldo*, 244 F. Supp. 2d at 569 (quoting *In re Breast Implant Litig.*, 11 F. Supp. 2d at 1233 n.5). Sir Bradford Hill, in explaining that an expert should not turn to his criteria to reach an opinion on

causation with first observing a "clear-cut" association in the epidemiologic literature, described the requirement of statistical significance: "Our observations reveal an association between two variables, perfectly clear-cut and beyond what we would care to attribute to the play of chance. What aspects of that association should we especially consider before deciding that the most likely interpretation of it is causation?" Austin Bradford Hill, *The Environment and Disease: Association or Causation*, 58 Proc. Royal Soc'y Med. 295, 295 (1965).

Appellants cannot claim that the epidemiological literature as a whole provides the requisite clear-cut association to support a Bradford Hill analysis. Instead, they argue that an expert may conduct a Bradford Hill analysis if there is a single cherry-picked epidemiological study that reports a statistically significant result, even though that finding was not replicated. Throughout their brief, appellants repeatedly contend that the district court abused its discretion by requiring that an expert's general causation opinion must be supported by "replicated statistically significant epidemiological studies." Appellants' Br. at 30. But scientists outside the courtroom recognize the impropriety of cherry picking isolated, statistical associations out of a larger data base of contrary findings.[22] For example, even if perfectly controlled and without bias, a finding that just reaches

[22] *See*, *e.g.*, *Arias v. DynCorp*, 928 F. Supp. 2d 10, 24-25 (D.D.C. 2013) (excluding expert causation opinion based upon cherry-picked results from epidemiological studies).

statistical significance has a 1 in 20 chance of being artificial. Accordingly, if one looks at a data base with 20 separate findings, one would expect to find a seemingly "significant" finding in the group by pure chance. (In mathematical terms, the likelihood of a finding a false, but statistically significant, result in a group of 20 studies is $1-(0.95)^{20}$ or 64.15 percent.)

The requirement of replication acknowledges the scientific fact that lone associations are prey to a host of different kinds of error and may very well be false. *See, e.g.*, John P.A. Ioannidis, *Why Most Published Research Findings Are False*, 2 Public Library of Science Medicine 0696 (Aug. 2005) (available at http://journals.plos.org/plosmedicine/article/asset?id=10.1371/journal.pmed.0020124.PDF). In fact, appellants' own expert acknowledged the importance of replication of statistically-significant results. *See In re: Zoloft*, 2015 WL 7776911, at *6 ("Dr. Jewell acknowledges the importance of replication of statistically significant results."). The need for replication is highlighted as well by the Federal Judicial Center's *Reference Manual on Scientific Evidence*. Green *et al.*, *Reference Guide on Epidemiology*, *supra* note 6, at 604 (3d ed. 2011) ("It is important that a study be replicated in different populations and by different investigators before a causal relationship is accepted by epidemiologists and other scientists."); *see also In re: Zoloft (Sertraline Hydrochloride) Prod. Liab. Litig.*, 26 F. Supp. 3d 449, 455 (E.D. Pa. 2014) (stating scientists assessing whether

substance is a teratogen require statistically significant associations "which are consistent and replicated across epidemiological studies, and . . . then apply the Bradford–Hill criteria").

A single finding can create scientific confusion when there are no other studies available to test its findings, and some courts have (incorrectly) permitted an expert witness to present a causation analysis where there was but one epidemiology study. But there can be no such confusion, and no possible, reliable basis for an expert causation opinion, where a study is contrary to a wider body of epidemiological literature.

Critically, as the district court rightly noted, Dr. Jewell was unable to reconcile the results found in certain studies finding a positive association between Zoloft and cardiac birth defects with a later and more comprehensive study that largely subsumed the same data as the prior studies into a larger pool of data—and found no increased risk. *See, e.g.*, *In re: Zoloft*, 2015 WL 7776911, at *16. The larger study in question was by Kari Furu *et al.*, *Selective Serotonin Reuptake Inhibitors and Venlafaxine in Early Pregnancy and Risk of Birth Defects: Population Based Cohort Study and Sibling Design*, 350 British Med. J. 1798 (2015) (hereinafter "Furu (2015)"). Notably, this study "includ[ed] virtually all the data from the earlier Danish studies" that Dr. Jewell had relied upon. *See In re: Zoloft*, 2015 WL 7776911, at *7. Yet although those earlier Danish studies had

found a tripling of the relative risk of a cardiac birth defect, the Furu (2015) study found "no association between Zoloft use and cardiac birth defects." *Id.*

Outside of the courtroom, when a scientist is confronted with a new and larger study that raises questions about his conclusions, the scientist needs to explain *why* this new study does not undermine those earlier conclusions. *See id.* ("Scientists are expected to address and reconcile data that does not support their opinions, and not simply rely upon data which does."). Yet Dr. Jewell was unable "to provide any methodological or statistical explanation for why this larger, later study failed to replicate the findings of the earlier study, or why the earlier studies should be considered more reliable than Furu (2015)." *Id.* Thus, Dr. Jewell's rejection of Furu (2015) was nothing more than the type of *ipse dixit* that scientists are no more permitted to use outside the courtroom than they are in it. *See Joiner*, 522 U.S. at 146 ("[N]othing 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.").

Of course, scientists can and do weigh scientific studies, deeming some to be persuasive while discounting others for various reasons. But they must be consistent and scientific in the criteria that they use to do so. What this case illustrates well is the importance of the gatekeeper in delving into the details of a proffered expert's reasoning. The check-box approach suggested by the

appellant—whereby an epidemiological study finding a statistically-significant association is offered to check the "association" box and permit the expert to proceed to his causation analysis—will not do. Here, the district court painstakingly reviewed Dr. Jewell's reasoning and found that he could not adequately explain why he was embracing the studies that suggested an association while simultaneously rejecting larger studies in the same population that found no association. Dr. Jewell did not show any flaw in that larger study, which the district court found to be "well-powered and designed to address issues of bias and confounding." *In re: Zoloft*, 2015 WL 7776911, at *9. When scientists cannot articulate an objective, principled basis for their selection of some evidence to follow and some to ignore, the gatekeeper is justified in concluding that they are engaged in something other than science. This is what Rule 702 and *Daubert* require. *See, e.g.*, *Arias*, 928 F. Supp. 2d at 25 (excluding expert testing where expert failed to "explain why he decided to credit [one study's] results and dismiss [another study's] results").

C. "P-Hacking," Or Recalculating Data In Search Of A Statistically-Significant Result, Is Not A Scientific Methodology

Where the science failed to support Dr. Jewell's conclusions, he offered different interpretations of the data applying a greatly relaxed standard (purporting to discern "trends" in non-significant data") or reanalyzed data to reach a different conclusion. Although there are procedures by which scientists can take existing

studies and data and apply statistical analyses that were not applied before, the district court properly found that Dr. Jewell did not follow such procedures.

There were multiple negative studies on Zoloft and heart defects—i.e., studies finding no statistically-significant association. Dr. Jewell tried to bring these negative studies into the fold by focusing on "trends" in odds ratios. *See, e.g.*, *In re: Zoloft*, 2015 WL 7776911, at **9-10. The problem of scientists deluding themselves that they see "trends" in data that are not present in reality is precisely why statistical significance was invented. And—as the district court correctly recognized—epidemiology and teratology have not "abandoned, or even reduced the importance of, the principle of statistical significance." *Id.* Courts have routinely rejected evidence that is not statistically significant because it is not scientifically reliable as the foundation of a causation opinion. *See, e.g.*, *Allen v. Pa. Eng'g Corp.*, 102 F.3d 194, 197 (5th Cir. 1996) ("While appellants' experts acknowledge the lack of statistically significant epidemiological evidence, they rely on certain studies as 'suggestive' of a link between EtO exposure and brain cancer. 'Suggestiveness' is not by the experts' own admission statistical significance . . .; this basis for their scientific opinion must be rejected.").

Dr. Jewell went further, selectively manipulating data in a way that (he said) produced significant results where none had previously existed. This is known in science as P-hacking: massaging data in various ways in order to try to achieve

statistical significance.[23] It is perhaps more often done by scientists hoping to make their data more publishable than by expert witnesses (because there are more of the former than the latter), but the phenomenon is the same in either domain, and is equally unscientific. Dr. Jewell testified that he had combined two independent studies with non-significant p-values and thereby created a statistically significant result. *See In re: Zoloft*, 2015 WL 7776911, at *10. This supposed methodology is not a scientific one. As the district court noted, not only is it "not a method used in the peer-reviewed, published meta-analyses the Court has reviewed," but the district court was "presented with no evidence that is accepted as a scientifically reliable methodology." *Id.* That it was a results-oriented endeavor was underscored by the fact that Dr. Jewell did not include in this analysis studies that would have undermined his ultimate conclusion. *See id.*

Finally, Dr. Jewell repeatedly, as the district court concluded, engaged in a results-driven approach to his analysis of certain studies. *See, e.g.*, *In re: Zoloft*, 2015 WL 7776911, at *11 ("Dr. Jewell selectively relies upon the principle of heterogeneity in a results-driven manner"), 14 ("[R]esults-oriented, *post-hoc* re-analyses of existing epidemiological studies are disfavored by scientists and often deemed unreliable by courts, unless the expert can validate the need for re-analysis

[23] For an overview of P-hacking, see Christie Aschwanden, *Science Isn't Broken*, fivethirtyeight.com (Aug. 19, 2015), http://fivethirtyeight.com/features/science-isnt-broken/#part1.

in some way."). Dr. Jewell's selection of which studies to re-examine, *see, e.g.*, *id.* at *11, 14, and which to include in his meta-analysis, *see id.* at *15, are hallmarks of result-driven "science." The district court ensured that such bad science would not enter the courtroom, the exact result that Rule 702 and *Daubert* are designed to achieve.[24]

CONCLUSION

For the foregoing reasons, the American Tort Reform Association and the Pharmaceutical Research and Manufacturers of America, *amici curiae* herein, urge the Court to affirm the ruling of the district court.

Respectfully submitted,

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[24] The court below is not the first to exclude Dr. Jewell's testimony for this reason. *See In re Lipitor (Atorvastatin Calcium) Mktg., Sales Pracs. & Prods. Liab. Litig.*, 145 F. Supp. 3d 573, 584 (D.S.C. 2015) ("Coming to a firm conclusion first and then doing research to support it is the antithesis of [the scientific] method. That is what Dr. Jewell has done here." (citation and quotation marks omitted)), *amended by* 2016 WL 827067 (D.S.C. Feb. 29, 2016).

CERTIFICATION OF COMPLIANCE

I, Joe G. Hollingsworth, hereby certify:

1. This brief complies with 3d Cir. L.A.R. 28.3(d) in that I, the signatory of the brief, am a member of the bar of this Court.

2. This brief complies with the type-volume limitations of Fed. R. App. P. 29(d) because it contains 5,016 words, excluding the parts of the brief exempted by Fed. R. App. P. 32(a)(7)(B)(iii).

3. This brief complies with the typeface requirements of Fed. R. App. P. 32(a)(5) and the type style requirements of Fed. R. App. P. 32(a)(6) because this brief has been prepared in a double-spaced typeface using Microsoft Word 2010, in 14 point font size and Times New Roman type style.

4. The text of the electronically filed brief is identical to the text of the paper copies sent to the Clerk of the Court of the United States Court of Appeal for the Third Circuit by Federal Express Overnight Delivery.

5. On October 18, 2016, a virus check was performed on the electronically filed copy of this brief using Microsoft System Center Endpoint Protection Client Version (4.1.509.0), definition version (1.229.1916.0 updated as of 10/17/2016), and, according to the program, no virus was detected.

s/ Joe G. Hollingsworth
Joe G. Hollingsworth

Dated: October 18, 2016

CERTIFICATE OF SERVICE

In accordance with Fed. R. App. P. 25 and 3d Cir. L.A.R. 25, I hereby certify that I have on this 18th day of October 2016, filed the foregoing with the Clerk of the Court by using the CM/ECF system. Participants in the case are registered CM/ECF users and service will be accomplished by the CM/ECF system. I further certify that, in accordance with this Court's April 29, 2013 Standing Order, seven paper copies of the foregoing were sent on this 18th day of October 2016, to the Clerk of the Court via Federal Express Overnight Delivery to:

Office of the Clerk
United States Court of Appeals for the Third Circuit
21400 U.S. Courthouse
601 Market Street
Philadelphia, Pennsylvania 19106

s/ Joe G. Hollingsworth
Joe G. Hollingsworth