IN THE UNITED STATES COURT OF APPEALS
FOR THE FOURTH CIRCUIT

Nos. 17-1140(L), 17-1136, 17-1137, 17-1189

In re: LIPITOR (ATORVASTATIN CALCIUM) MARKETING, SALES PRACTICES AND PRODUCTS LIABILITY LITIGATION

PLAINTIFFS APPEALING CASE MANAGEMENT ORDER 100; JUANITA HEMPSTEAD; PLAINTIFFS APPEALING CASE MANAGEMENT ORDER 99; PLAINTIFFS APPEALING CASE MANAGEMENT ORDER 109,
Plaintiffs-Appellants,

v.

PFIZER, INCORPORATED; MCKESSON CORPORATION; GREENSTONE, LLC; PFIZER INTERNATIONAL LLC,
Defendants-Appellees.

On Appeal from the United States District Court for the District of South Carolina (Charleston), Nos. 2:14-mm-02502-RMG, 2:14-cv-01879-RMG

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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PHARMACEUTICAL RESEARCH AND MANUFACTURERS OF AMERICA

UNITED STATES COURT OF APPEALS FOR THE FOURTH CIRCUIT
DISCLOSURE OF CORPORATE AFFILIATIONS AND OTHER INTERESTS

Disclosures must be filed on behalf of all parties to a civil, agency, bankruptcy or mandamus case, except that a disclosure statement is **not** required from the United States, from an indigent party, or from a state or local government in a pro se case. In mandamus cases arising from a civil or bankruptcy action, all parties to the action in the district court are considered parties to the mandamus case.

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If counsel is not a registered ECF filer and does not intend to file documents other than the required disclosure statement, counsel may file the disclosure statement in paper rather than electronic form. Counsel has a continuing duty to update this information.

No. 17-1140 Caption: In re: Lipitor

Pursuant to FRAP 26.1 and Local Rule 26.1,

American Tort Reform Association (ATRA)
(name of party/amicus)

who is Amicus, makes the following disclosure:
(appellant/appellee/petitioner/respondent/amicus/intervenor)

1. Is party/amicus a publicly held corporation or other publicly held entity? ☐ YES ☑ NO

2. Does party/amicus have any parent corporations? ☐ YES ☑ NO
If yes, identify all parent corporations, including all generations of parent corporations:

3. Is 10% or more of the stock of a party/amicus owned by a publicly held corporation or other publicly held entity? ☐ YES ☑ NO
If yes, identify all such owners:

4. Is there any other publicly held corporation or other publicly held entity that has a direct financial interest in the outcome of the litigation (Local Rule 26.1(a)(2)(B))? ☐ YES ☑ NO
If yes, identify entity and nature of interest:

5. Is party a trade association? (amici curiae do not complete this question) ☐ YES ☐ NO
If yes, identify any publicly held member whose stock or equity value could be affected substantially by the outcome of the proceeding or whose claims the trade association is pursuing in a representative capacity, or state that there is no such member:

6. Does this case arise out of a bankruptcy proceeding? ☐ YES ☑ NO
If yes, identify any trustee and the members of any creditors' committee:

Signature: /s/ Eric G. Lasker Date: July 7, 2017

Counsel for: ATRA

CERTIFICATE OF SERVICE

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I certify that on July 7, 2017 the foregoing document was served on all parties or their counsel of record through the CM/ECF system if they are registered users or, if they are not, by serving a true and correct copy at the addresses listed below:

/s/ Eric G. Lasker (signature) July 7, 2017 (date)

UNITED STATES COURT OF APPEALS FOR THE FOURTH CIRCUIT
DISCLOSURE OF CORPORATE AFFILIATIONS AND OTHER INTERESTS

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No. 17-1140 Caption: In re: Lipitor

Pursuant to FRAP 26.1 and Local Rule 26.1,

Pharmaceutical Research and Manufacturers of America (PhRMA)
(name of party/amicus)

who is Amicus, makes the following disclosure:
(appellant/appellee/petitioner/respondent/amicus/intervenor)

1. Is party/amicus a publicly held corporation or other publicly held entity? ☐ YES ☑ NO

2. Does party/amicus have any parent corporations? ☐ YES ☑ NO
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If yes, identify any trustee and the members of any creditors' committee:

Signature: /s/ Eric G. Lasker Date: July 7, 2017

Counsel for: PhRMA

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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 they are 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 *Daubert* and other 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 MDL court's proper exercising of its gatekeeping responsibility to exclude scientifically unreliable expert testimony and to efficiently manage the litigation through its resulting summary judgment ruling.[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 MDL court's ruling

[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.

below reflects this proper understanding of scientific methodology and prevents 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 MDL court's *Daubert* and summary judgment rulings.

ARGUMENT

The MDL court conducted a thorough and appropriate analysis of the flawed methodologies of the appellants' experts. *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 at any dose of causing an adverse event without any statistically-significant epidemiological support and in the face of a body of epidemiological studies failing 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, something scientists call (at least as it was done in this case) P-hacking. As the MDL court correctly recognized, neither is a scientifically reliable methodology. *Amici* also address plaintiffs' flawed contention that the MDL court lacked authority to grant summary judgment upon finding that they had failed to meet their burden of proof on general or specific causation or to efficiently manage the

litigation to require individual plaintiffs to show cause why their claims are not encompassed by such summary judgment ruling.

I. The MDL court properly excluded the testimony of Dr. Jewell and Dr. Singh as unreliable under *Daubert* and Rule 702.

A. Overview of epidemiology and its role in this case.

The science of epidemiology is at the heart of this appeal, both because the experts in question made it so by putting it at the heart of their methodologies and because it is the gold standard for establishing whether a substance can cause a particular outcome in humans. "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*, 295 F.3d at 1198.[2] Epidemiological studies are especially important in cases—like this one—where the drug or substance at issue is widely used and there is a substantial background rate of the alleged injury regardless of exposure. Of relevance here, diabetes is relatively common in the portion of the population that takes

[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).

cholesterol-lowering medicines, and so reliable scientific evidence is very important in attempting to discern whether such medicines create any *additional* risk of diabetes.

As a general proposition, the absence of epidemiology is not necessarily fatal to a plaintiff's case, and courts have allowed general causation testimony based primarily on other disciplines, particularly when little or no epidemiology about the substance in question existed. But numerous courts have held that a plaintiff seeking to establish causation without such evidence will face stiff evidentiary headwinds.[3] These headwinds strengthen to a gale when there is a substantial body of epidemiology pointing to an *absence* of causation. In such a case, the expert must overcome, using sound scientific methods, the strong evidence contradicting his conclusion. "[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 approach can simply ignore the epidemiology that exists."[4] This requirement was not judicially created, but arises

[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).

[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).

from the scientific method itself, as well as from the stated methodologies of both experts whose opinions were excluded below, Drs. Jewell and Singh.

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.[5] In an RCT, scientists test a predetermined hypothesized association by exposing a group of randomly-assigned individuals in a clinical setting either to the 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.[6]

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[5] *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.").

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

The finding in any one epidemiological study of an *association* between a substance and an injury is not equivalent to finding *causation.*[7] There are three reasons that a positive association may be observed in an epidemiological study: (1) chance, (2) bias, and (3) real effect.[8] Scientists protect against the possibility of chance by analyzing whether an association is "statistically significant."[9] As the United States Supreme Court has explained, epidemiological research cannot provide a scientifically reliable basis for an affirmative causation opinion if it is

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

[7] *See* Green *et al., Reference Guide on Epidemiology, supra* note 5, at 552.

[8] *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).

[9] *See, e.g., Craik v. Minnesota State Univ. Bd.*, 731 F.2d 465, 475 n.13 (8th Cir. 1984) ("Statistical significance is a measure of the probability that an observed disparity is not due to chance."); *In re Zoloft (Sertraline Hydrocloride) Prods. Liab. Litig.*, No. 12-MD-2342, 2015 WL 314149, at *2 n.9 (E.D. Pa. Jan. 23, 2015) ("[S]cientists generally use confidence intervals or other measures of statistical significance to demonstrate that a detected association is sufficiently greater than the background risk as to be unlikely due to chance alone.").

statistically insignificant.[10] The Third Circuit held—in another decision affirming the exclusion of Dr. Jewell's opinion, this time involving Zoloft and birth defects—statistical significance "remains an important metric to distinguish between results supporting a true association and those resulting from mere chance." *In re Zoloft (Sertraline Hydrochloride) Prods. Liab. Litig.*, 858 F.3d 787, 793 (3d Cir. 2017). Indeed, 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.").

In order to establish an association in the case of Lipitor and diabetes, plaintiffs sought to rely on epidemiological studies that do *not* report a statistically significant increased association between Lipitor and diabetes. Dr. Jewell performed scientifically improper statistical manipulations to try to achieve such statistical significance, and Dr. Singh chose a methodology—Bradford-Hill

[10] *See Joiner*, 522 U.S. at 145-46. The Court likewise explained that epidemiological research cannot support a causation opinion if it is inadequately controlled for bias. *Id.*

analysis—that has a threshold requirement of an association demonstrated by statistically-significant epidemiology. The MDL court did not abuse its discretion in finding these methodologies to be improper and excluding the experts' opinions.

B. Reliable science does not involve result-seeking statistical hacking.

Appellants contend that Dr. Jewell's re-analysis of some—and ignoring of other—peer-reviewed epidemiological studies constitutes good science and that the MDL court abused its discretion in excluding his testimony. Although there are procedures by which scientists can take existing studies and data and apply statistical analyses that were not applied before, the MDL court properly found that Dr. Jewell did not follow such procedures.

Dr. Jewell selectively manipulated data in a way that (he said) produced significant results where none had previously existed. When done the way that Dr. Jewell did it, this is known in science as P-hacking: massaging the data in order to try to achieve statistical significance, rather than following a correct statistical protocol and accepting the results that it yields.[11] As the MDL court noted, Dr. Jewell "performed, in his words, a 'whole lot' of analyses of the data, excluding from his report analyses that he 'didn't believe . . . supported . . . being the basis of the kinds of opinions I wanted to put in my summary,' (Dkt. No. 1247-

[11] 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.

8 at 230-31), and conducting multiple statistical tests when the first test did not produce the results that he wanted.'" *In re Lipitor (Atorvastatin Calcium) Mktg., Sales Practices & Prods. Liab. Litig.*, 145 F. Supp. 3d 573, 578 (D.S.C. 2015), *order amended on reconsideration.*, MDL No. 2:14–mn–02502–RMG, 2016 WL 827067 (D.S.C. Feb. 29, 2016). This supposed methodology is not a scientific one. 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.* at 578 n.4 (noting that "Dr. Jewell did not keep the analyses that were not part of his report.").

Dr. Jewell repeatedly, as the MDL court concluded, engaged in a results-driven approach to his analysis of certain studies. *See, e.g.*, *id.* at 584 ("To reach his conclusion, he included participants with elevated glucose at baseline, despite the fact that he excludes all such participants in his other analyses, and reverts to a less conservative test when the first statistical test he used did not produce the results he wanted."). Dr. Jewell's selection of models after seeing different results and which studies to re-examine, *see, e.g.*, *id.* at 582-84, are hallmarks of result-driven "science." The MDL court ensured that such bad science would not enter the courtroom, the exact result that Rule 702 and *Daubert* are designed to achieve.

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 plaintiffs—whereby an epidemiological study (or "expert re-analysis") 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.

A Bradford-Hill analysis, a methodology employed by Dr. Singh, is a set of criteria (*e.g.*, strength, biological plausibility, and temporal association) by which an *already-established* statistically-significant epidemiological association can be evaluated to determine if it is a *causal* association. Since Dr. Singh purported to apply a Bradford Hill analysis to show causation, it was the MDL court's duty to assure that he applied it correctly. *See Soldo*, 244 F. Supp. 2d at 561 (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)); *see also In re Zoloft*, 858 F.3d at 796 (holding that "despite the fact that both the Bradford Hill and the weight of the evidence analyses are generally reliable, the 'techniques' used to implement the analysis must be 1) reliable and 2) reliably applied" and affirming MDL court's conclusion that Dr. Jewell had failed to do so).

The Bradford Hill methodology requires as its first step that there be a statistically significant association between the two variables under examination (Lipitor and diabetes, in this case) demonstrated by epidemiology.[12] "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) (emphasis added) (quotation marks omitted). Sir Bradford Hill, in explaining that

[12] *See, e.g., Mathews v. Novartis Pharm. Corp.*, No. 3:12–CV–314, 2013 WL 5780415, at *27 (S.D. Ohio Oct. 25, 2013) ("Unless there is a statistically significant association between the drug and the disease, the Bradford–Hill analysis to determine causation is inapplicable." (citation omitted)); *McMunn v, Babcock & Wilcox Power Generation Grp., Inc.*, Civil Action No. 10-143, 2013 WL 3487560, at *15 (W.D. Pa. July 12, 2013) ("Step one looks to whether there is a statistically significant association between a substance and a specific disease. . . . If no association between the exposure and the disease is supported by the scientific literature, there is no basis to find a causal relationship exists and the analysis should end there."); *Frischhertz v. SmithKline Beecham Corp.*, Civil Action No. 10-2125, 2012 WL 6697124, at *3 (E.D. La. Dec. 21, 2012) ("The Bradford–Hill criteria can only be applied after a statistically significant association has been identified."); *Wagoner v. Exxon Mobil Corp.*, 813 F. Supp. 2d 771, 803 (E.D. La. 2011) ("[T]he set of criteria known as the Bradford Hill criteria has been widely acknowledged as providing an appropriate framework for assessing whether a causal relationship underlies a statistically significant association between an agent and a disease."); *In re Fosamax Prods. Liab. Litig.*, 645 F. Supp. 2d 164, 188 (S.D.N.Y. 2009) ("Several courts that have considered the question have held that it is not proper methodology for an epidemiologist to apply the Bradford Hill factors without data from controlled studies showing an association.").

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) (emphasis added).

Of course, the court is not called upon to find that proof of general causation always requires statistically-significant epidemiology when, as here, the experts in question select a methodology that itself demands a statistically-significant association. That experts must faithfully apply the standards of their own methodologies is fundamental *Daubert* jurisprudence. *See, e.g.*, *In re Ephedra Prods. Liab. Litig.*, 494 F. Supp. 2d 256, 258 (S.D.N.Y. 2007) ("[A]n expert's own failure to consistently apply his methodology can form the basis for the exclusion of any resulting opinions." (citing *Amorgianos v. National R.R. Passenger Corp.*, 303 F.3d 256, 269 (2d Cir. 2002)); *Soldo*, 244 F. Supp. at 560 ("The reliability of Dr. Kulig's opinions in this case is likewise undermined by his failure to follow his own standards.").

Here, the MDL court painstakingly reviewed Dr. Jewell's reasoning and found that he could not adequately explain why he was reanalyzing certain studies and not others or why he was embracing those that suggested an association while simultaneously rejecting others. Dr. Jewell did not show any flaw in the rejected studies. 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. Such scientific basis is what Rule 702 and *Daubert* require. *See, e.g.*, *Arias v. DynCorp*, 928 F. Supp. 2d 10, 25 (D.D.C. 2013) (excluding expert testing where expert failed to "explain why he decided to credit [one study's] results and dismiss [another study's] results").

C. Reliable science does not presume that effects observable at one dose apply to all doses.

Appellants contend that the MDL court abused its discretion by requiring that Dr. Singh support his general causation opinion with "statistically significant evidence at every administered dosage of a drug," Appellants' Br. at 57, or that he had to "rule out the possibility that there is a so-called 'no effect threshold'—*i.e.*, a dose below which Lipitor cannot cause diabetes." The MDL court imposed no such standard, but merely held Dr. Singh to his *own* stated causation principle that the dose makes the poison. Dr. Singh testified that "there's a dose responsiveness,"

and that "it's clearly possible that [a] drug has an effect at higher dose, but no effect at lower dose." *Id.* at 921.

The notion that a substance's harmfulness must be established *at the doses actually encountered by the plaintiffs* is fundamental to *Daubert* because it is fundamental to toxicology. In *Yates v. Ford Motor Co.*, the court found that "a 'central tenet' in the science of the harmful effects of chemical and physical agents on organisms" is that "'the dose makes the poison,' i.e. 'all chemical agents are intrinsically hazardous, whether they cause harm is only a question of dose.'" 113 F. Supp. 3d 841, 851 (E.D.N.C. 2015) (quoting Bernard D. Goldstein and Mary Sue Henifin, "Reference Guide on Toxicology," in *Federal Reference Manual on Scientific Evidence,* 636 (3d ed. 2011))); *see Mancuso v. Consol. Edison Co. of New York, Inc.*, 56 F. Supp. 2d 391, 403 (S.D.N.Y. 1999) ("A fundamental tenet of toxicology is that the 'dose makes the poison' and that all chemical agents, including water, are harmful if consumed in large quantities, while even the most toxic substances are harmless in minute quantities."), *aff'd in part, vacated in part*, 216 F.3d 1072 (2nd Cir. 2000). In *Westberry v. Gislaved Gummi AB,* this Court held that "[i]n order to carry the burden of proving a plaintiff's injury was caused by exposure to a specified substance, the plaintiff must demonstrate 'the levels of exposure that are hazardous to human beings generally as well as the plaintiff's actual level of exposure." 178 F.3d 257, 263 (4th Cir.1999) (quotation

marks omitted). Simply stated, expert evidence that might support a causation opinion at a higher dose, without more, cannot provide a reliable basis for a causation opinion at a lower dose.

The MDL court *admitted* Dr. Singh's testimony for individuals receiving a dose of 80 mg and properly required him to show that he had relied on scientifically reliable evidence that his opinion applied as well to plaintiffs at *lower* doses of 10 mg to 40 mg. *See In re Lipitor (Atorvastatin Calcium) Mktg., Sales Practices & Prods. Liab. Litig.*, 174 F. Supp. 3d 911, 922 (D.S.C. 2016). Based on demonstrable flaws in his methodology, it found that he had not. In grouping together the lower doses, the court took Dr. Singh at his word: Dr. Singh said that he was relying on the same evidence that Lipitor was harmful at 10 mg as he was for 20 mg and 40 mg. *Id.* at 927 (Dr. Singh conceding that "he cannot reach an opinion about whether 20 mg and 40 mg of Lipitor causes diabetes without the conclusion that 10 mg of Lipitor causes diabetes."). By Dr. Singh's own testimony the evidence on doses below 80 mg stood or fell together.

In rejecting the proffered testimony regarding the lower doses, the MDL Court focused on serious flaws in Dr. Singh's methodology. Dr. Singh sought to rely on non-statistically significant results and on "trends" that he purported to discern in those results—exactly the kind of evidence that Dr. Jewell sought to rely upon in his rejected *Zoloft* testimony. *See In re Zoloft*, 858 F.3d at 797-98; *see also*

In re Lipitor, 145 F. Supp. 3d. at 586 & n.23 (discussing Dr. Jewell's selective reliance on trends in insignificant data). Dr. Singh admitted the weaknesses in this approach: "Dr. Singh, himself, testifies that a lack of statistical significance means that either a study has 'low power' or 'no risk exists,' and that he 'does not know' which of these possibilities is the case. Thus, his own testimony demonstrates that studies without statistical significance are insufficient to support a causation opinion." *In re Lipitor*, 174 F. Supp. 3d at 926 (citation omitted).

II. MDL courts have the power to dismiss cases when plaintiffs fail to come forward with evidence on specific causation after being given a chance to do so.

Plaintiffs take issue with the MDL court's dismissal of multiple claims after they failed to present scientifically reliable evidence on specific causation. But the MDL court's action was perfectly appropriate and squarely within its powers. It is beyond dispute that "§ 1407 empowers transferee courts to enter a dispositive pre-trial order terminating a case." *In re Donald J. Trump Casino Sec. Litig. – Taj Mahal Litig.*, 7 F.3d 357, 367 (3d Cir. 1993).[13] In fact, as this Court has noted, "the

[13] *See also* Manual for Complex Litigation, § 22.36 (4th ed. 2004) ("An MDL transferee judge has authority to dispose of cases on the merits—for example, by ruling on motions for summary judgment."); *In re Korean Air Lines Co., Ltd.*, 642 F.3d 685, 698-99 (9th Cir. 2011) ("A district judge exercising authority over cases transferred for pretrial proceedings 'inherits the entire pretrial jurisdiction that the transferor district judge would have exercised if the transfer had not occurred.' Such authority is broad and encompasses the power to decide dispositive pretrial motions. *In re PPA*, 460 F.3d at 1231 (stating that a transferee judge's power "includes authority to decide all pretrial motions such as motions to

vast majority of transferred cases are disposed of completely in the transferee court, either through pretrial dispositions such as summary judgment, or by trial." *In re Food Lion, Inc., Fair Labor Standards Act Effective Scheduling Litig.*, 73 F.3d 528, 532 (4th Cir. 1996).

Although plaintiffs imply that the MDL court should not have addressed the issue of specific causation beyond the first cases selected for trial, the court has broad discretion to decide which pretrial matters it will rule on. *See, e.g.*, *In re Evergreen Valley Project Litig*., 435 F. Supp. 923, 924 (J.P.M.L. 1977) ("It is not contemplated that a Section 1407 transferee judge will necessarily complete all pretrial proceedings in all actions transferred and assigned to him by the Panel, but rather that the transferee judge *in his discretion* will conduct the common pretrial proceedings with respect to the actions and any additional pretrial proceedings *as he deems otherwise appropriate*." (emphasis added)). Plaintiffs' authorities saying that an MDL court *may* remand cases for specific causation analysis are correct; they would be just as correct to say that it may choose *not* to do so. *See, e.g.*, Appellants' Brief at 79-80 (citing, e.g., Manual for Complex Litigation, § 22.87

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dismiss, motions for summary judgment, motions for involuntary dismissal under Rule 41(b), motions to strike an affirmative defense, and motions for judgment pursuant to a settlement") (quoting 15 Charles Alan Wright *et al., Federal Practice & Procedure* § 3866 (3d ed. 2010))); *In re Temporomandibular Joint (TMJ) Implants Prods. Liab. Litig.*, 113 F.3d 1484, 1488 (8th Cir. 1997) (holding that "transferee court in federal multidistrict proceedings has the authority to enter dispositive orders terminating cases consolidated under 28 U.S.C. § 1407").

(4th ed. 2004) ("[I]t *may* be appropriate" for MDL court to address general causation and leave specific causation post-remand.)).

MDL courts have repeatedly recognized the need for devices such as *Lone Pine*[14] and Show Cause Orders to effectively manage an MDL and to grant summary judgment against plaintiffs who could not meet their evidentiary burden on specific causation. Many courts have used the former device to require plaintiffs to provide evidence at the outset of a case and face potential dismissal in light of what is (or is not) provided. *See, e.g., In re Digitek Prod. Liab. Litig.*, 264 F.R.D. 249, 255-56 (S.D. W. Va. 2010) (citing cases)); *see also Arias v. DynCorp*, 752 F.3d 1011, 1015-16 (D.C. Cir. 2014) (affirming decision of district court dismissing 163 plaintiffs "for failure to provide complete responses to the court-ordered questionnaires"). Likewise, MDL courts have chosen to determine individualized issues such as specific causation in light of a prior ruling. *See, e.g., In re Fosamax Prod. Liab. Litig.*, No. 06 MD 1789 (JFK), 2012 WL 5877418, at *1, 4-5 (S.D.N.Y. Nov. 20, 2012) (entering *Lone Pine* order requiring certain plaintiffs to produce expert reports regarding specific causation or face dismissal

[14] "*Lone Pine* orders, which derive their name from *Lore v. Lone Pine Corp.*, 1986 WL 637507 ([N.J. Super. Ct.] Nov. 18, 1986), are pre-discovery orders designed to handle the complex issues and potential burdens on defendants and the court in mass tort litigation by requiring plaintiffs to produce some evidence to support a credible claim." *Steering Committee v. Exxon Mobil Corp.*, 461 F.3d 598, 604 n.2 (5th Cir. 2006)).

and rejecting plaintiffs' argument that "Court has fulfilled its mission in this MDL" and cases should be remanded); *see also In re Allstate Ins. Co. Fair Labor Standards Act Litig.*, MDL No. 1541, No. 2:03-md-1541, 2009 WL 3011042, at *1 (D. Ariz. Sept.16, 2009) ("[I]n this MDL action . . . summary judgment would be granted in the defendants' favor as to all claims of any Continuing Plaintiff who did not show cause in writing . . . explaining why the Court's reasoning in the summary judgment order . . . which the Court entered in the . . . member case, should not be applied to him or her.").

Here, the MDL court's decision that it was "familiar with the science and issues present and can dispose of the issues far more quickly and efficiently than dozens of courts spread across the country" was perfectly proper. *In re Lipitor (Atorvastatin Calcium) Mktg., Sales Practices & Prod. Liab. Litig.*, --- F. Supp. 3d ----, 2017 WL 83509, at *15 (D.S.C. Jan. 3, 2017); *see In re Fosamax*, 2012 WL 5877418, at *2 ("The parties—and the Court—are intimately familiar with the discovery in this MDL."). In issuing its show cause order, the MDL court focused on an issue common to all of the cases before it, whether any plaintiff could provide a reliable basis for a specific causation opinion and distinguish her case from the specific causation opinion offered by Dr. Murphy, which was based solely on a temporal relationship between Lipitor and diabetes. The MDL court properly held that such methodology could not pass muster under *Daubert*, *see*,

e.g., *Schmaltz v. Norfolk & W. Ry. Co.*, 878 F. Supp. 1119, 1122 (N.D. Ill. 1995) ("[I]t is well settled that a causation opinion based solely on a temporal relationship is not derived from the scientific method and is therefore insufficient to satisfy the requirements of [Rule] 702."); *see also Guinn v. AstraZeneca Pharm. LP*, 602 F.3d 1245, 1255 (11th Cir. 2010) ("The fact that exposure to [a substance] may be a risk factor for [a disease] does not make it an actual cause simply because [the disease] developed."), and it would be contrary to the very purpose of the MDL to secure the efficient management of mass litigation to hold that an MDL court cannot apply its generally-applicable ruling to all cases before it:

> The goal of the multidistrict litigation process is to "promote the just and efficient conduct" of "civil actions involving one or more common questions of fact" that are pending in different districts. If realized, hundreds or—as here, thousands—of cases, coordinated, will proceed toward resolution on the merits with less burden and expense overall than were each litigated through pretrial individually.

In re Phenylpropanolamine (PPA) Prod. Liab. Litig., 460 F.3d 1217, 1229 (9th Cir. 2006) (quoting 28 U.S.C. § 1407(a)); *In re Guidant Corp. Implantable Defibrillators Prod. Liab. Litig.*, 496 F.3d 863, 867 (8th Cir. 2007) ("Congress established MDL protocols to encourage efficiency.").

The MDL court gave plaintiffs repeated opportunities to give notice as to whether they could offer specific causation evidence that would enable them to

survive summary judgment. *See* 2017 WL 83509, at *2-6. In light of the plaintiffs' failure to respond to the show cause orders with sufficient evidence, the MDL court properly granted summary judgment on all of plaintiffs' claims.

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 rulings of the MDL court.

Respectfully submitted,

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CERTIFICATION OF COMPLIANCE

I, Eric G. Lasker, hereby certify:

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s/ Eric G. Lasker
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I hereby certify that I have on this 7th day of July 2017, 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.

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UNITED STATES COURT OF APPEALS FOR THE FOURTH CIRCUIT

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I certify that on July 7, 2017 the foregoing document was served on all parties or their counsel of record through the CM/ECF system if they are registered users or, if they are not, by serving a true and correct copy at the addresses listed below:

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