REDACTED VERSION

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

UNITED STATES COURT OF APPEALS
FOR THE FOURTH CIRCUIT

In Re: LIPITOR (ATORVASTATIN CALCIUM) MARKETING, SALES PRACTICES AND PRODUCTS LIABILITY LITIGATION (NO II) MDL 2502

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

PAGE-PROOF OPENING BRIEF FOR PLAINTIFFS-APPELLANTS

H. Blair Hahn
Christiaan A. Marcum
RICHARDSON, PATRICK, WESTBROOK & BRICKMAN, LLC
1037 Chuck Dawley Blvd.
Mt. Pleasant, SC 29464
Telephone: (843) 727-6500
Facsimile: (843) 727-6642
bhahn@rpwb.com
cmarcum@rpwb.com

Derek T. Ho
Silvija A. Strikis
Hilary P. Gerzhoy
KELLOGG, HANSEN, TODD, FIGEL & FREDERICK, P.L.L.C.
1615 M Street, N.W., Suite 400
Washington, D.C. 20036
Telephone: (202) 326-7900
Facsimile: (202) 326-7999
dho@kellogghansen.com
sstrikis@kellogghansen.com
hgerzhoy@kellogghansen.com

Counsel for Plaintiffs-Appellants

April 21, 2017

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.

Corporate defendants in a criminal or post-conviction case and corporate amici curiae are required to file disclosure statements.

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: Plaintiffs Appealing CMO 100 v. Pfizer, Inc. et al.

Pursuant to FRAP 26.1 and Local Rule 26.1,

Plaintiffs listed in Exhibit A to Doc. No. 16
(name of party/amicus)

who is Appellant, 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/ Derek T. Ho Date: April 21, 2017

Counsel for: Plaintiffs Appealing CMO 100

CERTIFICATE OF SERVICE

****

I certify that on April 21, 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/ Derek T. Ho
(signature)

April 21, 2017
(date)

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.

Corporate defendants in a criminal or post-conviction case and corporate amici curiae are required to file disclosure statements.

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. 17-1136 Caption: Juanita Hempstead v. Pfizer, Inc. et al.

Pursuant to FRAP 26.1 and Local Rule 26.1,

Juanita Hempstead
(name of party/amicus)

who is Appellant, 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/ Derek T. Ho Date: April 21, 2017

Counsel for: Juanita Hempstead

CERTIFICATE OF SERVICE

****

I certify that on April 21, 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/ Derek T. Ho (signature) April 21, 2017 (date)

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.

Corporate defendants in a criminal or post-conviction case and corporate amici curiae are required to file disclosure statements.

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. 17-1137 Caption: Plaintiffs Appealing CMO 99 v. Pfizer, Inc. et al.

Pursuant to FRAP 26.1 and Local Rule 26.1,

Plaintiffs listed in Exhibit A to Doc. No. 16
(name of party/amicus)

who is Appellant, 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/ Derek T. Ho Date: April 21, 2017

Counsel for: Plaintiffs Appealing CMO 99

CERTIFICATE OF SERVICE

****

I certify that on April 21, 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/ Derek T. Ho (signature) April 21, 2017 (date)

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.

Corporate defendants in a criminal or post-conviction case and corporate amici curiae are required to file disclosure statements.

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. 17-1189 Caption: Plaintiffs Appealing CMO 109 v. Pfizer, Inc. et al.

Pursuant to FRAP 26.1 and Local Rule 26.1,

Plaintiffs listed in Exhibit A to Doc. No. 21
(name of party/amicus)

who is Appellant, 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/ Derek T. Ho Date: April 21, 2017

Counsel for: Plaintiffs Appealing CMO 109

CERTIFICATE OF SERVICE

****

I certify that on April 21, 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/ Derek T. Ho (signature) April 21, 2017 (date)

TABLE OF CONTENTS

TABLE OF AUTHORITIES

Page

CASES

STATUTES AND RULES

OTHER AUTHORITIES

JURISDICTIONAL STATEMENT

The district court had jurisdiction under 28 U.S.C. § 1332 and 28 U.S.C. § 1407(a). This Court has jurisdiction under 28 U.S.C. § 1291. Pursuant to the court's grant of summary judgment, final judgment was entered for Defendants on December 29, 2016 (Case Management Order ("CMO") 97, *Hempstead*), January 3, 2017 (CMOs 99 and 100), and February 3, 2017 (CMO 109). JA__, __, __, __(Dkts. 1791, 1796, 1797, 1844). Plaintiffs filed timely notices of appeal on January 26, 2017 (CMO 100), January 27, 2017 (CMOs 99 and 97, *Hempstead*), and February 8, 2017 (CMO 109). JA__, __, __, __(Dkts. 1829, 1830, 1831, 1846).

STATEMENT OF THE ISSUES

This appeal involves 3,128 Plaintiffs from 35 states whose cases were transferred to the United States District Court for the District of South Carolina by the United States Judicial Panel on Multidistrict Litigation ("JPML"). JA__-__(Docket Sheet). Plaintiffs contended that Pfizer failed to warn that its cholesterol drug Lipitor causes new-onset diabetes. The district court (Gergel, J.) excluded the opinions of Plaintiffs' experts on general causation (the capacity of Lipitor to cause diabetes) in all cases involving Lipitor doses less than 80 mg, and excluded Plaintiffs' expert on specific causation (whether Lipitor caused a particular plaintiff's diabetes) in the *Hempstead* bellwether case. The court

thereafter granted summary judgment to Defendants in all 3,128 cases. *See* JA__(Dkt. 1845). The issues raised by this appeal are:

1. Whether the district court erred in excluding the expert opinions of Nicholas P. Jewell, Ph.D., a world-renowned biostatistician, whose analysis of unpublished data from Pfizer's "ASCOT" study showed that Lipitor is associated with a statistically significant increased risk of diabetes even when taken at its lowest administered dose (10 mg) and when controlled for other independent predictors of diabetes.

2. Whether the district court committed reversible error in excluding Dr. Jewell's separate analysis of Pfizer's New Drug Application ("NDA") data based on a mischaracterization of Dr. Jewell's opinions.

3. Whether the district court erred in excluding the general-causation expert opinions of Sonal Singh, M.D., M.P.H., an Associate Professor of Medicine specializing in pharmaco-epidemiology, to the extent they were not supported by studies finding an association between Lipitor and diabetes at each available dose of the drug that reached statistical significance at a 95% confidence level.

4. Whether the district court committed legal error by granting summary judgment to Defendants on general causation notwithstanding the admissions by Pfizer's own scientist that Lipitor "increases the risk of developing diabetes" at both 10 mg and 80 mg doses.

5. Whether the district court erred in excluding the specific causation opinion of Elizabeth Murphy, M.D., D.Phil., in the *Hempstead* bellwether case, which was based on a rigorous differential diagnosis.

6. Whether the MDL statute, 28 U.S.C. § 1407, authorized the transferee court to adjudicate the issue of specific causation for non-bellwether cases given the case-specific nature of the issue and the existence of material variations in applicable state substantive law.

INTRODUCTION

The scientific community widely recognizes that statin drugs such as Lipitor (atorvastatin calcium) increase the risk of new-onset diabetes, a severe and debilitating disease that can cause serious and deadly complications including stroke, blindness, and amputations. Multiple peer-reviewed studies support that causal link. Indeed, in 2012, the FDA required Pfizer, Lipitor's manufacturer, to include a warning on the drug's label that Lipitor increases the risk of hyperglycemia; the FDA website also warns that Lipitor increases the risk of diabetes. But for many years before that, Pfizer failed to warn patients and healthcare professionals, even though it knew or should have known of these potentially devastating consequences from its own internal data.

Appellants are more than 3,000 women from across the country who took Lipitor and claim that they developed diabetes as a result. Their cases were

transferred to the court below (Gergel, J.) for the limited purpose of consolidated pre-trial proceedings pursuant to the MDL statute. But the court below far exceeded its proper role and instead took it upon itself to be both judge and jury in rendering a nationwide holding that Pfizer is immune from liability for manufacturing and selling a dangerous and defective drug.

The district court's conclusion that there is no evidence that Lipitor can *ever* cause diabetes at doses less than 80 mg exemplifies the court's failure to respect its limited gatekeeping role. Rule 702 and *Daubert* guard against junk science, but the testimony of Plaintiffs' general causation experts – Nicholas P. Jewell, Ph.D., a professor at the University of California (Berkeley) and one of the nation's foremost scholars in biostatistics, and Sonal Singh, M.D., a professor of medicine at the University of Massachusetts who studies pharmaco-epidemiology – is as far from junk science as one can imagine. The court reached its conclusion only because it repeatedly mischaracterized the experts' testimony and fundamentally misunderstood basic statistical principles by, among other things, erroneously adopting statistical significance as a talismanic criteria for relevance and reliability. Indeed, not only is there substantial epidemiological support for general causation at all doses, but Pfizer's own senior scientist and Vice President, Dr. David DeMicco, admitted in an internal document that "[a]torvastatin increases the risk of developing diabetes" and "[t]he risks of 10 and 80 mg are similar." JA__(CMO

100, at 45 (Dkt. 1797)) (quoting JA__(Dkt. 1586-2)). Especially given that admission, the exclusion of Plaintiffs' expert testimony and the grant of summary judgment were manifestly erroneous.

The court also exceeded its gatekeeping function in excluding Plaintiffs' specific causation expert in the *Hempstead* bellwether case – one of only two where case-specific expert discovery was conducted. Ms. Hempstead's expert, Dr. Elizabeth J. Murphy, is Chief of the Endocrinology and Metabolism Division and Director of the Diabetes Center for High Risk Populations at San Francisco General Hospital and a Professor of Clinical Medicine at the University of California, San Francisco, one of the nation's leading medical schools. Using a "differential diagnosis" technique that is widely recognized as reliable, and after reviewing the relevant literature and Ms. Hempstead's medical history, Dr. Murphy opined that Ms. Hempstead's Lipitor use was a substantial contributing factor in her diabetes.

The district court believed that Dr. Murphy did not do enough to rule out the possibility that other risk factors accounted for Ms. Hempstead's diabetes. But numerous circuits have held that where an expert employs a well-accepted methodology like differential diagnosis, as Dr. Murphy did here, criticisms of the expert's application of that methodology to the facts should be ventilated through cross-examination and resolved by the jury. Outright exclusion is properly

reserved for those unusual cases where there can be no reasonable disagreement that the expert's analysis is fatally flawed. Dr. Murphy's careful and rigorous analysis in the exercise of her indisputably qualified medical judgment does not remotely approach that extreme. Indeed, it was the district court's ruling that is extreme – as it sets the bar for a reliable differential diagnosis so high that it will make it functionally impossible for any plaintiff to show specific causation where other risk factors are present.

Finally, the district court violated non-bellwether Plaintiffs' procedural rights in granting summary judgment against them on specific causation. Under the MDL statute, the court below was authorized to conduct consolidated pretrial proceedings on common questions of fact, but specific causation is an individualized question not appropriately consolidated. Moreover, none of the non-bellwether plaintiffs had an opportunity to conduct case-specific discovery on specific causation. In its zeal to dispose of all Plaintiffs' claims in one fell swoop, the court below erroneously arrogated to itself the power to adjudicate even case-specific issues and improperly deprived Plaintiffs of the right to individualized proceedings. On remand, the proper course is for specific causation to be adjudicated by the transferor court after full discovery in each case.

The decision below should be reversed and remanded for further proceedings.

STATEMENT OF THE CASE

I. Factual Background

A. Lipitor and Diabetes

Lipitor (atorvastatin calcium), manufactured by Pfizer, is a "statin" drug approved by the Food and Drug Administration ("FDA") to lower cholesterol and prevent cardiovascular injuries. Lipitor is prescribed in four different therapeutic doses in the U.S.: 10, 20, 40, and 80 mg.

Diabetes is a group of metabolic diseases characterized by hyperglycemia (elevated blood glucose). Diabetes affects the way the body metabolizes sugar, and results from progressive changes in the body's resistance to, or production of, insulin.[1] Diabetes affects approximately 21 million Americans, and accounts for an estimated $250 billion in medical costs. JA__, __(Nat'l Diabetes Statistic Rep. 1, 8 (Dkt. 972-11)). Type II diabetes ("T2DM"), also referred to as new-onset diabetes (hereinafter referred to as "diabetes"), accounts for 95% of U.S. diabetes cases.[2] Under current American Diabetes Association ("ADA") standards, patients have diabetes if they meet any of three diagnostic criteria: (1) two fasting blood-glucose levels above 125 milligrams per deciliter ("mg/dL"), (2) glycated

[1] JA__-__(ADA, *Diagnosis & Classification of Diabetes Mellitus*, 37 Diabetes Care S81, S81-82 (fig. 1) (2014) (Dkt. 972-16)).

[2] Type 2 Diabetes is distinct from Type 1 Diabetes, which is not implicated in this case.

hemoglobin ("HbA1c") greater than 6.5%,[3] or (3) an oral glucose tolerance test with plasma glucose above 200 mg/dL after two hours.

The scientific community widely accepts that Lipitor causes diabetes. This past September, even leading pro-statin scientists affirmed that statins including Lipitor "have been reliably shown" to cause diabetes.[4] The label for all available doses of Lipitor currently contains warnings about the risk of hyperglycemia and describes diabetes as an adverse event; the FDA website also warns that "[p]eople being treated with statins may have an increased risk of raised blood sugar levels and the development of Type 2 diabetes."[5] The ADA likewise warns that "[t]here is an increased risk of [new-onset] diabetes with statin use."[6] The American Heart Association Task Force on Practice Guidelines states that "statin therapy is

[3] HbA1c measures a person's three-month average blood-glucose level.

[4] Rory Collins et al., *Interpretation of the Evidence of the Efficacy and Safety of Statin Therapy*, 388 Lancet 2532, 2546 (2016) ("Collins (2016)").

[5] JA__(2012 Lipitor Prescribing Information § 5.3 (Dkt. 1586-9)); JA__(2015 Lipitor Prescribing Information § 6.1 (Dkt. 972-5)); FDA Consumer Update, *FDA Expands Advice on Statin Risks* (Jan. 2014), https://wayback.archive-it.org/7993/20170111225802/http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm293330.htm ("FDA Consumer Update").

[6] JA__(*Standards of Medical Care in Diabetes—2015*, 38 Diabetes Care S1, S54 (2015) (Dkt. 972-24)).

associated with an excess risk for incident diabetes"[7] and that "[i]ndividuals receiving statin therapy should be evaluated for new-onset diabetes."[8]

B. The Scientific Framework for Determining Causation

Scientists have adopted a two-step framework for determining general causation – *i.e.*, whether exposure to a drug (here, Lipitor) can cause a particular disease (here, diabetes). The first step is to determine whether exposure to a particular drug is statistically associated with higher incidence of disease. Fed. Judicial Ctr., *Reference Manual on Scientific Evidence* 552 (3d ed. 2011) ("RMSE"). The strength of an association is generally expressed as a relative risk ("RR"), which also can be approximated as an odds ratio ("OR") or hazard ratio ("HR"). *Id*. at 566-69. Relative risk expresses the ratio of the risk of disease among people exposed to a substance divided by the risk of disease among those not exposed. The more the relative risk exceeds 1.0, the stronger the association.

Randomized, placebo-controlled studies are the "gold standard" of epidemiological evidence. Such studies may not always be available, however, and scientists therefore often rely on observational studies, which look at data to

---

[7] Neil J. Stone et al., *A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults*, 63 J. Am. Coll. Cardiol. 2889, 2927 (2014), http://www.onlinejacc.org/content/63/25_Part_B/2889/T3.

[8] *Id.* at 2908.

determine if an association exists between a drug and disease. *See id.* at 217-18. Because both types of studies estimate the relative risk based on a sample rather than the entire population, statisticians also calculate a "confidence interval" ("CI") to indicate the estimate's precision. Scientists conventionally determine the confidence interval using either a 90% or 95% confidence level. *See* Kenneth J. Rothman et al., *Modern Epidemiology* 157 (3d ed. 2008). A 95% confidence level means that if the study were replicated many times, "the confidence interval would include within it the correct value of the measure 95% of the time." Kenneth J. Rothman et al., *Epidemiology: An Introduction* 150 (2d ed. 2012). For example, a relative risk of 1.5 with a 95% confidence interval of 1.25-1.75 (conventionally reported as (RR = 1.50; 95% CI 1.25-1.75)) means that the best estimate is that the drug increases the risk of the disease by 50% and that there is a very high probability that the "true" relative risk is between a 25% and 75% increase. Where the lower bound of the confidence interval is greater than 1.0, as in the foregoing example, the relative risk is considered "statistically significant." As explained further below (at pp. 52-57), however, scientists do not view statistical significance as a "magic" criterion when analyzing the results of studies. An RR greater than 1.0 supports a positive association even if it is non-statistically significant. The absence of statistical significance does not imply that an association is not causal.

Once an association is established, the second step is to apply the widely accepted Bradford-Hill criteria to determine whether the association is causal. *See* RMSE at 598-600. These factors are: (1) strength of the association; (2) replication of the findings; (3) specificity of the association; (4) temporal relationship; (5) biological gradient (dose-response relationship); (6) biological plausibility; (7) coherence, (8) experimental evidence; and (9) analogy. *See* JA__-__(Sir Austin Bradford Hill, *The Environment and Disease: Association or Causation?*, 58 Proc. Royal Soc'y Med. 295, 295-300 (1965) (Dkt. 972-32)); *see also* RMSE at 600. The Bradford-Hill criteria require evaluation of *all* the evidence, with no one factor being dispositive. *See, e.g.*, Restatement (Third) of Torts § 28 cmt. c(3) (2010); Douglas L. Weed, *Epidemiologic Evidence and Causal Inference*, 14 Hematology/Oncology Clinics N. Am. 797, 802 (2000) ("Weed"). Whether an established association is causal is a matter of scientific judgment, and scientists appropriately employing this method "may come to different judgments" about whether a causal inference is appropriate. *Milward v. Acuity Specialty Prods. Grp.*, 639 F.3d 11, 18 (1st Cir. 2011). When a randomized controlled trial shows positive association, there is generally little doubt that there is a causal relationship. *See* David H. Kaye & David A. Freedman, *Reference Guide on Statistics* 218, 220, *in* RMSE (stating that "controlled experiments are ideally suited for demonstrating causation").

C. Evidence of Association Between Lipitor and Diabetes

Since Pfizer started selling Lipitor in 1996, numerous studies have found that statins generally, and Lipitor specifically, are associated with an increased risk of elevations in blood-glucose levels and diabetes.

In 1996, Pfizer's Integrated Summary of Safety ("ISS"), associated with its new drug application ("NDA") for Lipitor, showed a three-fold increase in the risk of blood-glucose abnormalities from taking Lipitor as compared to placebo. Among individuals identified by Pfizer as suffering clinically meaningful elevations in glucose levels, the average increase was approximately 30.8 mg/dL, an amount sufficient to raise blood-glucose levels from normal (less than 100 mg/dL) to diabetic (more than 125 mg/dL) during the course of statin therapy. Pfizer thus knew as early as 1996 that Lipitor was potentially associated with increased diabetes risk.

In 2003, Pfizer published the Anglo-Scandinavian Cardiac Outcomes Trial ("ASCOT"), a randomized, placebo-controlled clinical trial that primarily studied the effect of blood-pressure-lowering medicines.[9] The study's "lipid-lowering arm" ("LLA") tested Lipitor's efficacy in prevention of cardiovascular events in

---

[9] JA__(Peter S. Sever et al., *Prevention of Coronary and Stroke Events with Atorvastatin in Hypertensive Patients who Have Average or Lower-than-Average Cholesterol Concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial – Lipid Lowering Arm (ASCOT-LLA): A Multicentre Randomised Controlled Trial*, 361 Lancet 1149 (2003) (Dkt. 972-26)).

patients without coronary heart disease. Patients were randomly assigned to receive either a 10 mg dose of Lipitor or placebo. Diabetes was an "endpoint" of the ASCOT-LLA trial, meaning that the study collected data on diabetes and was designed to assess whether Lipitor was associated with a higher rate of diabetes. The ASCOT-LLA results published in the *Lancet* reported a positive association between Lipitor and diabetes, though the result was not statistically significant, HR = 1.15; 95% CI: 0.91-1.44. JA__(tbl. 3).

In June 2003, after extensive discussions with Japanese regulators, Pfizer updated its Japanese Lipitor label to warn patients that "[h]yper-glycemia and diabetes [mellitus] may occur." *See* JA__-__(Japanese Lipitor Label (Dkt. 1586-5)).[10] The Japanese label made no distinctions regarding dosage, and at the time, only 5 and 10 mg dosages of Lipitor were marketed in Japan. *See id.*; *see also* JA__(LePetri Dep. 192:17-22 (Dkt. 1586-6)).

In the 2005 Treating to New Targets ("TNT") trial, patients were given either 80 mg or 10 mg of Lipitor. The percentage of patients who developed diabetes was 9.24% for the 80 mg group, compared to 8.11% for the 10 mg group, HR = 1.10; 95% CI: 0.94-1.29. *See* JA__(John C. LaRosa, *Intensive Lipid Lowering with Atorvastatin in Patients with Stable Coronary Disease*, 352 New Eng. J. Med. 1425 (2005) ("LaRosa") (Dkt. 972-51)).

[10] "Diabetes mellitus" refers to Type II diabetes.

In 2006, the Stroke Prevention through Aggressive Cholesterol Lowering ("SPARCL") trial tested whether 80 mg Lipitor prevented stroke in patients who already had a stroke. While diabetes was not an endpoint in SPARCL, there was an increased risk of diabetes reported as an adverse event, a fact not disclosed in the published article. *See* JA__(SPARCL Investigators, *High-Dose Atorvastatin after Stroke or Transient Ischemic Attack*, 355 New Eng. J. Med. 549 (2006) (Dkt. 972-28)). Later, in 2007, Pfizer reported the difference in diabetes adverse event reports to the FDA, which led to Pfizer adding language to Lipitor's label in 2009 that "[d]iabetes was reported as an adverse reaction in 144 subjects (6.1%) in the [Lipitor] group and 89 subjects (3.8%) in the placebo group." Lipitor Prescribing Information § 6.1 (2009), https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/020702s056lbl.pdf.

Around the time of that 2009 label change, several Pfizer employees conducted a series of subsequent analyses of the SPARCL data, as well as the data from TNT and a third study known as "IDEAL,"[11] to determine whether the increased risk of diabetes associated with Lipitor was explained by independent diabetes predictors, such as baseline fasting blood glucose. In September 2009, Pfizer sent the results of that re-analysis to David DeMicco, D.Pharm., a Pfizer

[11] JA__-__(Terje R. Pedersen et al., *High-Dose Atorvastatin vs Usual-Dose Simvastatin for Secondary Prevention After Myocardial Infarction – The IDEAL Study*, 294 JAMA 2437 (2005) (Dkt. 972-27)).

Vice President, and David Waters, M.D., also a Pfizer consultant. After reviewing the data, Dr. Waters stated, [redacted] JA__(Dkt. 1586-2), and "I would draw these conclusions based on this data: (1) Atorvastatin increases the risk of developing diabetes. (2) The risks of 10 and 80 mg are similar. (3) Fasting blood sugar and features of the metabolic syndrome are strong predictors of the development of diabetes in both populations." Dr. DeMicco responded, "I concur with your assessment below," JA__(CMO 100, at 45), and added, [redacted] JA__(Dkt. 1586-2).

DeMicco and Waters eventually published a 2011 article based on Pfizer's re-analysis of SPARCL, TNT, and IDEAL[12] that reported that 80 mg of Lipitor was associated with a statistically significant increased risk of diabetes in SPARCL, HR = 1.37; 95% CI: 1.08-1.75, when adjusted for other independent predictors of diabetes. However, the authors used a definition of diabetes that was more restrictive than the ADA's. JA__.

[12] JA__-__(David D. Waters et al., *Predictors of New-Onset Diabetes in Patients Treated With Atorvastatin*, 57 J. Am. Coll. Cardiol. 1535 (2011) ("Waters (2011)") (Dkt. 972-29)).

In 2010, Koh et al.[13] published a randomized, placebo-controlled study showing that use of 20-40 mg of Lipitor for two months resulted in a statistically significant increase in (1) insulin resistance; (2) fasting insulin levels; and (3) HbA1C levels. The authors also concluded that use of 10 mg of Lipitor led to a statistically significant increase in HbA1C levels, which "strongly suggest[s] that atorvastatin causes glucose intolerance that is due, in part, to decreased insulin sensitivity." JA__(55 J. Am. Coll. Cardiol. at 1213).

Another 2010 article, Sattar et al.[14] reported the results of a meta-analysis that found that statin use was associated with a statistically significant 9% increased risk for diabetes, OR = 1.09; 95% CI: 1.02-1.17. JA__(375 Lancet at 735).

In 2012, Culver et al. published an observational study which concluded that Lipitor use was associated with a statistically significant 61% increased risk of

[13] JA__(Kwang Kon Koh et al., *Atorvastatin Causes Insulin Resistance and Increases Ambient Glycemia in Hypercholesterolemic Patients*, 55 J. Am. Coll. Cardiol. 1209 (2010) (Dkt. 1383-31)).

[14] JA__(Naveed Sattar et al., *Statins and Risk of Incident Diabetes: A Collaborative Meta-Analysis of Randomised Statin Trials*, 375 Lancet 735 (2010) (Dkt. 1053-8)).

developing diabetes in women, HR = 1.61; 95% CI: 1.26-2.06.[15] The study did not differentiate by dose.

In 2012, FDA announced a change to the physician-directed prescribing information for Lipitor and multiple other statins to state in the warning section that "[i]ncreases in HbA1c and fasting serum glucose levels" – biological markers used to diagnose diabetes – "have been reported with [statins], including LIPITOR." JA__(2012 Lipitor Prescribing Information § 5.3).

The following year, Chen et al. published a case-control study that analyzed the effect of "low," "moderate," and "high" doses of Lipitor.[16] The study identified an increased risk of diabetes at all three levels in two out of three age groups studied. The authors concluded that "[s]tatin-exposure was statistically significantly associated with increased new-onset diabetes risks." JA__(PloS One at 4).

In 2015, Cederberg et al. published a study that found that 20-40 mg of Lipitor is associated with a statistically significant increase in the risk of diabetes,

---

[15] JA__(Annie L. Culver et al., *Statin Use and Risk of Diabetes Mellitus in Postmenopausal Women in the Women's Health Initiative*, 172 Arch. Intern. Med. 144 (2012) (Dkt. 1053-4)).

[16] JA__(Chih-Wei Chen et al., *Differential Impact of Statin on New-Onset Diabetes in Different Age Groups: A Population Based Case-Control Study in Women from an Asian Country*, 8 PLoS One 1 (2013) (Dkt. 1159-21)).

HR = 1.21; 95% CI: 1.04-1.40.[17] The authors also found increased insulin resistance and impaired beta-cell function at 10, 20, and 40 mg of Lipitor.

In September 2016, a group of statin advocates published a peer-reviewed article agreeing that statins, including Lipitor, "have been reliably shown" to cause diabetes.[18]

II. Plaintiffs' General Causation Experts

A. Expert Opinion of Nicholas Jewell, Ph.D.

Dr. Nicholas Jewell has been a professor of biostatistics – a field that covers the statistical design and analysis of studies that investigate risk factors for disease – for nearly four decades, first at Princeton University and then, for the last 33 years, at the University of California (Berkeley). He obtained his Ph.D. in Mathematics from the University of Edinburgh. He authored a widely used textbook, *Statistics for Epidemiology*, and 160 peer-reviewed articles on biostatistics. JA__(Jewell Rep. ¶ 3 (Dkt. 972-10)). He is also the editor of the *Journal of the American Statistical Association*, the country's preeminent peer-reviewed statistics journal. *See id.* The district court did not dispute Dr. Jewell's qualifications. JA__(CMO 54, at 1 (Dkt. 1258)).

---

[17] JA__(Henna Cederberg et al., *Increased Risk of Diabetes with Statin Treatment is Associated with Impaired Insulin Sensitivity and Insulin Secretion: A 6 Year Follow-up Study of the METSIM Cohort*, 58 Diabetologia 1109 (2015) (Dkt. 1159-1)).

[18] Collins (2016), at 2546.

As relevant to this appeal, Dr. Jewell conducted an analysis of the original data used in the ASCOT-LLA trial, which reported on 10 mg of Lipitor and diabetes. *See supra* p. 12. As Dr. Jewell explained, he went back to the original data because of a number of anomalies in the published ASCOT study. The published results reported that 288 patients who took Lipitor developed diabetes, while the underlying data showed that 344 patients met the World Health Organization's ("WHO") accepted criteria for diabetes. The ASCOT study did not disclose what criteria were used for determining whether a patient met the diabetes endpoint. Moreover, internal study documents contained conflicting descriptions of which criteria the investigators used. Some of these criteria were more restrictive than those of the ADA and the WHO. In addition to whichever criteria the study investigators used, they also employed an "adjudication" process in which an "Endpoints Committee" used their own criteria – which were not documented or disclosed in the study – to ultimately decide which patients would be treated as having met the diabetes endpoint.

Moreover, as Pfizer itself demonstrated in a 2010 analysis submitted to the United Kingdom's Medicines & Healthcare products Regulatory Agency ("MHRA"), the *Lancet* article contained errors. Patients with pre-existing diabetes or blood-glucose values in the range diagnostic of diabetes were erroneously included even though the study's "Endpoint Manual" stated that such patients were

not to be considered new-onset diabetics. Furthermore, and critically, the study's protocol called for additional analysis of all endpoints that adjusted for important variables. That analysis was not included in the published article.

For all these reasons, Dr. Jewell re-analyzed the original data from the ASCOT-LLA trial using the accepted WHO criteria based on patient fasting glucose levels as provided by Pfizer during discovery. Dr. Jewell performed precisely the analysis that the ASCOT study itself called for but neither Pfizer nor the ASCOT authors ever published. And he used standard statistical methods applied by Pfizer's own investigators and Pfizer's own expert. *See infra* p. 41. [redacted] after adjusting for potential confounding factors using a "multivariate" analysis. JA__-__(Jewell Rebuttal Rep. ¶¶ 32-34 (Dkt. 972-34)) [redacted] It is uncontested that Dr. Jewell's adjustments followed the method "pre-specified in the ASCOT protocol and the statistical analysis plan." JA__(CMO 54, at 31 n.33).

In addition to his ASCOT analysis, Dr. Jewell also analyzed Pfizer's NDA data, which reported on the incidence of clinically meaningful blood-glucose elevations in patients taking Lipitor versus patients taking a placebo during the NDA trials. Using standard, well-accepted statistical methods, Dr. Jewell found

that Lipitor is associated with a more than three-fold statistically significant risk of a clinically meaningful blood-glucose increase. JA__(Jewell Rep. ¶¶ 13-22).

B. Expert Opinion of Sonal Singh, M.D., M.P.H.

Dr. Singh is an Associate Professor of Medicine at University of Massachusetts School of Medicine. Dr. Singh researches the adverse effects of pharmacologic therapies used for chronic disease such as diabetes. Dr. Singh teaches clinical epidemiology, epidemiologic research methods, and pharmaco-epidemiology, and he previously served as the Associate Director for the Center for Drug Safety and Effectiveness at Johns Hopkins University. Dr. Singh published on statins and diabetes prior to his involvement in this litigation. JA__(Singh Rep. Ex. A at 4 (Dkt. 972-6)). The district court took no issue with Dr. Singh's qualifications. JA__-__(CMO 68, at 13-24 (Dkt. 1469)).

To evaluate whether Lipitor can cause diabetes, Dr. Singh conducted a systematic review of the epidemiological studies and meta-analyses that reported on the association between Lipitor and diabetes. JA__(Singh Rep. 6). Dr. Singh concluded that "[m]ost agree that there is an association between the use of statins and diabetes." JA__(*Id*. at 30). Dr. Singh also performed his own meta-analysis, which showed that statins generally, and Lipitor specifically, increase the risk of developing diabetes in a statistically significant manner. JA__-__, __(*Id*. at 8-10, 15).

After finding that "statins are associated with diabetes," Dr. Singh considered the Bradford-Hill factors to determine whether the weight of the evidence supports a causal link between Lipitor and diabetes. JA__(*Id*. at 32). Dr. Singh explained that (1) the association is strong, noting that his meta-analysis "shows a more than 104% increased risk of diabetes associated with atorvastatin among women" (*strength*), JA__(*id*. at 34); (2) the "direction and strength of association" is "generally consistent" among studies (*consistency*), *id*.; (3) statins are "an additional risk factor and cause" of diabetes (*specificity*), JA__-__(*id*. at 35-36); (4) in each of the studies, exposure preceded the development of diabetes (*temporality*), JA__(*id*. at 36); (5) a dose-response relationship was reported in numerous studies (*biological gradient*), JA__-__(*id*. at 36-37); (6) several studies show evidence of biological plausibility (*biological plausibility*), JA__-__(*id*. at 37-38); (7) "[t]he cause and effect relationship between statins and diabetes is consistent with our knowledge of the natural history and biology of diabetes" (*coherence*), JA__(*id*. at 38); (8) "meta-analyses of randomized controlled trials show an increased risk of" diabetes with statin use (*experiment*), JA__(*id*.); and (9) "[s]everal other drugs such as thiazide diuretics . . . have been shown to increase the risk of new onset diabetes" (*analogy*), JA__(*id*. at 39). Dr. Singh then considered alternative hypotheses and limitations and concluded that Lipitor is "causally linked with type 2 diabetes." JA__-__(*Id*. at 39-41).

On October 22, 2015, the district court required Dr. Singh to perform a separate general causation analysis for each Lipitor dose. JA__-__(CMO 49, at 11-12 (Dkt. 1197)). In his supplemental report on December 6, 2015,[19] Dr. Singh reaffirmed his original opinion that Lipitor at all administered doses is "causally related to an increase in the risk of type 2 diabetes." JA__(*Id.* at 30).

As to 80 mg, Dr. Singh found that multiple studies – including one statistically significant study (SPARCL) – showed that Lipitor at 80 mg doses is associated with an increased risk of diabetes. JA__-__, __-__(Singh Supp. Rep. 26-27, 31-32).

Dr. Singh also opined that there is reliable evidence of association between 10 mg of Lipitor and diabetes based on (1) the ASCOT study; (2) his own comparison of the SPARCL and TNT studies; and (3) the blood-glucose elevations reported in Pfizer's Clinical Safety Updates. Dr. Singh opined that "[d]espite [ASCOT's] lack of statistical significance, the direction of effect [in the ASCOT study] is consistent with the increase in risk seen at the 80 mg dose, albeit of lower magnitude." JA__(Singh Supp. Rep. 27). Dr. Singh then conducted his own comparison of SPARCL (which reported a 37% increased risk for 80 mg) and TNT

[19] Dr. Singh's supplemental report was admissible even if Dr. Jewell's testimony was properly excluded because Dr. Singh's causation opinions did not rely on Dr. Jewell's. JA__(Singh Supp. Rep. 2 (Dkt. 1383-1)) (explaining that his opinions are "independent of Dr. Jewell's testimony"); *see also* JA__(Singh Supp. Dep. 418:5-12 (Dkt. 1383-5)) (same).

(which reported a 10% increased risk of 80 mg versus 10 mg). He explained that if the effect of 10 mg were actually similar to placebo, then TNT should have found the risk of 80 mg to be similar to what SPARCL found. He then conducted an indirect treatment comparison that found a statistically non-significant 25% increased risk of diabetes with 10 mg of Lipitor versus placebo, HR = 1.25; 95% CI: 0.93-1.66. JA__(*Id.* at 28). Dr. Singh found that the data from the Safety Updates that Pfizer submitted in 1999 and 2001 indicate that "the risk of developing a clinically meaningful glucose elevation with the 10 mg atorvastatin dose compared to placebo is significantly elevated." JA__(*Id*. at 20).

Dr. Singh explained that while no clinical trial has reported on the risk of diabetes associated with 20 mg and 40 mg of Lipitor, "[i]t is difficult to imagine how atorvastatin 10 mg and 80 mg can increase the risk of diabetes without similar risk seen with atorvastatin 20 and 40 mg."[20] Dr. Singh's 20-40 mg causation opinion is based on (1) Koh's finding that use of 20-40 mg of Lipitor for two months resulted in a substantial increase in insulin resistance, fasting insulin levels, and HbA1C levels; (2) Cederberg's finding that 20-40 mg of Lipitor increased the risk of diabetes in a statistically significant manner, HR = 1.37; 95% CI: 1.14-1.65; and (3) the 2001 Clinical Safety Update, which [redacted] at 20 and 40 mg of Lipitor. JA__(*Id.* at 26).

[20] JA__(Singh Supp. Rep. 33).

III. Procedural History

The MDL currently includes more than 3,000 women who claim Pfizer failed to warn healthcare professionals and patients of the risk of developing diabetes from taking Lipitor. JA__(Master Long Form Compl. (Dkt. 160)).

A. General Causation

All parties agreed to the pretrial consolidation of the question of general causation, which is common to all Plaintiffs. Plaintiffs submitted common general causation expert reports from Drs. Jewell and Singh, and Michael Quon, M.D., Ph.D., Barbara Roberts, M.D., and Edwin Gale, M.D.[21] JA__(CMO 29 (Dkt. 746)); JA__(CMO 34 (Dkt. 869)). These initial reports did not differentiate by dose, but rather evaluated the totality of the evidence that Lipitor causes diabetes.

On October 22, 2015, over Plaintiffs' objections, the district court excluded Dr. Singh's expert report for failing to demonstrate "that particular doses of Lipitor are capable of causing diabetes." JA__(CMO 49, at 11). The court permitted Dr. Singh to file a supplemental dose-specific report.

On November 20, 2015, the district court excluded Dr. Jewell's expert opinions regarding ASCOT and NDA under Rule 702. JA__(CMO 54). The court admitted his SPARCL analysis. *See id.*

[21] Plaintiffs have elected to appeal only the exclusion of Drs. Jewell and Singh.

Dr. Singh submitted his supplemental dose-specific report on December 6, 2015, but was not able to rely on Dr. Jewell's excluded re-analysis. On March 30, 2016, the Court excluded Dr. Singh's supplemental report in part. JA__(CMO 68). The district court held that before applying the Bradford-Hill factors, an expert must point to an association between Lipitor and diabetes "through studies with statistically significant results." JA__(*Id*. at 19). Because there are no studies reporting a statistically significant association between 10 mg of Lipitor and diabetes – and because the court had excluded Dr. Jewell's re-analysis of the ASCOT data that resulted in a statistically significant association at 10 mg – the court held that Dr. Singh's 10 mg opinion was "not based on sufficient facts and data." JA__-__(*Id*. at 22-23). The court also excluded Dr. Singh's opinion at 20-40 mg, because Dr. Singh testified that his 20-40 mg opinion was premised on his 10 mg opinion, which the court found unreliable. JA__(*Id.* at 24).

The district court permitted Dr. Singh's causation opinion at 80 mg because "studies have found a statistically significant increase in the risk of diabetes in patients taking 80 mg of Lipitor, satisfying the first step of the epidemiological method for determining causation." JA__(*Id.* at 15). The court also held that Dr. Singh's application of the Bradford-Hill factors in the second step of the analysis was reliable. JA__-__(*Id*. at 13-14). In particular, the court held that Dr. Singh appropriately "consider[ed] and weigh[ed] biological plausibility." JA__(*Id*. at

14); *see also* JA__-__(Singh Rep. 37-38) (describing each of the plausible biological mechanisms by which Lipitor is capable of causing diabetes). Scientists have routinely held that "the more the factor of interest is known to be key to the biologic mechanisms or pathways, the more likely the association is to be causal." Weed at 801; *see also* Restatement (Third) of Torts § 28 cmt. c(3).

After the exclusion of Drs. Jewell and Singh, Pfizer moved for summary judgment as to all Plaintiffs who had taken doses of Lipitor less than 80 mg. In opposition, Plaintiffs argued that they could prove general causation through Defendants' admissions. Those admissions included the admission by Dr. DeMicco, Pfizer's Senior Vice President, agreeing that SPARCL's results [redacted] JA__(Dkt. 1586-2), and that "(1) Atorvastatin increases the risk of developing diabetes. (2) The risks of 10 and 80 mg are similar. (3) Fasting blood sugar and features of the metabolic syndrome are strong predictors of the development of diabetes in both populations," JA__(CMO 100, at 45). In addition, Plaintiffs offered four additional Pfizer admissions that Lipitor either causes diabetes or increases blood-glucose levels: (1) Pfizer's Japanese label insert for Lipitor, stating that "[h]yper-glycemia and diabetes [mellitus] may occur" as an adverse reaction to Lipitor[22]; (2) Pfizer's U.S. Lipitor label, which

[22] JA__(Japanese Lipitor Label § 4.1).

states that elevated blood sugar levels "have been reported with . . . LIPITOR"[23]; (3) Pfizer's predecessor's (Parke-Davis) admission in its NDA that Lipitor increases blood-glucose levels[24]; and (4) Pfizer's admission on the official Lipitor website that "[i]ncreases in HbA1c and fasting serum glucose levels have been reported with . . . LIPITOR."[25] The district court nonetheless granted summary judgment.

B. Specific Causation

Unlike general causation, litigation over specific causation was not consolidated for pretrial proceedings. Rather, the district court adopted a bellwether trial process in which two cases would be selected out of a Discovery Pool and prepared for trial. *See* JA__-__(CMO 19, at 4-6 (Dkt. 539)). Certain fact discovery was to occur for all the Discovery Pool cases prior to the selection of the first two bellwether cases. *See* JA__(*Id.* at 4). Expert discovery, however, was required only for the "first two cases selected for trial." JA__(*Id.* at 5) (due April 24, 2015). *Daubert* motions on case-specific experts and dispositive motions likewise were limited to "case-specific experts and . . . dispositive motions for the first two cases selected for trial." JA__(*Id.* at 6) (due July 17, 2015).

---

[23] JA__(2012 Lipitor Prescribing Information § 5.3).

[24] *See* JA__(Lipitor, NDA 20-702 (Dkt. 1586-7)).

[25] JA__(2012 Lipitor Prescribing Information § 5.3).

Daniels v. Pfizer, No. 2:14-cv-01400, and *Hempstead v. Pfizer*, No. 2:14-cv-01879, were selected as the two bellwether cases. Only *Hempstead* is relevant to this appeal.[26] Juanita Hempstead, a Missouri resident, was prescribed and began taking 20 mg of Lipitor in 1999. Seven years later, she was diagnosed with diabetes. JA__-__(Pl. Fact Sheet at 4-5 (Dkt. 1004-34)); JA__(Pl. Fact Sheet at 5 (Dkt. 1563-1)). Ms. Hempstead offered two specific causation experts: Drs. Murphy and David Handshoe. As described more fully below (at pp. 71-74), Dr. Murphy conducted a comprehensive "differential diagnosis" after a review of relevant scientific literature and Ms. Hempstead's medical records. She concluded that in her medical judgment Lipitor was a substantial contributing factor in Ms. Hempstead's diabetes. The district court excluded Dr. Murphy's specific causation expert testimony, JA__(CMO 55 (Dkt. 1283)), and denied reconsideration, JA__(CMO 75 (Dkt. 1514)). After also excluding the testimony of Dr. Handshoe, JA__(CMO 76 (Dkt. 1517)),[27] the court granted summary judgment against Ms. Hempstead. JA__(CMO 97 (Dkt. 1791)).

Following the district court's exclusion of Dr. Murphy, Plaintiffs' appointed lead counsel suggested that that ruling would likely be fatal to all Plaintiffs' ability to prove specific causation. Dkt. No. 1611-1. As a result, on January 25, 2016, the

[26] Plaintiff has not appealed in *Daniels*.

[27] Plaintiffs have not appealed the district court's exclusion of Dr. Handshoe.

court issued a show-cause order requiring non-bellwether Plaintiffs in the MDL to come forward if they believed they could adduce expert evidence of specific causation that would survive *Daubert* in light of the court's exclusion of Dr. Murphy. JA__(CMO 65 (Dkt. 1352)). No Plaintiffs came forward at that time.

On June 8, 2016, over Plaintiffs' objection, the district court set a schedule for omnibus summary judgment motions in all cases. JA__(CMO 79 (Dkt. 1548)). In response to Defendants' summary judgment motion on specific causation, Dkt. 1564, Plaintiffs asserted that specific causation was not appropriately resolved through consolidated pretrial proceedings without a full opportunity for case-specific discovery. *See* Dkt. 1586; *see also* Dkt. 1611. In response, on August 23, 2016, the district court issued another show-cause order requiring non-bellwether Plaintiffs to come forward with all *nonexpert* evidence they believed created a material issue for trial. JA__(CMO 82 (Dkt. 1616)). Plaintiffs submitted an omnibus response objecting to the court's show-cause process. *See* Dkt. 1684.

On January 3, 2017, the district court issued an additional show-cause order that required all Plaintiffs who were not part of the MDL as of January 25, 2016, to come forward with case-specific evidence if they believed they "could produce expert testimony on specific causation that would survive *Daubert* should the Court's ruling in CMO 55 [excluding Dr. Murphy] be upheld on appeal." JA__(CMO 101, at 2 (Dkt. 1798)). No Plaintiff proffered additional specific

causation evidence. Plaintiffs opposed summary judgment, arguing among other things that it was procedurally improper for the court to demand additional specific causation evidence after having excluded the general causation experts. Dkt. 1813. The court nonetheless granted summary judgment against those Plaintiffs as well. JA__(CMO 109 (Dkt. 1844)).

SUMMARY OF ARGUMENT

I. The district court's grant of summary judgment on general causation was erroneous for three independent reasons.

A. The district court committed reversible error in excluding the expert opinions of Dr. Jewell. Dr. Jewell, one of the nation's preeminent biostatisticians, used standard statistical techniques – the same techniques he has taught for decades at two of the country's leading universities – to analyze Pfizer's own clinical data underlying its ASCOT-LLA report and its NDA report to the FDA. The district court's exclusion of Dr. Jewell's testimony rests on repeated mischaracterizations of his opinions and on a profound misunderstanding of basic statistical principles.

B. The district court erred in excluding the expert opinions of Dr. Singh on the ground that they were unsupported by evidence of *statistically significant* studies showing association between 10, 20, and 40 mg Lipitor doses and diabetes. The court's bright-line requirement of statistically significant studies is contrary to

sound statistical principle and numerous precedents, including the Supreme Court's decision in *Matrixx Initiatives, Inc. v. Siracusano*, 563 U.S. 27 (2011), which held that "[a] lack of statistically significant data does not mean that medical experts have no reliable basis for inferring a causal link between a drug and adverse events." *Id.* at 40. The district court was particularly unjustified in requiring statistically significant studies *at every dose* of Lipitor. The lower court cited no case supporting such a requirement, which is also inconsistent with established scientific practice.

C. Summary judgment was also improper because Defendants' own admissions created a factual dispute for the jury. Defendant's own senior executive admitted in an internal communication that "*[a]torvastatin increases the risk of developing diabetes*" and that "*[t]he risks of 10 mg and 80 mg are similar*." JA__(CMO 100, at 45) (emphases added). That statement is admissible against Defendants for the truth of the matter asserted, and a reasonable jury could rely on it to find general causation. The district court violated basic summary judgment principles by interpreting the statement in the light most favorable to Defendants rather than Plaintiffs. It committed further legal error by holding, in the absence of a single state-law case on point, that the law of all 35 states at issue in this MDL preempts the Federal Rules and bars the jury from relying on Defendants' own admissions.

II. The district court also committed legal error in its grant of summary judgment on specific causation.

A. The district court's grant of summary judgment to Defendants in the *Hempstead* bellwether case should be reversed because the court erroneously excluded the specific causation testimony of Ms. Hempstead's highly qualified medical expert, Dr. Elizabeth Murphy. Dr. Murphy used a differential diagnosis methodology that this Court has long accepted as reliable, and she did precisely what numerous courts have required of a medical doctor performing a differential diagnosis: provide reasoned explanations why, in her medical judgment, Ms. Hempstead's other risk factors were not likely to be the sole cause of her diabetes.

B. The court below erred in adjudicating summary judgment on specific causation in the non-bellwether cases. Specific causation is a quintessentially case-specific issue that is properly adjudicated by the transferor court in light of full case-specific discovery and the law of the relevant state. Apart from the *Hempstead* bellwether case, the more than 3,000 Plaintiffs in this appeal have never had an opportunity to conduct full discovery, including expert discovery, to develop their individual proof that they developed diabetes because of Lipitor. The court below overzealously sacrificed fairness to individual litigants for mass-tort efficiency by using an omnibus procedure that deprived Plaintiffs of their right to individualized discovery and adjudication.

STANDARD OF REVIEW

The district court's grant of summary judgment is reviewed *de novo*. *See Henry v. Purnell*, 652 F.3d 524, 531 (4th Cir. 2011) (en banc). Summary judgment is proper only if the record as a whole "show[s] that there is no genuine dispute as to any material fact and the movant is entitled to judgment as a matter of law." Fed. R. Civ. P. 56(a).

Expert testimony is admissible under Rule 702 if it is reliable and relevant. *See Daubert v. Merrell Dow Pharm. Inc.*, 509 U.S. 579, 597 (1993). The district court's exclusion of Plaintiffs' experts is reviewed for abuse of discretion. A district court abuses its discretion if it applies an erroneous legal standard, mischaracterizes the expert's testimony, or makes a clearly erroneous factual finding. *See Bryte ex rel. Bryte v. American Household, Inc.*, 429 F.3d 469, 475 (4th Cir. 2005).

The district court's interpretation of state law and its decision to apply that law instead of the Federal Rules are reviewed *de novo*. *See Epps v. JP Morgan Chase Bank, N.A.*, 675 F.3d 315, 320 (4th Cir. 2012).

ARGUMENT

I. Summary Judgment On General Causation Should Be Reversed

A. The District Court's Exclusion Of Dr. Jewell's ASCOT And NDA Analyses Mischaracterized His Opinions And Applied The Wrong Legal Standard

The district court excluded Dr. Jewell's re-analysis of the original ASCOT-LLA trial data on the ground that he (1) provided no explanation for doing the analysis and (2) could not show that the ASCOT study authors "got it wrong." Both of those holdings were erroneous.

1. The District Court Erroneously Mischaracterized Dr. Jewell As Having Re-analyzed The ASCOT Data "Without Explanation"

The district court's exclusion of Dr. Jewell's analysis on the ground that he re-analyzed the original ASCOT data "***without any explanation***," JA__(CMO 54, at 32), is reversible error because it mischaracterizes Dr. Jewell's opinions. *See Adams v. Laboratory Corp. of Am.*, 760 F.3d 1322, 1328-29 (11th Cir. 2014) (per curiam) (reversible error to exclude expert because she made "an *ipse dixit* assessment," when the record was to the contrary); *United States v. Alabama Power Co.*, 730 F.3d 1278, 1284-88 (11th Cir. 2013) (holding that exclusion of an expert was an abuse of discretion because the district court mischaracterized evidence supporting expert's opinion); *see also Silver Sage Partners, Ltd. v. City of Desert Hot Springs*, 251 F.3d 814, 821 (9th Cir. 2001) (holding the district court abused its discretion by excluding damages based on mischaracterization of

expert's testimony). In fact, Dr. Jewell repeatedly explained that his re-analysis was justified by (1) the ASCOT study authors' failure to provide any explanation for how they determined whether a patient had diabetes and the multiple contradictory and non-standard definitions found in study documents and Pfizer's regulatory submissions; (2) Pfizer's own re-analysis of the ASCOT data, which demonstrated errors in the original study; and (3) the fact that pre-specified analyses were not performed.[28]

In particular, Dr. Jewell explained that he reassessed the ASCOT results using the original data because the ASCOT-LLA results published in the *Lancet* provided no definition of diabetes, and the ASCOT study documents and other Pfizer documents contained different and conflicting diabetes criteria. ASCOT-related documents indicate that three inconsistent definitions of diabetes were used by the study investigators in making their initial determination of which patients met objective criteria for diabetes. *See* JA__-__, __(Jewell Rebuttal Rep. ¶¶ 7-9, 14) (citing (1) ASCOT endpoint manual; (2) the ASCOT-LLA Protocol; and (3) Pfizer's submission to the MHRA).

[28] The district court also erroneously suggested that Dr. Jewell "chose" to ignore ASCOT in his first expert report. In fact, he explained that his initial report "*followed the protocol outlined by Pfizer's consultant Dr. David Waters and his co-authors, including three Pfizer employees*, in their 2011 paper on the incidence of new onset diabetes associated with atorvastatin exposure, which did not analyze ASCOT." JA__(Jewell Rebuttal Rep. ¶ 1) (emphasis added).

The ASCOT endpoint manual described the accepted WHO criteria for diabetes, which are satisfied by any of three findings:

> (i) Fasting plasma glucose ≥ 7.0mmol/l [126 mg/dL] on two occasions[;] (ii) 2 hour post 75g glucose load plasma glucose > 11.1 mmol/1[; and/or] (iii) Unequivocal hyperglycaemia with acute metabolic decompensation or obvious symptoms.

JA__(CMO 54, at 27) (citing JA__(ASCOT Endpoint Manual § 3.5 (v.3) (Dkt. 1292-21)).

The ASCOT Protocol defined the criteria differently from the endpoint manual. JA__(ASCOT Working Protocol (Dkt. 1292-23)). The Protocol referred to [redacted] JA__(*Id.* at 50) (emphasis added). The limitation to [redacted] is inconsistent with the first two WHO definitions, which do not require that the patient have any clinical symptoms. Thus, as Dr. Jewell explained, the ASCOT Protocol's narrower definition "would likely underestimate the incidence of diabetes." JA__(Jewell Rebuttal Rep. ¶ 8).

Pfizer's 2010 submission to the MHRA describing the ASCOT-LLA trial contains yet a third inconsistent description of the study's definition of diabetes. In that submission, Pfizer stated that the ASCOT-LLA endpoint manual defined diabetes "as random plasma glucose > 11.1 mmol/l on two occasions *plus symptoms* consistent with diabetes." JA__(CMO 54, at 27) (citing JA__(Dkt. 1292-22, at 12)) (emphasis added). It also described ASCOT as using the

WOSCOPS study's more restrictive definition of diabetes.[29] The MHRA submission thus corroborates the ASCOT Protocol's statement that the researchers applied a narrower definition of diabetes than what is accepted by the WHO.

The district court ignored Dr. Jewell's explanations, and instead asserted that Dr. Jewell "made an assumption that the endpoint committee used a 'non-standard' definition of diabetes." JA__(CMO 54, at 28). Again, that mischaracterizes his testimony and the evidence. Dr. Jewell made no such "assumption" – he correctly stated that the definition described in the ASCOT protocol and the MHRA report were, in fact, non-standard because both required symptoms of diabetes or other criteria in addition to two glucose measurements greater than 125 mg/dL.

Dr. Jewell also explained that re-analysis was warranted because of the ASCOT study's undocumented adjudication process, which made it impossible to replicate the study's results. After making their initial determination, the ASCOT researchers apparently narrowed the number of patients deemed to have developed diabetes by using an "adjudication process" undertaken by an "Endpoints Committee." That committee performed a subjective evaluation and determined

[29] *See* Dilys J. Freeman et al., *Pravastatin and the Development of Diabetes Mellitus: Evidence for a Protective Treatment Effect in the West of Scotland Coronary Prevention Study*, 103 Circulation 357 (2001). This definition of diabetes is more restrictive than the WHO's because it requires not only two glucose values > 125 mg/dL, but that one of them is at least 36 mg/dL higher than a patient's baseline.

that certain patients that met the objective diabetes criteria nonetheless did not actually have diabetes. Dr. Jewell was unable to fully replicate the Endpoints Committee's adjudications, because the study authors did not report the criteria in the published study, and Pfizer did not provide any documentation explaining the criteria used. *See* JA__ (Sever, 361 Lancet 1149); JA__(Jewell Dep. 407:11-14 (Dkt. 972-40)) [redacted].[30]

Contrary to the district court's opinion, Dr. Jewell explained the lack of reproducibility at length. [redacted] JA__(Jewell Dep. 410:20-25). Dr. Jewell testified [redacted] JA__-__(*Id.* at 406:18-407:5); *see also* JA__(*id.* at 451:4-10 [redacted]

[30] Dr. Jewell was able to and did exclude all patients with baseline diabetes and glucose values in the range diagnostic of diabetes.

[redacted]; *see also* JA__(Jewell Rebuttal Rep. ¶ 14) ("In sum, it is unclear how diabetes was defined in ASCOT-LLA."). The district court's assertion that Dr. Jewell offered no reasons for his re-analysis simply is not accurate.

2. The District Court Erred In Requiring "Validation" To Perform A Re-analysis

In addition to mischaracterizing Dr. Jewell's opinions, the district court held Dr. Jewell could not reliably "testify that the data support a conclusion opposite that of the studies' authors in a peer-reviewed publication" without a showing that ASCOT suffered from "methodological flaws" and "got it wrong." JA__(CMO 54, at 32); *see id.* (stating that Dr. Jewell needed to "validate" his re-analysis). That holding was erroneous for several reasons.

First, Dr. Jewell was not required to show that the study authors "got it wrong" in order to justify his re-analysis of the ASCOT study. *Daubert* does not require scientific certainty, nor does it focus on the correctness of the expert's conclusions. It requires that the expert's *methods* be no less rigorous than those used in the field. *See Kumho Tire Co. v. Carmichael*, 526 U.S. 137 (1999); *Westberry v. Gislaved Gummi AB*, 178 F.3d 257, 261 (4th Cir. 1999) (*Daubert* focuses on "the principles and methodology employed by the expert, not on the conclusions reached"); *Pugh v. Louisville Ladder, Inc.*, 361 F. App'x 448, 452 (4th Cir. 2010) (same). The district court cited no evidence that Dr. Jewell used non-

standard statistical methods. Dr. Jewell applied standard methodology validated by the statistical community, techniques that he has used countless times outside of litigation. In fact, Dr. Jewell has taught such methods for almost 40 years at two of the finest universities in the country. And, critically, Dr. Jewell used the exact same statistical methods used by Pfizer's investigators in peer-reviewed publications, and by Pfizer's own expert in this litigation. *See* JA__(Wei Dep. 328:9 (Dkt. 1292-10)); JA__-__(Waters (2011)).

Second, the district court's deference to the study authors' published conclusions was misplaced. Peer review is an indicator of reliability under *Daubert*, but it is not talismanic. *See Daubert*, 509 U.S. at 593 (peer review does not necessarily indicate reliability). That is especially the case here: the *Lancet* report was of doubtful reliability because its results could not be reproduced or replicated. Moreover, as explained above (at pp. 19-20), Pfizer's own MHRA report demonstrated that the report erroneously included patients as having met the diabetes endpoint when they were ineligible according to the criteria set forth in the Endpoint Manual. *See id.* ("[T]he criterion of the scientific status of a theory is its falsifiability, or refutability, or testability"). And the peer reviewers did not have access to the underlying data. For all these reasons, it was improper for the court to assume the study's results were correct just because they were peer-reviewed and published.

Finally, even if it were proper to focus on conclusions rather than methodology, Dr. Jewell did *not* reach a conclusion "opposite" to the study authors. Dr. Jewell's re-analysis was *consistent* with the published ASCOT article. It was only when he performed the additional analysis that was pre-specified in the trial's protocol, that he found a stronger association that was statistically significant. *See* JA__(CMO 54, at 31 n.33) (Defendants do not contest that Dr. Jewell performed an analysis pre-specified in ASCOT protocol). The district court viewed Dr. Jewell's results as *contrary* to ASCOT because the original published and unadjusted results were not statistically significant, but it is a fundamental statistical error – which the district court repeated in excluding Dr. Singh, *see infra* Point I.B. – to view statistically significant results as the "opposite" of non-statistically significant results.[31]

[31] In denying reconsideration, the district court cited a three-page affidavit by Dr. Henry Hemingway, the chairperson of the ASCOT Endpoints Committee, which Pfizer introduced four months after Dr. Jewell filed his expert reports. JA__(CMO 67, at 13 (Dkt. 1412)); *see also* JA__(Hemingway Decl. (Dkt. 1091-1)). To the extent the district court credited that affidavit, it erroneously resolved a factual dispute for the jury. *See, e.g.*, *i4i Ltd. P'ship v. Microsoft Corp.*, 598 F.3d 831, 856 (Fed. Cir. 2010) ("[I]t is not the district court's role under *Daubert* to evaluate the correctness of facts underlying an expert's testimony."), *aff'd*, 564 U.S. 91 (2011); *Westberry*, 178 F.3d at 261. Moreover, Dr. Hemingway's affidavit heightens the doubts regarding the ASCOT study's reliability. For example, he stated that the committee "would review available information . . . to determine if the glucose values were fasting or non-fasting." JA__(Hemingway Decl. ¶ 13). But the underlying data produced by Pfizer and analyzed by Dr. Jewell contained *only* fasting glucose values, and Dr. Hemingway offered no explanation as to how

Fundamentally, by requiring Plaintiffs to show that Dr. Jewell's conclusions were right, and the ASCOT study "got it wrong," the district court functionally put the burden on *Plaintiffs* to prove that they were entitled to summary judgment. That is not the proper test under Rule 56, and it certainly is not the proper test under *Daubert*.

3. The District Court Erred in Excluding Dr. Jewell's Analysis Of Pfizer's NDA Data, Which Bolsters The Results Of His ASCOT Re-analysis

The district court also erroneously excluded Dr. Jewell's analysis of Pfizer's NDA data, which found that Lipitor is associated with a more than three-fold statistically significant risk of a clinically meaningful blood-glucose increase. There is no dispute that the NDA data demonstrated an increased risk of abnormal and clinically meaningful blood-glucose elevations with Lipitor. Pfizer's ISS acknowledged it;[32] FDA's Medical Reviewer noted it;[33] and Pfizer's own expert confirmed it.[34] What the parties dispute is the *reason* for this increased risk.

---

the Endpoints Committee determined that certain blood-glucose levels were, contrary to the actual records, *not* fasting.

[32] JA__(ISS § 5.2.3 (Dkt. 974-21)) [redacted]

[33] JA__(NDA 20-702, Medical Review 106): "The increased incidence of glucose elevations in the atorvastatin-treated patients bears comment."

[34] JA__(Wei Dep. 312:2-9) ("Q. [Y]ou would agree that under your analysis in the overall combined men and women, two of the three tests were statistically significant, correct? . . . A. Including all the patients? Q. Yes. A. Yes.").

Plaintiffs argue it was Lipitor; Pfizer, that it was baseline glucose imbalances. As explained above, diabetes is defined as having *two* fasting blood-glucose values > 125 mg/dL. *See supra* p. 7. The fact that Pfizer had data as early as 1996 showing that Lipitor dramatically increases the risk of even *one* elevated blood-glucose reading is highly relevant to Plaintiffs' failure-to-warn claims because it "should have alerted Parke-Davis and Defendant to the *possibility* of increased risk of new-onset diabetes associated with atorvastatin treatment." JA__(CMO 54, at 8) (citing JA__(Jewell Rep. ¶ 6)) (emphasis added); *see, e.g.*, *Hollister v. Dayton Hudson Corp.*, 201 F.3d 231, 241 (6th Cir. 2000) (failure to warn can be predicated on constructive knowledge of the danger).

Dr. Jewell's analysis quantified the *degree* of this acknowledged increased risk of blood-glucose elevations using Pfizer's own data and standard statistical methods. Each of the district court's grounds for excluding Dr. Jewell's testimony was erroneous.

First, the district court stated that Dr. Jewell's opinion was unreliable because it treated elevated blood glucose as if it were sufficient to diagnose a patient with diabetes. *See* JA__-__(CMO 54, at 7-8). But Dr. Jewell clearly and repeatedly acknowledged that a single elevated blood-glucose reading does not equate to diabetes. *See also supra* p. 38 (discussing Dr. Jewell's familiarity with the clinical diabetes criteria). His opinion was that the NDA data showed that

exposure to Lipitor increased the occurrence of *abnormal glucose increases*. *See, e.g.*, JA__(Jewell Rep. ¶ 21) (describing his finding as [redacted]; JA__(Jewell Dep. 95:23-25 (Dkt. 972-7)) [redacted]; JA__, __Jewell Rep. ¶¶ 19, 22). As it did with ASCOT, the court mischaracterized Dr. Jewell's NDA analysis, and attributed to him conclusions that he never purported to draw.

Second, the district court criticized Dr. Jewell for including patients whose blood-glucose levels were already elevated prior to taking Lipitor, rather than limiting himself to "***new*** cases of elevated glucose." JA__(CMO 54, at 11). But, again, Dr. Jewell did not purport to draw any conclusions about *new-onset* blood-glucose increases from the limited NDA data – only that [redacted] *See* JA__-__(Jewell Rep. ¶¶ 19-22).

Indeed, the district court's accusation that Dr. Jewell lacked methodological integrity is completely unfounded. JA__-__(CMO 54, at 13-14) (asserting that "including participants with elevated baseline glucose is contrary to Dr. Jewell's methodology in all of his other analyses"). In his other analyses, including his SPARCL analysis, which the court admitted, Dr. Jewell was measuring the

association between Lipitor and *new-onset diabetes*, so it was appropriate to exclude patients with elevated blood glucose at baseline. Here, the NDA data only reported abnormal blood-glucose elevations, and that is all Dr. Jewell was attempting to measure. In short, the court fundamentally misunderstood Dr. Jewell's analysis, which is emblematic of its entry into a statistical fray it was unqualified to resolve. *See Daubert*, 509 U.S. at 600-01 (Rehnquist, C.J., concurring) (Rule 702 does not authorize district judges to play "amateur scientist[ ]").[35]

Third, the court excluded Dr. Jewell's opinion as unreliable because he used a test for statistical significance known as the "mid-p" test, which generated a statistically significant result at a 95% level ($p = 0.04$), after first using the "Fisher exact" p-test, which generated a result that barely missed 95% statistical significance ($p = 0.0654$). As an initial matter, Dr. Jewell's opinion did not depend on the selection of a particular p-test. He performed [redacted] *See* JA__-__(Jewell Rep. ¶¶ 17-18). Moreover,

[35] The district court also criticized Dr. Jewell for assuming that all reported cases of elevated glucose were "clinically meaningful." JA__(CMO 54, at 18). But Dr. Jewell simply adopted the ISS's own conclusions, which the court had no factual basis – and certainly no expertise – to question. *See* JA__(ISS § 5.2) (clinical laboratory parameters "[redacted]"). Unlike with diabetes in ASCOT, where Dr. Jewell could independently ascertain whether Pfizer correctly applied the accepted WHO criteria to the clinical data, the NDA reported no criteria for "clinically meaningful" changes, and Dr. Jewell had no reason to reassess the ISS's stated conclusions.

Dr. Jewell explained that he used the mid-p test because it "is more powerful than the Fisher Exact Test" and because "statisticians believe it's better." JA__-__(Jewell Dep. 212:1-214:8); *see also* JA__(Jewell Rep. ¶ 17 n.16) ("it is well-known that the mid-p approach is slightly improved" in comparison to the Fisher Exact Test). Dr. Jewell's choice of a particular statistical test is well within the range of reasonable methodological choices, and does not establish that Dr. Jewell's methodology was unsound. *See In re Celexa & Lexapro Prods. Liab. Litig.*, 927 F. Supp. 2d 758, 764-65 (E.D. Mo. 2013) ("There is no requirement that Dr. Healy reach the same conclusion as Dr. Kahn just because he relied on Dr. Kahn's data."); *see* JA__-__(CMO 54, at 14-15) (acknowledging the mid-p test is reliable and widely used).

The district court accused Dr. Jewell of turning to the mid-p test only "when the first test did not produce the results that he wanted." JA__(CMO 54, at 6). But that assertion is based on a gross mischaracterization of Dr. Jewell's deposition testimony. What he actually said was because the NDA data only reported data regarding abnormal blood-glucose elevations, and not diabetes, "I decided that was the limit of what the data could really support." JA__, __(Jewell Dep. 228:4-21, 229:10-15); *see also* JA__(*id.* at 230:6-10) ("Whether the opinion [of a study] is negative or positive is irrelevant . . . I will only put in [my report] statistical analyses that . . . have the weight of evidence necessary to support a strong opinion

one way or the other."). In addition, the district court adopted a heads-I-win-tails-you-lose double-standard when it erroneously criticized Dr. Jewell for going beyond the published ASCOT study but not doing so in his NDA analysis. *See supra* note 35 (explaining why Dr. Jewell had sound statistical reasons for both decisions). There was nothing unprincipled about Dr. Jewell's use of a standard statistical technique wholly appropriate for the circumstances, and any criticism to that effect should be resolved by the jury after live cross-examination, not based on a court's faulty interpretation of a deposition transcript.

B. The District Court Erroneously Held That A Reliable General Causation Opinion Requires Dose-Specific Studies Showing Positive Association That Rises To A 95% Level Of Statistical Significance

The district court admitted Dr. Singh's causation opinions at 80 mg, but excluded Dr. Singh's causation opinions at 10, 20, and 40 mg. The court reached that result in two steps. *First*, it held that Dr. Singh could not reliably opine on general causation without addressing each dose of Lipitor separately. JA__(CMO 49, at 11). *Second*, after Dr. Singh revised his expert report to conform with CMO 49, the court held that Dr. Singh's 80 mg causation opinion was reliable because studies had "found a statistically significant increase in the risk of diabetes in patients taking 80 mg of Lipitor." JA__(CMO 68, at 15). By contrast, it deemed Dr. Singh's 10 mg causation opinion unreliable because although there are multiple studies showing positive association, none of them rose to the level of

statistical significance. *See* JA__-__(*id.* at 16-19). It also deemed Dr. Singh's testimony as to 20 mg and 40 mg unreliable because although "several studies show a statistically significant association between exposure to" 20 and 40 mg doses of Lipitor and diabetes, JA__(*id.* at 10), Dr. Singh testified that his causation opinion at 20-40 mg depended on evidence of association at 10 mg.

1. The District Court Erroneously Considered Statistical Significance A Bright-Line Requirement For Admissibility

The district court's adoption of a bright-line rule requiring evidence of association rising to statistical significance constitutes reversible error. As a matter of both law and science, it is erroneous to equate statistical significance with reliability.

a. A Bright-Line Statistical Significance Requirement Contravenes The Supreme Court's *Matrixx* Decision And Prevailing Federal Case Law

As the Supreme Court stated in *Matrixx Initiatives, Inc. v. Siracusano*, "[a] lack of statistically significant data does not mean that medical experts have no reliable basis for inferring a causal link between a drug and adverse events." 563 U.S. 27, 40 (2011). Given that medical researchers "do not limit the data they consider to the results of randomized clinical trials or to statistically significant evidence," there is no justification for excluding an expert solely on the ground that he lacks such evidence. *Id.* at 41. The district court violated that principle. Indeed, the court repeatedly and erroneously equated "no *statistically significant*

association" with "no association." *See, e.g.*, JA__(CMO 68, at 10) (stating that not a single study "shows an association" between 10 mg of Lipitor and diabetes, because "all find no statistically significant difference"); JA__(*id.* at 16) ("None of this evidence establishes an association between 10 mg of Lipitor and diabetes.").

The district court's decision also contravenes numerous other federal court decisions that have rejected a bright-line requirement that causation opinions be supported by statistically significant studies. *See Ambrosini v. Labarraque*, 101 F.3d 129, 136 (D.C. Cir. 1996) (in making inferences about causation, "epidemiologists evaluate the totality of the data," not just data that reaches statistical significance); *Milward*, 639 F.3d at 25 (holding district court erred in excluding an expert's testimony supported "with data that concededly lacks statistical significance" as "a deviation from sound practice of the scientific method"); *In re Prempro Prods. Liab. Litig.*, 738 F. Supp. 2d 887, 892 (E.D. Ark. 2010) ("We agree that statistical significance, by itself, should not mechanically control whether an epidemiological analysis is sufficiently reliable to be admissible."); *In re Chantix (Varenicline) Prods. Liab. Litig.*, 889 F. Supp. 2d 1272, 1277-86 (N.D. Ala. 2012) ("[C]ourts frequently permit expert testimony on causation based on evidence other than statistical significance.") (refusing to exclude testimony based on absence of statistically significant association); *In re Viagra Prods. Liab. Litig.*, 572 F. Supp. 2d 1071, 1090 (D. Minn. 2008) (holding

that scientific studies need not be statistically significant to support a general causation opinion); *In re Neurontin Mktg., Sales Practices & Prods. Liab. Litig.*, 612 F. Supp. 2d 116, 141 (D. Mass. 2009) (same); *Allen v. United States*, 588 F. Supp. 247, 417 (D. Utah 1984) ("The cold statement that a given relationship is not 'statistically significant' cannot be read to mean there is no probability of a relationship."); *Cook v. Rockwell Int'l Corp.*, 580 F. Supp. 2d 1071, 1103 (D. Colo. 2006) (statistical significance goes to weight of expert testimony, not admissibility); *Mack v. AmerisourceBergen Drug Corp.*, 671 F. Supp. 2d 706, 711 (D. Md. 2009) (permitting general causation opinion that relied only on a single statistically non-significant study); *In re Trasylol Prods. Liab. Litig.*, No. 08-MD-01928, 2010 WL 1489793, at *7 (S.D. Fla. Feb. 24, 2010) (expert's opinion should not be excluded simply because it is based on data that are not statistically significant).[36]

Insisting on statistical significance is inappropriate because it raises the bar for admissibility under Rule 702 higher than the ultimate preponderance-of-the-evidence standard of proof. As Judge Rakoff explained in *In re Ephedra Liability Litigation*, the conventional 95% confidence level demands that there can be "no more than one chance in twenty of a finding a false association due to sampling

[36] None of the cases cited by the district court (JA__-__(CMO 68, at 19-20)) are to the contrary, because they did not squarely address whether statistically significant studies are required for a reliable causation opinion.

error." 393 F. Supp. 2d 181, 193 (S.D.N.Y. 2005). "Plaintiffs, however, need only prove that causation is more-probable-than-not." *Id.* "*Daubert* was designed to exclude 'junk science.' . . . Rule 702, a rule of threshold admissibility, should not be transformed into a rule for imposing a more exacting standard of causality than more-probable-than-not simply because scientific issues are involved." *Id.* at 190.

b. A Bright-Line Statistical Significance Requirement Is Also Inconsistent With Scientific Practice

For similar reasons, many in the scientific community reject statistical significance as a prerequisite to a reliable causation opinion. *First*, a binary distinction between "significant" and "insignificant" leads to arbitrariness. *See* David H. Kaye, *Is Proof of Statistical Significance Relevant?*, 61 Wash L. Rev. 1333, 1344-45 (1986) ("[T]here is no sharp border between 'significant,' and 'insignificant.'"). It is scientifically unsound to suggest that if the lower bound of a 95% confidence interval is 1.01, the study proves association, but if it is 0.99, the study disproves association. The latter study falls just short of 95% probability, but 95% is still highly probative of association, far higher than the preponderance of the evidence. *See H.B. Rowe Co. v. Tippett*, 615 F.3d 233, 250 (4th Cir. 2010) (recognizing that statistical evidence of racially disparate treatment "at a confidence level of approximately 85 percent" still "demonstrates a high likelihood of actual disparity").

A binary distinction between significance and non-significance is also inconsistent with scientists' usage of different *levels* of statistical significance. *See* RMSE at 576-78. A study that misses statistical significance at a 95% level may well be statistically significant at a lower 90% level; a study that reaches 95% statistical significance may not be significant if a 99% confidence level is chosen. *See id.* at 580-81 & fig. 4. The appropriate level of statistical significance is a matter of scientific convention and judgment, not a law of nature or an inexorable statistical command. *See* Michael D. Green, *Expert Witnesses and Sufficiency of Evidence in Toxic Substances Litigation: The Legacy of Agent Orange and Bendectin Litigation*, 86 Nw. U.L. Rev. 643, 683 (1992) ("the choice of .05 is an arbitrary one").

Second, statistical significance reduces false *positives* (or "Type I error"), but at the cost of creating many more false *negatives* ("Type II errors"). *See* RMSE at 581-82; Green, 86 Nw. U.L. Rev. at 687; *In re Ephedra Liability Litig.*, 393 F. Supp. 2d at 191-93. Reflecting these concerns, leading scientists reject a bright-line insistence that causation opinions be supported by statistically significant studies. *See* RMSE at 578-79.[37] Leading statisticians in the field have

[37] The district court cited the RMSE as evidence that scientists always require statistical significance, but the pages following those cited say that the issue is the subject of "controversy among epidemiologists and biostatisticians" and that many are "critical of using strict significance testing." RMSE at 578-79.

recognized that when assessing causation, it is generally accepted to examine the effect estimates (*i.e.*, Odds Ratio) without exclusion of non-significant results. *See* Kenneth J. Rothman & Sander Greenland, *Causation and Causal Inference in Epidemiology*, 95 Am. J. Pub. Health S144, S148 (2005). Likewise, a leading academic, Professor Carl Cranor, rejects statistical significance as a "bright-line rule that epidemiological studies must satisfy" because a strict definition of significance results in a high rate of false negative results. Carl F. Cranor, *Judicial Boundary Drawing and the Need for Context-Sensitive Science in Toxic Torts After* Daubert v. Merrell Dow Pharmaceuticals, Inc., 16 Va. Envtl. L.J. 1, 30-37 (1996). And Sir Bradford Hill himself emphasized that "[n]o formal tests of significance can answer those questions [regarding causation]." JA__(58 Proc. Royal Soc'y Med. at 299); *see also* Restatement (Third) of Torts § 28 reporters note cmt. c(3) ("A quite substantial body of case law and commentary rejects an epidemiologic threshold for sufficient proof of general causation."); Green, 86 Nw. U.L. Rev. at 685 ("dismissing all non-statistically significant studies is inconsistent with making the best assessment of causation based on the available evidence"); RSME at 579 (cautioning against "rejecting all studies that are not statistically significant").

Insistence on statistical significance is particularly inappropriate where, as here, multiple scientific studies show a positive association even if they do not reach statistical significance. As the Third Circuit stated in *DeLuca v. Merrell*

Dow Pharmaceuticals, Inc., "[d]ifferent studies may each be rejected as insignificant, yet, when the studies are looked at collectively, a majority of the data may be moderately or strongly contradictory to the null hypothesis." 911 F.2d 941, 948 (3d Cir. 1990). "[R]esearchers focusing solely on significance testing tolerate a high risk of . . . error." *Id.*; *see also* Green, 86 Nw. U.L. Rev. at 686 ("Peremptorily rejecting all studies that are not statistically significant would be a cursory and foolish judgment, particularly if there are multiple studies tending to show a consistent effect."); David E. Lilienfeld et al., *Foundations of Epidemiology* 264 (3d ed. 1994) ("Repeated findings of weak association in well-conducted studies can still support an inference of causation.").

In March 2016, the American Statistical Association, the second oldest continuously operating professional society in the U.S., for the first time in its 177-year history released a public statement about a specific matter of statistical practice.[38] Noting that statistical significance is "too often misunderstood and misused," the ASA stated that "[s]tatistical significance is not equivalent to scientific, human, or economic significance." Wasserstein, 70 Am. Statistician at 132; *accord Brown v. Nucor Corp.*, 785 F.3d 895, 908 (4th Cir. 2015) ("[S]tatistical significance is not always synonymous with legal significance.").

[38] *See* Ronald L. Wasserstein & Nicole A. Lazar, *The ASA's Statement on pvalues: Context, Process, and Purpose*, 70 Am. Statistician 129 (2016).

The district court's holding in this case rests on just such a misunderstanding of scientific principle.[39]

As the foregoing authorities reflect, the scientific community disagrees whether evidence of association must rise to the level of statistical significance. Where an expert's testimony is within "the range where experts might reasonably differ," it is for the jury, not the court, to decide which "among the conflicting views" should be credited. *Kumho Tire*, 526 U.S. at 153; *see Johnson v. Mead Johnson & Co.*, 754 F.3d 557, 564 (8th Cir. 2014); *S.M. v. J.K.*, 262 F.3d 914, 921 (9th Cir. 2001), *amended*, 315 F.3d 1058 (9th Cir. 2003); *see also Daubert v. Merrell Dow Pharm., Inc.*, 43 F.3d 1311, 1319 (9th Cir. 1995) (experts must "show that they have followed the scientific method, as it is practiced by (at least) a recognized minority of scientists in their field"); *Ruiz-Troche v. Pepsi Cola*, 161 F.3d 77, 85 (1st Cir. 1998) ("*Daubert* neither requires nor empowers trial courts to determine which of several competing scientific theories has the best provenance."). Pfizer can urge the jury to reject Dr. Singh's opinions to the extent

[39] *See also, e.g.*, Deborah G. Mayo, *Don't Throw Out the Error Control Baby with the Bad Statistics Bathwater: A Commentary*, Am. Statistician, Online Discussion (2016) (warning it is erroneous to "tak[e] nonsignificant results as uninformative"); Sander Greenland et al., *Statistical Tests, P Case Values, Confidence Intervals, and Power: A Guide to Misinterpretations*, Am. Statistician, Online Discussion (2016) ("[T]he arbitrary classification of results into 'significant' and 'non-significant' is unnecessary for and often damaging to valid interpretation of data.").

they are not supported by statistically significant studies, but it was error to exclude his testimony on that ground.[40]

2. The District Court Exacerbated Its Error By Requiring Statistically Significant Association At Every Lipitor Dose

The district court compounded its legal error by requiring that Dr. Singh's causation opinions be supported by at least one statistically significant study *for every dose of Lipitor*. *See* JA__(CMO 54). The court required Dr. Singh to rule out the possibility that there is a so-called "no effect threshold" – *i.e.*, a dose below which Lipitor cannot cause diabetes. But that unprecedented ruling misapplies the well-accepted Bradford-Hill criteria and demands a degree of scientific certainty that goes well beyond the court's proper gatekeeping function.

To our knowledge, no case has ever held that a plaintiff must adduce statistically significant evidence at every administered dosage of a drug in order to establish a general causal relationship between the drug and a particular disease. The court in *In re Zicam Cold Remedy Marketing, Sales Practices & Products Liability Litigation*, 797 F. Supp. 2d 940 (D. Ariz. 2011), correctly rejected any such requirement. And numerous courts in pharmaceutical products liability cases have denied motions to exclude general causation expert opinions even though

[40] Strict insistence on statistical significance is particularly inappropriate in the case of the ASCOT 10 mg trial because the misclassification and adjudication of the diabetes endpoint likely biased the results toward the "null" hypothesis.

they were not dose-specific. *See In re Fosamax Prods. Liab. Litig.*, 645 F. Supp. 2d 164 (S.D.N.Y. 2009); *In re Neurontin*, 612 F. Supp. 2d at 123; *McClellan v. I-Flow Corp.*, 710 F. Supp. 2d 1092, 1111 (D. Or. 2010); *In re Avandia Mktg., Sales Practices & Prods. Liab. Litig.*, No. 07-MD-18771, 2011 WL 13576 (E.D. Pa. 2011); *In re Chantix*, 889 F. Supp. 2d at 1278; *In re Seroquel Prods. Liab. Litig.*, No. 6:06-MD-1769-ORL-22D, 2009 WL 3806434 (M.D. Fla. June 18, 2009).

Those decisions are well supported by scientific principles. The first step of the Bradford-Hill framework requires that a general causation opinion be supported by evidence – but not necessarily statistically significant evidence – of association between the drug and the disease in question. Dose-specific evidence is not required at this step. The *Reference Manual on Scientific Evidence*, for example, characterizes the general causation question as whether "exposure to a substance can cause a particular disease (e.g., that smoking cigarettes can cause lung cancer)." RMSE at 444 (2d ed. 2000). Scientists can reliably answer that general causation question – yes or no – without determining precisely *how many* cigarettes a person has to smoke to get lung cancer. Indeed, the FDA does not

demand dose-specific causation evidence when evaluating drug safety, even when drugs come in various doses.[41]

If evidence of association exists, scientists evaluate the "weight of the evidence" guided by the Bradford-Hill criteria to assess whether that evidence supports an inference of causation. *See*, *e.g.*, Lilienfeld, *Foundations of Epidemiology* 263-66. The existence of a dose-response relationship, as has been established with statins, is "strong, but not essential, evidence" of a causal relationship at this second step. RMSE at 603. There is no basis in scientific method or practice, however, to invoke the existence of a dose-response relationship to impose a *heightened* requirement for proof of association at the first step of the Bradford-Hill framework.

The district court stated that *In re Bextra & Celebrex Marketing Sales Practices & Products Liability Litigation*, 524 F. Supp. 2d 1166, 1174 (N.D. Cal. 2007), is "particularly on point," JA__-__(CMO 49, at 2-3), but in that case Plaintiffs' experts *volunteered* dose-specific causation opinions. The court thus did not address – and had no occasion to address – whether dose-specific causation opinions were *required*.

[41] Of the 16 most recent FDA Safety Communications that addressed drugs that are available in different doses, dating to 2015, only one – Invokana (May 18, 2016) – provided dose-specific data. *See* https://www.fda.gov/Drugs/DrugSafety/ucm199082.htm.

The district court also misinterpreted this Court's statement in *Westberry* that "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 at 263. That comment related to *specific* causation, not general causation. *See also* RMSE at 669-70. In addition, the court ignored the opinion's next sentence, which clarified that, "while precise information concerning the exposure necessary to cause specific harm to humans and exact details pertaining to the plaintiff's exposure are beneficial, such evidence is not always available, or necessary, to demonstrate that a substance is toxic to humans given substantial exposure and need not invariably provide the basis for an expert's opinion on causation." *Westberry*, 178 F.3d at 264.

Moreover, even if some minimum-dose evidence were required, *Westberry* certainly did not require *statistically significant* studies. The district court held that the Defendants' own admissions were sufficient to establish general causation, as they should have been here. *See infra* Part I.C. Likewise, as this Court held in *City of Greenville v. W.R. Grace & Co.*, 827 F.2d 975 (4th Cir. 1987), "one technique accepted in the scientific community for predicting the risks associated with low-level exposures is to extrapolate the risk downward from results obtained in studies involving high-level exposures." *Id.* at 980 n.2. Here, in addition to relying on multiple studies showing positive association at 10 mg, Dr. Singh

reasonably concluded from multiple studies showing statistically significant association at 20 to 80 mg doses that 10 mg of Lipitor can cause diabetes. The TNT published study found that there was no statistically significant difference between 10 mg and 80 mg of Lipitor. JA__(LaRosa). Pfizer's own scientist, Dr. DeMicco, agreed that the effect of 10 mg and 80 mg are the same. *See infra* Part I.C. The FDA has treated all doses of Lipitor similarly by requiring the same warnings on all doses, including 10 mg. JA__(Singh Supp. Rep. 24).

Under the correct legal standard, Dr. Singh's opinion that Lipitor can cause diabetes at all administered doses should have been admitted. Only by demanding that Dr. Singh provide separate statistically significant studies to support separate causation opinions *for each specific dose* could the district court slice-and-dice the scientific evidence and come to the conclusion that there is no evidence of association at doses lower than 80 mg. The court erroneously imposed an unprecedented requirement that finds no legal or scientific justification.

C. The District Court Committed Legal Error In Granting Summary Judgment On General Causation Despite Defendants' Admissions

1. Under The Federal Rules, Pfizer's Admissions Create A Genuine Factual Issue For Trial

As explained above (at pp. 14-15), Dr. DeMicco, a Pfizer Vice President and scientist, exchanged emails with his co-author and Pfizer consultant, Dr. Waters, regarding the results of the SPARCL and TNT studies. Upon reviewing Pfizer's

re-analysis of the SPARCL data, Dr. DeMicco agreed that "*[a]torvastatin increases the risk of developing diabetes*" and that "*[t]he risks of 10 mg and 80 mg are similar*." JA__(CMO 100, at 45) (quoting JA__(Dkt. 1586-2)) (emphases added). When asked about the exchange during his deposition, Dr. DeMicco reiterated: [redacted] JA__(DeMicco Dep. 291:23-24 (Dkt. 1586-3)) (emphasis added); *see* JA__-__(*id.* at 289:14-290:1) (again reiterating the same). Dr. DeMicco's statement is consistent with the admission in Pfizer's Japanese label, which warned that "diabetes [mellitus] may occur" if Lipitor is taken at doses as low as 5 mg.

Under Federal Rule of Evidence 801(d)(2)(D), these statements constitute party admissions by Pfizer that (1) Lipitor can cause diabetes and (2) the general causal effect exists at both 10 mg and 80 mg of Lipitor.[42] As such, a jury is entitled to consider those statements as substantive evidence of the matters asserted. *See, e.g.*, 30B Michael H. Graham, *Federal Practice and Procedure* § 7015 (Int. ed. 2011) ("Admissions are substantive evidence."); *Pitrolo v. County of Buncombe*, 407 F. App'x 657, 658 (4th Cir. 2011) ("Camby's statement to Pitrolo was admissible evidence as a 'party-opponent admission' under Federal Rule of Evidence 801(d)(2)."). And at summary judgment, those admissions

[42] *See, e.g.*, JA__(Waters (2011) at 1535 n.†) (listing Dr. DeMicco as a Pfizer employee); JA__-__(DeMicco Dep. 43:17-44:3).

create a genuine issue of material fact for trial. *See* Fed. R. Civ. P. 56(c)(1)(A) (providing that the summary judgment record includes "admissions").

2. The District Court Erred By Interpreting Dr. DeMicco's Statement As A Mere Assertion That Lipitor Is Associated With Diabetes

The district court held Dr. DeMicco's admission insufficient to avoid summary judgment because it was "at best, evidence of association, not causation." JA__(CMO 97, at 22); JA__(CMO 100, at 46). That ruling is contrary to the plain language of Dr. DeMicco's email. The verb "increase," when used in the transitive active voice (*i.e.*, with a direct object, here, "the risk") means "to make greater" – *i.e.*, to cause an increased risk. *See Webster's Third New International Dictionary* 1145 (2002). That is the very definition of general causation. *See, e.g.*, *Kuhn v. Wyeth, Inc.*, 686 F.3d 618, 626 (8th Cir. 2012) (defining general causation as the requirement "that use of [a drug] increases the risk of [a disease]"); *Jenkins v. Slidella L.L.C.*, No. 05-370, 2008 WL 2649510, at *4 (E.D. La. June 27, 2008) (defining general causation in a toxic tort as the requirement that "exposure to the substance at issue increases the risk of a particular injury").[43]

[43] The district court likewise erred in concluding that the language of Pfizer's Japanese label for Lipitor – which warned that "diabetes [mellitus] may occur" – referred only to "possible association" rather than causation. The warning label plainly advises that diabetes "may occur" *upon taking Lipitor*, which speaks to causation, not merely association.

Given the plain language of Dr. DeMicco's email, the district court could only have believed that Dr. DeMicco himself confused causation and association by writing "increases the risk" when he really meant "is associated with an increased risk." But that interpretation is inconsistent with Dr. DeMicco's own statement, which acknowledged that the effect of Lipitor at 10 mg is the same as the effect at 80 mg, which even the court acknowledges is causal. At any rate, at the summary judgment stage, the court was not entitled to impose its own gloss on Dr. DeMicco's words, or adopt Pfizer's gloss on them. *See, e.g., Fortress Re, Inc. v. Central Nat'l Ins. Co. of Omaha*, 766 F.2d 163, 166 (4th Cir. 1985) ("When conflicting inferences reasonably can be drawn from undisputed facts, summary judgment is inappropriate."). Whether Dr. DeMicco would be credible if he back-tracked from his own words is properly an issue for the jury.

3. The District Court Erroneously Granted Summary Judgment Based On An Invented State-Law Rule

The district court also held that Pfizer's admissions were inadequate to create a triable fact issue because, notwithstanding the Federal Rules, party admissions "could not replace expert testimony when expert testimony is required by substantive state law." JA__(CMO 100, at 48). That ruling was legally erroneous, for three reasons.

First, the district court erred in holding that the substantive laws of all 35 states in this MDL preclude use of admissions to prove causation. As the court

conceded, not a single case from any of the states in the MDL holds that defendant admissions cannot be used to prove general causation. *See, e.g.*, JA__-__(*id.* at 23-24) (acknowledging that "state courts have not had an opportunity to pass on the specific question" whether "party-opponent admissions can substitute for expert evidence"); JA__(*id.* at 41) (acknowledging that it could find no state court cases addressing the question). The most the court could muster is cases standing generally for the proposition that expert evidence is required on complex medical issues, from which it purported to "predict" under the *Erie* doctrine that all 35 states would bar proof through Defendants' own admissions. But cases saying that *lay testimony* cannot substitute for expert testimony fall far short of establishing that *any* state – much less *all* of them – would depart from the well-settled principle that a party's own words can be used as substantive evidence.

Indeed, use of a defendant's own admissions is wholly consistent with state-law policies to the extent they preclude use of lay testimony when "the lay jury does not possess the experience or knowledge of the subject matter sufficient to enable them to reach an intelligent opinion without help." JA__(*Id.* at 31). Lay juries do not need help to reach an intelligent opinion when a defendant's own admissions are involved, because the factual question is one of witness credibility, not scientific reliability. *See United States v. Goins*, 11 F.3d 441, 443-44 (4th Cir. 1993) ("No guarantee of trustworthiness is required in the case of an admission.")

(quoting Fed. R. Evid. 801(d)(2) advisory committee's note); *Jordan v. Binns*, 712 F.3d 1123, 1128 (7th Cir. 2013) ("Treating party admissions as nonhearsay is rooted in the nature of the adversarial system, and trustworthiness is not a requirement for admission."). Indeed, witness credibility is the quintessential jury question. *See, e.g.*, *Glazebrook v. Murray*, 51 F.3d 266 (Table), 1995 WL 140681, at *1 (4th Cir. 1995) (per curiam). The district court erred in refusing to apply the Federal Rules because they do not conflict with any state-law rule or state policy.

Second, even if there were a conflict, the Federal Rules would preempt state law. Because the original Federal Rules of Evidence, including Rule 801(d), were enacted by Congress, they govern in diversity cases "without regard to the *Erie* doctrine." 9A Charles A. Wright et al., *Federal Practice and Procedure* § 2405 (3d ed. 2008); *see Sims v. Great Am. Life Ins. Co.*, 469 F.3d 870, 880 (10th Cir. 2006) ("*Erie* is inapplicable to the Federal Rules of Evidence."). Unless the Federal Rules themselves provide that state substantive law should apply, which Rule 801(d)(2) does not, they preempt even contrary state law. *See* 19 Charles A. Wright et al., *Federal Practice and Procedure* § 4512 (2016). And certainly *speculation* that a state *might* adopt a particular substantive rule is not sufficient to displace federal law. *See In re C.R. Bard, Inc., MDL. No. 2187, Pelvic Repair Sys. Prods. Liab. Litig.*, 810 F.3d 913, 919 n.1 (4th Cir. 2016) (mere judicial "rulings"

cannot create a conflict with federal rules; only a "competing *rule*" can do so) (emphasis added).[44]

Third, the district court erred in its analysis of the federal-court cases that have directly addressed the use of party admissions to prove causation. In *Westberry*, this Court held that a defendant's admissions were sufficient to prove general causation. 178 F.3d at 264. The plaintiff there did not put forward a general causation expert, just a personal physician, who issued a specific causation opinion via differential diagnosis. *Id.* at 260, 263. As this Court noted, plaintiff's physician "had no scientific literature on which to rely to 'rule in' talc as a possible basis for [plaintiff's] sinus condition." *Id.* at 264. The only evidence on that score was the defendant's admission in a Material Safety Data Sheet ("MSDS") that talc could irritate mucous membranes, and this Court held that admission sufficient to establish general causation without additional expert evidence.

The district court attempted to distinguish *Westberry* on the ground that it held that the MSDS could support a reliable expert opinion, not that it could independently create a jury question on causation. *See* JA__(CMO 100, at 44

[44] The district court correctly cited this Court's admonition that courts sitting in diversity should proceed "conservatively" when making *Erie* predictions, JA__(CMO 100, at 24) (citing *Rhodes v. E.I. du Pont de Nemours & Co.*, 636 F.3d 88, 97-98 (4th Cir. 2011)), but it ignored that guidance and created a needless conflict with the Federal Rules by making a highly speculative *Erie* guess that 35 states would depart from our adversarial system's longstanding principle that party admissions are substantive evidence for the truth of the matter asserted.

n.18). On even the district court's erroneous reading of *Westberry*, summary judgment should have been denied because Dr. Singh should have been permitted to rely on Dr. DeMicco's admission to support his opinion that Lipitor at 10, 20, and 40 mg is associated with an increased risk of diabetes. In any event, it makes no sense to conclude that a defendant's admission of general causation can be the sole basis for a reliable expert opinion but cannot support a reasonable jury finding. To the contrary, the admission renders the expert opinion unnecessary. *See also Lewis v. Johnson & Johnson*, 601 F. App'x 205, 212 (4th Cir. 2015) (per curiam) (suggesting in *dicta* that defendant's own admissions could establish causation); *In re Accutane Prods. Liab.*, 511 F. Supp. 2d 1288, 1296 (M.D. Fla. 2007) (holding that if "[d]efendants ha[d] admitted Accutane causes [Inflammatory Bowel Disease] . . . this Court could have saved a lot of time – this opinion would have been unnecessary"); *Howell v. Centric Grp.*, No. 09-CV-02299-MSK-CBS, 2011 WL 4499372, at *5 (D. Colo. Sept. 27, 2011) (holding that the defendant statements in a MSDS "alone might be sufficient to raise an issue of fact regarding general causation"), *aff'd*, 508 F. App'x 834, 836 (10th Cir. 2013) ("[T]he MSDS might alone be sufficient to show that anise oil could cause injury.").

The district court's reasoning also conflicts squarely with *In re Meridia Products Liability Litigation*, 328 F. Supp. 2d 791 (N.D. Ohio 2004) ("*Meridia I*"), *aff'd sub nom. Meridia Products Liability Litigation Steering Committee v. Abbott*

Labs., 447 F.3d 861, 866 (6th Cir. 2006) ("*Meridia II*"). In *Meridia*, the district court held that the warning on defendant's product label that "Meridia substantially increases blood pressure in some patients" constituted an admission of general causation sufficient to survive summary judgment, *Meridia I*, 328 F. Supp. 2d at 810, and the Sixth Circuit agreed, *see Meridia II*, 447 F.3d at 866. The *Meridia* warning language ("Meridia substantially increases blood pressure in some patients") and Dr. DeMicco's statement ("[a]torvastatin increases the risk of developing diabetes" (JA__(CMO 100, at 45))) are indistinguishable in substance, and the court should have followed *Meridia* in holding that Pfizer's admission here likewise was sufficient to overcome summary judgment.

The district court attempted to distinguish *Meridia* on the ground that the admission in *Meridia* was "the product of discussion between the FDA and the regulated party, not a statement by one employee shot off in an email." JA__(*Id.* at 49). But that ruling impermissibly invades the *jury's* province to determine the *weight* to be given the admission. A reasonable jury could certainly reject any suggestion that Dr. DeMicco made an ill-considered remark in a "shot off" email. Indeed, Dr. DeMicco himself said that the finding of causation would have [redacted] and he and Dr. Waters later published their findings. *See* JA__-__(Waters (2011)). The court also suggested that *Meridia* was wrong because it "assumed [that] no state law required expert testimony to prove causation." JA__-

__(CMO 100, at 42-43). But, as explained above, that assumption is correct – there is not a single state-court case holding that party admissions cannot be used to prove causation. And even if there were such a state-law rule, it would be preempted by the Federal Rules of Evidence.

The district court's reliance on *In re Mirena IUD Products Liability Litigation*, Nos. 13-MD-2434 (CS) *et al.*, 2016 WL 4059224, at *9 (S.D.N.Y. July 28, 2016), *appeal pending*, Nos. 16-2890 *et al.* (2d Cir.), was likewise erroneous. Much of *Mirena*'s analysis, by the court's own admission, "wad[ed] into the policy implications" of permitting a drug company's warning label to substitute for expert testimony. JA__(CMO 100, at 43). But those policy considerations have no bearing on a party's own admissions in internal documents, such as Dr. DeMicco's email. Moreover, federal courts are not permitted to override the Federal Rules in particular cases based on policy concerns. Under a straightforward application of the Federal Rules, Pfizer's admissions created a genuine issue of material fact as to general causation, there is no basis in state law to override those rules, and district the court therefore erred in granting summary judgment.

II. The Court's MDL-Wide Grant of Summary Judgment On Specific Causation Suffered From Multiple Legal Errors

A. The Court's Grant Of Summary Judgment On Specific Causation In *Hempstead* Should Be Reversed

1. Dr. Murphy Conducted A Reliable Differential Diagnosis To Conclude That Lipitor Was A Substantial Contributing Factor In Ms. Hempstead's Diabetes

Dr. Elizabeth Murphy is a Professor of Clinical Medicine at the University of California, San Francisco, and Chief of the Division of Endocrinology and Metabolism and Director of the Diabetes Center at San Francisco General Hospital. JA__(Murphy Rep. 2 (Dkt. 1006-1)). She has a doctoral degree in biochemistry from Oxford and an M.D. from Harvard Medical School. *Id*. It is undisputed that Dr. Murphy is a highly qualified medical expert. JA__(CMO 55, at 11).

Based on more than 20 years of experience as a practicing endocrinologist, her extensive review of Ms. Hempstead's medical records, and her own independent review of the scientific literature, Dr. Murphy performed a differential diagnosis and concluded that Lipitor was a substantial contributing factor in Ms. Hempstead's diabetes.

Dr. Murphy explained that at the time Ms. Hempstead began taking Lipitor, she had a normal fasting glucose, but that after two years of taking Lipitor, her fasting glucose increased to 114 mg/dL putting her in the [redacted] JA__(Murphy Rep. 15). Dr. Murphy explained [redacted]

[redacted] JA__(*Id.* at 10). [redacted]

Id. In February 2004, approximately four and a half months after she restarted Lipitor, Ms. Hempstead's random blood glucose [redacted] JA__(*Id.* at 15). In May 2004, seven months after resuming her Lipitor use, [redacted] JA__(*Id.* at 10).

Dr. Murphy's differential diagnosis comprehensively evaluated the potential role of eleven other known risk factors for diabetes – [redacted] – and provided reasoned explanations for her conclusion that they alone did not cause Ms. Hempstead's diabetes. JA__-__(*Id.* at 11-15). Dr. Murphy ruled out factors (5) through (11) because Ms. Hempstead did not have those risk factors. JA__(*Id.* at 15). She then persuasively ruled out the four remaining risk factors.

As to family history, Dr. Murphy explained that [redacted] JA__(*Id.* at 11). [redacted]

[redacted] JA__(*Id*. at 12). Given the [redacted] risk from having a large family [redacted] Dr. Murphy concluded it was insufficient to explain her diabetes. JA__, __(*Id.* at 12, 15).

As for weight and BMI, Dr. Murphy noted that at the first follow-up after her hospital discharge, Ms. Hempstead had a [redacted] JA__(*Id*. at 10). Ms. Hempstead has [redacted] JA__(*Id*. at 13). Dr. Murphy categorized Ms. Hempstead as "[m]oderate[ly] physical[ly] active," noting that, as a middle and high school principal, Ms. Hempstead "had significant daily activity" and that she testified that she exercised three days a week. *Id.* This activity level "did not put [Ms. Hempstead] at increased risk of diabetes." *Id*.

Dr. Murphy explained that [redacted] JA__, __(*Id*. at 8, 11). As to age, Dr. Murphy noted that Ms. Hempstead [redacted] JA__(*Id.* at 12). Dr. Murphy explained that "[b]ecause age is easy to measure and is an established risk factor," "all adjusted risk assessments adjust for age." JA__-__(*Id*. at 12-13).

Dr. Murphy also considered a number of other risk factors. She noted that Ms. Hempstead was on [redacted], which can potentially increase blood glucose due to low potassium levels, but concluded that any increased

diabetes risk was minimal because Ms. Hempstead's [redacted] JA__-__(*Id.* at 13-14). Finally, Dr. Murphy noted that Ms. Hempstead is a former occasional smoker, but that her smoking was neither "significant [n]or recent enough to constitute a significant risk factor for the development of diabetes." JA__(*Id.* at 15).

Based on her in-depth evaluation of all of Ms. Hempstead's risk factors, Dr. Murphy concluded that her ingestion of Lipitor was a "substantial contributing factor" in her development of diabetes. JA__(*Id.* at 16).

2. The District Court Committed Reversible Error By Excluding Dr. Murphy Based On A Mischaracterization of Her Opinions

There is no dispute about the reliability of differential diagnosis, which this Court has called "a standard scientific technique of identifying the cause of a medical problem by eliminating the likely causes until the most probable one is isolated." *Westberry*, 178 F.3d at 262; *see id.* at 263 ("the overwhelming majority of the courts of appeals that have addressed the issue have held that a medical opinion on causation based upon a reliable differential diagnosis is sufficiently valid to satisfy the first prong of the Rule 702 inquiry").

The district court abused its discretion in holding that Dr. Murphy did not reliably perform her differential diagnosis because it mischaracterized Dr.

Murphy's opinion as based solely on the fact "that Ms. Hempstead developed diabetes after taking Lipitor." JA__(CMO 55, at 11). Dr. Murphy made clear that while temporal proximity was a necessary condition for her causation opinion, she also systematically considered all of Ms. Hempstead's other risk factors and, in the exercise of her medical judgment, concluded that they did not account for Ms. Hempstead's diabetes. The court also caricatured Dr. Murphy's opinion when it stated that "so long as the patient took Lipitor and developed diabetes," Dr. Murphy would conclude that Lipitor "was a substantial contributing factor." JA__(*Id.* at 27). In fact, at her deposition, Dr. Murphy said the opposite. JA__, __(Murphy Dep. 123:16-20, 124:8-19 (Dkt. 1006-3)). It was reversible error for the court to exclude Dr. Murphy based on a mischaracterization of her opinions. *See Seamon v. Remington Arms*, 813 F.3d 983, 989 (11th Cir. 2016) (reversing exclusion of causation expert for failing to consider alternative causes when he actually did so).

The district court also held that Dr. Murphy's differential diagnosis was unreliable because she could not definitively exclude the possibility that Ms. Hempstead's BMI, adult weight gain, family history, age, hypertension, and metabolic syndrome contributed to her diabetes. JA__-__(CMO 55, at 16-19). But it is well settled in this Court and other Circuits that a differential diagnosis need not conclusively rule out every other potential contributing factor. *See Westberry*,

178 F.3d at 265; *Cooper v. Smith & Nephew, Inc.*, 259 F.3d 194, 202 (4th Cir. 2001). Rather, unless the expert "utterly fails to consider alternative causes or fails to offer an explanation for why the proffered alternative cause was not the sole cause," criticisms like the district court's "affect the weight that the jury should give the expert's testimony and not the admissibility of that testimony." *Id.*; *accord Best v. Lowe's Home Ctrs., Inc.*, 563 F.3d 171, 182 (6th Cir. 2009) ("Any weaknesses in [a doctor's differential diagnosis] will affect the weight that his opinion is given at trial, but not its threshold admissibility."); *Kudabeck v. Kroger Co.*, 338 F.3d 856, 861-62 (8th Cir. 2003) ("[A]ttacks regarding the completeness of [a doctor's] methodology go to the weight and not the admissibility of his testimony."); *Granfield v. CSX Transp., Inc.*, 597 F.3d 474, 487 (1st Cir. 2010) ("[D]isputes as to . . . [an expert's] use of differential etiology . . . go[es] to the weight, not the admissibility, of his testimony."); *McCullock v. H.B. Fuller Co.*, 61 F.3d 1038, 1044 (2d Cir. 1995) (same); *Zuchowicz v. United States*, 140 F.3d 381, 387 (2d Cir. 1998) (same); *Kennedy v. Collagen Corp.*, 161 F.3d 1226, 1230-31 (9th Cir. 1998) (same); *Kannankeril v. Terminix Int'l, Inc.*, 128 F.3d 802, 808 (3d Cir. 1997) (same).

The district court was candid in its view that *no* expert could have performed a reliable differential diagnosis to determine the cause of Ms. Hempstead's diabetes, because diabetes has multiple risk factors and "[t]here is no test that tells

us" that Lipitor caused a given individual's diabetes. JA__-__(Hr'g Tr. 68:22-69:5 (Dkt. 1634)). The court's view that a reliable differential diagnosis is *impossible* in this case demonstrates that it applied the wrong legal standard. As the Ninth Circuit stated in *Messick v. Novartis Pharmaceuticals Corp.*, 747 F.3d 1193 (9th Cir. 2014), "we do not require that an expert be able to identify the sole cause of a medical condition in order for his or her testimony to be reliable. . . . [T]he district court abused its discretion in excluding Dr. Jackson's causation testimony when it found that testimony to be unreliable largely because Dr. Jackson could not 'determine in a patient who has multiple risk factors at one time which of those particular risk factors is causing [the disease].' Such an unduly exacting standard goes beyond the district court's proper gatekeeping role." *Id.* at 1199.

As with general causation, the district court usurped the role of the jury to decide the weight to be given to Dr. Murphy's opinions. Dr. Murphy performed a rigorous evaluation of Ms. Hempstead's medical condition and history, and provided reasoned explanations for her conclusion that Lipitor was a substantial contributing cause. That is exactly what Dr. Murphy would have done for any patient that came into her treatment room, and precisely what *Daubert* requires. It was improper under Rule 702 for the court to play amateur scientist and substitute its own conclusions for those of one of the nation's foremost medical doctors, with two decades of medical training.

B. This Court Should Vacate The District Court's Omnibus Grant Of Summary Judgment on Specific Causation In All Non-Bellwether Cases

If the exclusion of Dr. Murphy's opinions is reversed, the grant of summary judgment on summary judgment in all cases should be reversed. Independent of the admissibility of Dr. Murphy's testimony, this Court should vacate the district court's grant of summary judgment on specific causation in the non-bellwether cases because the district court's omnibus procedure was improper. *See* JA__-__, __-__, __-__(CMOs 99, 100, and 109).

1. Specific Causation Was Not Appropriately Resolved On An Omnibus Basis Because It Raises Individualized, Plaintiff-Specific Issues Under Various State-Law Standards

The MDL statute provides that "[w]hen civil actions *involving one or more common questions of fact* are pending in different districts, such actions may be transferred to any district for coordinated or consolidated pretrial proceedings." 28 U.S.C. § 1407(a) (emphasis added). But "merits questions that are predicated on the existence or nonexistence of historical facts *unique to each Plaintiff* . . . generally are not amenable to across-the-board resolution" by an MDL court. *In re Fosamax (Alendronate Sodium) Prods. Liab. Litig.*, 852 F.3d 268, 2017 WL 1075047, at *24 (3d Cir. 2017) (emphasis added). As the Third Circuit stated recently, "[a] mass tort MDL is not a class action." *Id.* Where issues raise individualized facts, "[e]ach Plaintiff deserves the opportunity to develop those

sort of facts separately, and the District Court's understandable desire to streamline proceedings cannot override the [p]laintiffs' basic trial rights." *Id.*

The issue of specific causation is clearly individualized and thus not appropriate for resolution on an MDL-wide basis. Among the thousands of individual Plaintiffs in this MDL, there is substantial variation in the dosage of Lipitor, family history and other risk factors for diabetes, the temporal relationship between exposure to Lipitor and the onset of disease, and numerous other factors relevant to whether, under governing state law, a given Plaintiff could convince a reasonable jury of causation by a preponderance of the evidence. For example, [redacted] a Georgia plaintiff, had a family history of diabetes, had hypertension herself and high triglycerides, and a normal body mass index ("BMI") (21.3) when she was diagnosed with diabetes, a mere 78 days after she began treatment. By contrast, [redacted] a Florida plaintiff, had no history of hypertension or high triglycerides, and was diagnosed 115 days after she began Lipitor treatment.

Because of the fact-intensive nature of specific causation, the Manual for Complex Litigation states: "Where causation issues dominate litigation, it may be appropriate for the transferee court in an MDL proceeding to conduct a *Daubert* hearing on general causation issues, leaving specific causation issues for the transferor courts on remand. Such a division in the appropriate case efficiently

separates the role of the MDL court from that of the trial courts after remand." Manual of Complex Litigation (Fourth) § 22.87 (2004) (footnote omitted); *see also Sterling v. Velsicol Chem. Corp.*, 855 F.2d 1188 (6th Cir. 1988) (specific causation requires individualized proceedings in class actions).

Remand to the transferor court for adjudication of specific causation is standard MDL practice. *See, e.g., In re Activated Carbon-Based Hunting Clothing Mktg. & Sales Practices Litig.*, 840 F. Supp. 2d 1193, 1201 (D. Minn. 2012) ("Although the Court is leaving some pretrial work undone by suggesting remand, it believes that the central purpose of the JPML referral has been achieved now that discovery is over, class certification has been denied, and what remain are a handful of cases requiring *individualized proof on many state-specific issues*.") (emphasis added); *In re Factor VIII or IX Concentrate Blood Prods. Litig.*, 169 F.R.D. 632, 639 (N.D. Ill. 1996) ("We see no point in retaining jurisdiction of the cases during the case-specific discovery, which can probably be best conducted after remand.").

It was particularly inappropriate for the district court to grant omnibus summary judgment because of material variations in state law governing the standard of proof for specific causation. *See In re Light Cigarettes Mktg. Sales Practices Litig.*, 832 F. Supp. 2d 74, 77 (D. Me. 2011) ("[T]ransferor courts, each of which is familiar with the state law of their respective jurisdictions, are in a

better position to assess the parties' state law arguments."). Under the substantive law of many states, for example, expert evidence is not the only means to prove specific causation. Rather, a plaintiff may prove specific causation through a combination of expert and nonexpert evidence, even though neither would alone be sufficient. *See In re C.R. Bard*, 810 F.3d at 929 (calling it "established under Georgia law" that plaintiffs "may present medical as well as non-medical evidence to show causation"); *accord Estate of Patterson v. Fulton-DeKalb Hosp. Auth.*, 505 S.E.2d 232, 236 (Ga. Ct. App. 1998) (expert testimony showing a "reasonable possibility rather than a probability" is sufficient in conjunction with nonexpert evidence); *see also, e.g.*, *Hills v. Ozark Border Elec. Coop.*, 710 S.W.2d 338, 341 (Mo. Ct. App. 1986) (per curiam); *Smith v. Hines*, 261 P.3d 1129 (Okla. 2011) (reversing summary judgment).[45]

The difference in that substantive standard of proof directly affects the analysis of the reliability of any expert testimony under Rule 702, because the expert need only have "sufficient facts and data" to support the *possibility* of specific causation if other nonexpert evidence exists. In *Hempstead*, the district court found Dr. Murphy's specific causation opinion unreliable because she "offer[ed] no data or facts to make the leap from a possibility to a probability that Lipitor was a substantial contributing factor." JA__(CMO 55, at 27). But under a

[45] Plaintiffs' research found at least 13 states that have adopted this rule.

standard requiring expert evidence only to show a possibility that Lipitor could have caused a particular plaintiff's diabetes, the facts and data relied on by Dr. Murphy would have been sufficient to support a reliable conclusion that specific causation was *possible*. And under the law of numerous states, that reliable opinion would be sufficient to survive summary judgment if Plaintiffs could adduce circumstantial or other nonexpert evidence to permit a reasonable jury "to make the leap from a possibility to a probability." *Id.*; *see*, *e.g.*, *McCarney v. PA Lex Glen, LLC*, 784 S.E.2d 438, 441 (Ga. Ct. App. 2016) ("[E]ven if the medical testimony had been stated only in terms of 'possible' cause, it would be sufficient because it is supplemented by probative nonexpert testimony on causation.") (reversing summary judgment).[46] Given the need to apply varying state laws to the different facts of each case, the issue of specific causation is not properly "coordinated or consolidated" and should be left to the transferor court. *See* 28 U.S.C. § 1407(a) (actions "shall be remanded" after completion of coordinated proceedings).

[46] The district court was thus incorrect that summary judgment turns on the pure legal question of "whether a claim can survive summary judgment without expert testimony on specific causation." JA__(CMO 99, at 41).

2. Non-Bellwether Plaintiffs Are Entitled To Further Proceedings On Specific Causation Notwithstanding The MDL Court's Improper Omnibus Procedures

The district court attempted to short-circuit the need for individualized case-specific analysis through an omnibus summary judgment procedure that is inconsistent with the MDL statute. Under the court's initial case management orders, only two cases – *Hempstead* and *Daniels* – were selected as bellwether cases, and disclosure of Plaintiffs' case-specific expert reports was required *only* for those two cases. JA__(CMO 19, at 5). The court erroneously excluded the specific causation expert opinion of Dr. Murphy in *Hempstead* on December 11, 2015, in a ruling addressed above. *See supra* p. 29. By that time, the court had also already excluded the general causation opinions of Dr. Jewell and precluded his critical re-analysis of Pfizer's own ASCOT data. *See* JA__(CMO 54). And it had erroneously and severely hamstrung the ability of Dr. Singh to render a general causation expert opinion by requiring him to support it with statistically significant evidence at each individual Lipitor dose. *See id.*

Despite having already crippled their cases, the district court issued a show-cause order (JA__(CMO 65) that required any Plaintiff in the MDL as of that date (January 25, 2016) to come forward if she believed she could adduce a differential diagnosis that could survive *Daubert* notwithstanding the exclusion of Dr. Murphy's expert testimony in *Hempstead*. *See id.* The order provided that the

court would then set a schedule for expert reports, expert discovery, and further dispositive motion practice. In short, the court put thousands of individual plaintiffs in the untenable position of having to go through full-blown fact and expert discovery on a case-specific issue even though the court had all but doomed their cases through its erroneous general causation rulings and the erroneous exclusion of Dr. Murphy's opinions in *Hempstead*.

Plaintiffs' decision not to come forward with new specific causation experts under these circumstances cannot constitute waiver of their right to individualized proceedings, and summary judgment should not have been granted until they had a fair opportunity to develop case-specific evidence. *See, e.g.*, *Call Ctr. Techs., Inc. v. Interline Travel & Tour, Inc.*, 622 F. App'x 73, 74-75 (2d Cir. 2015) (holding that an issue that "will not be considered waived unless a party had both an opportunity and an incentive to raise it"). Indeed, courts have long recognized that a ruling made under circumstances where the party lacks the ability to litigate the case does not give the party his proper day in court. *See Canonsburg Gen. Hosp. v. Sebelius*, 989 F. Supp. 2d 8, 30 (D.D.C. 2013) ("[A] party" who "has had its day in court" has "every incentive to litigate its case fully."), *aff'd*, 807 F.3d 295 (D.C. Cir. 2015).

3. The District Court's Summary Judgment In CMO 109 Was Reversible Error Because Those Plaintiffs Had No Meaningful Opportunity To Litigate Specific Causation

The prejudicial effect of the district court's omnibus procedure was especially severe for the CMO 109 appellants, who did not even become part of this MDL until after January 25, 2016, the date of the court's first show-cause order (JA__(CMO 65)). Recognizing that its initial show-cause order could not even arguably bind these Plaintiffs, the court issued a new show-cause order on January 2, 2017, requiring them to come forward with additional specific causation evidence. JA__(CMO 101). Their objection to those procedures was well founded. By that time, the court had definitively excluded Dr. Singh's dose-specific general causation opinions and Dr. Jewell's ASCOT and NDA opinions, and it had further held that no Plaintiff could survive summary judgment on general causation. *See* JA__-__(CMO 100, at 51-52). The CMO 109 Plaintiffs had literally *no* reason to litigate specific causation insofar as the Court's general causation rulings were fatal to their claim. It was procedurally improper to grant summary judgment on specific causation against these Plaintiffs under those circumstances.

CONCLUSION

For the foregoing reasons, the district court's grant of summary judgment to Defendants should be reversed.

REQUEST FOR ORAL ARGUMENT

Plaintiffs respectfully request oral argument, which would be helpful to the Court because this appeal presents an extensive procedural and factual record and several important legal questions affecting claims brought by more than 3,000 injured plaintiffs in a nationwide MDL. These questions are also of broader significance to the legal standards governing other mass-tort cases beyond this MDL. Plaintiffs would welcome an opportunity to address the Court and respond to any questions the Court may have.

Respectfully submitted,

/s/ *Derek T. Ho*

H. Blair Hahn
Christiaan A. Marcum
RICHARDSON, PATRICK, WESTBROOK & BRICKMAN, LLC
1037 Chuck Dawley Blvd.
Mt. Pleasant, SC 29464
Telephone: (843) 727-6500
Facsimile: (843) 727-6642
bhahn@rpwb.com
cmarcum@rpwb.com

Derek T. Ho
Silvija A. Strikis
Hilary P. Gerzhoy
KELLOGG, HANSEN, TODD, FIGEL & FREDERICK, P.L.L.C.
1615 M Street, N.W., Suite 400
Washington, D.C. 20036
Telephone: (202) 326-7900
Facsimile: (202) 326-7999
dho@kellogghansen.com
sstrikis@kellogghansen.com
hgerzhoy@kellogghansen.com

Counsel for Plaintiffs-Appellants

April 21, 2017

CERTIFICATE OF COMPLIANCE WITH TYPE-VOLUME LIMIT

Pursuant to Federal Rule of Appellate Procedure 32(g)(1), this brief complies with the Court's March 2, 2017 order allocating Plaintiffs 19,500 words for their opening brief. Excluding the parts exempted by Federal Rule of Appellate Procedure 32(f), this brief contains 19,500 words.

This brief complies with the typeface and type style requirements because this brief was prepared using a proportionally spaced typeface using Microsoft Word 2013 (Times New Roman, 14 point). This certificate was prepared in reliance on the word-count function of the word-processing system (Word 2013) used to prepare this brief.

/s/ *Derek T. Ho*
Derek T. Ho

April 21, 2017

CERTIFICATE OF SERVICE

I hereby certify that, on April 21, 2017, I electronically filed the foregoing REDACTED Page-Proof Opening Brief for Plaintiffs-Appellants with the Clerk of the Court for the United States Court of Appeals for the Fourth Circuit using the appellate CM/ECF system. Participants in the case who are registered CM/ECF users will be served by the appellate CM/ECF system.

/s/ *Derek T. Ho*
Derek T. Ho