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November 11, 2015

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BY FEDERAL EXPRESS
Mr. Joseph H. Orlando
Appellate Division Clerk
P.O. Box 006
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Re: In re: Accutane® Litigation
Docket No. A-4698-14T1

Dear Mr. Orlando:

Hollingsworth LLP represents the Pharmaceutical Research and Manufacturers of America ("PhRMA") in the above-referenced matter. PhRMA submits this Motion for Leave to Appear as Amicus Curiae "on or before the day when the last brief is due from any party," which is on November 30, 2015. R. 1:13-9(c). On behalf of PhRMA, enclosed for filing please find an original and six (6) copies of the following:

1. Notice of Motion for Leave to Appear as Amicus Curiae;
2. Certification of Gregory S. Chernack;
3. Proposed Amicus Brief; and
4. Certification of Service.

Kindly return a stamped "Filed" copy of each document (a prepaid envelope has been provided).

Respectfully submitted,

Gregory S. Chernack

Enclosures

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IN RE: ACCUTANE® LITIGATION

SUPERIOR COURT OF NEW JERSEY
APPELLATE DIVISION

DOCKET NO.: A-4698-14T1

On Appeal from Superior Court,
Law Division, Atlantic County
Case No. 271

Sat Below:
Hon. Nelson C. Johnson, J.S.C.

NOTICE OF MOTION ON BEHALF OF THE PHARMACEUTICAL RESEARCH AND MANUFACTURERS OF AMERICA FOR LEAVE TO APPEAR AS AMICUS CURIAE

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PLEASE TAKE NOTICE that the Pharmaceutical Research and Manufacturers of America ("PhRMA") hereby moves pursuant to Rule 1:13-9 before the Superior Court of New Jersey, Appellate Division, for an Order allowing it to appear in this matter pursuant to Rule 1:13-9 as amicus curiae and to file an amicus brief.

PLEASE TAKE FURTHER NOTICE that PhRMA will rely on the accompanying Certification of Gregory S. Chernack identifying

the applicant's identity, the issue to be addressed, the nature of the public interest, and the applicant's special interest as amicus curiae in this matter.

Respectfully submitted,

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Dated: November 11, 2015

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IN RE: ACCUTANE® LITIGATION	SUPERIOR COURT OF NEW JERSEY APPELLATE DIVISION DOCKET NO.: A-4698-14T1 On Appeal from Superior Court, Law Division, Atlantic County Case No. 271 Sat Below: Hon. Nelson C. Johnson, J.S.C.

CERTIFICATION OF GREGORY S. CHERNACK IN SUPPORT OF PHARMACEUTICAL RESEARCH AND MANUFACTURERS OF AMERICA MOTION FOR LEAVE TO APPEAR AS *AMICUS CURIAE*

I, Gregory S. Chernack, hereby certify as follows:

1. I am a member of the bar of the State of New Jersey and a partner with Hollingsworth LLP, attorneys for the Pharmaceutical Research and Manufacturers of America ("PhRMA"), which seeks leave to file a motion for leave to appear as *amicus curiae* in the above-captioned matter.

2. If leave is granted, PhRMA will address the vital role played by New Jersey trial courts in serving as gatekeepers

against the admission of scientifically unreliable expert testimony in the courtroom. Its brief would seek to assist the court in understanding how scientists outside the courtroom would view the methodology applied by plaintiff's experts in reaching their causation opinions below.

3. PhRMA is a voluntary nonprofit association representing the country's leading innovative biopharmaceutical research companies, which are devoted to discovering and developing medicines that enable patients to live longer, healthier, and more productive lives.

4. PhRMA's mission is to conduct effective advocacy for public policies that encourage discovery of important new medicines for patients by pharmaceutical and biotechnology research companies.

5. PhRMA has filed numerous briefs as *amicus curiae* in courts of this state and around the nation, presenting perspectives relevant to the defense of civil lawsuits and to promote improvements in the administration of justice.

6. The issues involved in this matter are of significant public interest as New Jersey is home to many pharmaceutical and medical device manufacturers, and has strong public policies to encourage product safety and promote public health.

7. PhRMA's brief as *amicus curiae* will help the Court put in proper context the issues before the Court on this appeal.

I hereby certify that the foregoing statements are true to the best of my knowledge, information and belief. I am aware that if any of the foregoing statements are willfully false, I am subject to punishment.

Gregory S. Chernack

Dated: November 11, 2015

IN RE: ACCUTANE® LITIGATION	SUPERIOR COURT OF NEW JERSEY APPELLATE DIVISION DOCKET NO.: A-4698-14T1 On Appeal from Superior Court, Law Division, Atlantic County Case No. 271 Sat Below: Hon. Nelson C. Johnson, J.S.C.

AMICUS CURIAE BRIEF OF PHARMACEUTICAL RESEARCH AND MANUFACTURERS OF AMERICA IN SUPPORT OF DEFENDANTS-RESPONDENTS

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Donald Berry, *Multiplicities in Cancer Research: Ubiquitous and Necessary Evils*, 104(15) J. Nat. Cancer Inst. 1124 (2012) 18

Drug Development, *Costs of Developing A New Drug* (Nov. 18, 2004) 3

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Howard Hu & Frank E. Speizer, *Influence of Environmental and Occupational Hazards on Disease* in Harrison's Principles of Internal Medicine 19 (Braunwald, *et al.* eds. 15th ed. 2001) 25

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J.A. Arnaiz *et al.*, *The use of evidence in pharmacovigilence: Case reports as the reference source for drug withdrawals*, 57 Eur. J. Clin. Pharmacol 89 (2001) 25

J. Ashby & R.W. Tenant, *Prediction of Rodent Carcinogenicity for 44 Chemicals: Results*, 9 Mutagenisis 7 (1994) 23, 24

John R. Thompson, *Invited Commentary: Re: "Multiple Comparisons and Related Issues in the Interpretation of Epidemiologic Data,"* 147 Am. J. Epid. 801 (1998) 18

Karl K. Rozman & Curtis D. Klaassen, *Absorption, Distribution, and Excretion of Toxicants*, in Casarett & Doull's Toxicology: The Basic Science of Poisons (6th ed. 2001) 21

M.N.G. Dukes, *et al.*, *Responsibility for Drug-Induced Injury: A Reference Book for Lawyers, the Health Professionals and Manufacturers* 45 (2d ed. 1998) 27

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Michael D. Green *et al.*, *Reference Guide on Epidemiology*, Reference Manual on Scientific Evidence 555 (3d ed. 2011) 13, 14, 17

Neil Shanks *et al.*, *Are Animal Models Predictive for Humans?*, Philosophy, Ethics and Humanities in Medicine 4:1 (2009) 20

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NTP Report on Carcinogens Background Document for Saccharin (March 1999) 20

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Ronald H.B. Mayboom *et. al.*, *Causal or Casual? The Role of Causality Assessments in Pharmacovigilance*, 17 Drug Safety 374 (1997) 27, 28

S. Stanley Young & Alan Karr, *Deming, Data and Observational Studies: A Process Out of Control and Needing Fixing*, Significance 116 (2011) 17

Survey and Status Report, 13 SAR and QSAR in Environmental Research 1 (2002) 23

I. STATEMENT OF INTEREST

Amicus curiae Pharmaceutical Research and Manufacturers of America ("PhRMA") represents the country's leading innovative biopharmaceutical research companies, which are devoted to discovering and developing medicines that enable patients to live longer, healthier, and more productive lives. PhRMA submits this brief to urge the Court to reaffirm the vital role played by New Jersey trial courts in serving as gatekeepers against the admission of scientifically unreliable expert testimony in the courtroom.

PhRMA has a particular interest in preserving the fair adjudication of scientific issues in New Jersey courts. Because of its proximity to a number of the nation's leading academic and research centers and to two of the nation's largest cities, New Jersey has long been a leader in the pharmaceutical, medical device, and biotechnology industries (i.e., the biopharmaceutical industry). Described by former Governor Jon S. Corzine as the "Medicine Chest of the World," Governor Jon S. Corzine, Press Release (Aug. 18, 2008), the state is home to 14 of the 20 largest pharmaceutical companies, including Novartis Pharmaceuticals, Johnson & Johnson, and Merck. *See www.nj.gov/njbusiness/industry/pharmaceutical*. Indeed, Johnson & Johnson was founded in New Brunswick in 1886 and remains

headquartered there to this day. *See http://www.jnj.com/about-jnj/company-history*.

In addition to be being home to the majority of the nation's largest pharmaceutical companies, New Jersey has, as of 2013, more than 3,000 biopharmaceutical employers, employing over 115,000 workers. *See* New Jersey Dep't of Labor & Workforce Development ("NJDPWP"), Quarterly Census of Employment and Wages, 2013 Third Quarter & 2013 Annual Average. These employers paid over $15 billion in annual payroll, constituting 7.9% of the State's total wages (despite only 3.6% of total employment). *See* New Jersey Dep't of Labor & Workforce Development ("NJDPWP"), Quarterly Census of Employment and Wages (2013). These companies added $33.54 billion to the State's 2012 Gross Domestic Product. *See Life Sciences in New Jersey: Looking Beyond Biotech*, BioNJ (2013 Study).

New Jersey has played an active role in supporting growth in these sectors though a historically favorable tax and regulatory climate. This includes providing grants and tax credits to these companies, *see www.nj.gov/njbusiness/industry/pharmaceutical*, and through government programs under the rubric of the "Edison Innovation Fund," *see www.njeda.com/technology_lifesciences/Edison-Innovation-Fund*. This Fund "seeks to develop, sustain, and grow technology and life sciences businesses that will lead to well-

paying job opportunities for New Jersey residents." *Id.* Moreover, New Jersey designated three "Edison Innovation Zones," each located around a research university. *See www.state.nj.us/scitech/university/izones.* Companies within these Zones are eligible for "enhanced financial incentives," including tax benefits and cash credits. *See www.state.nj.us/scitech/university/izones.* The State also provides an R&D transferrable tax credit for certain life science companies. *See www.njeda.com/technology_lifesciences/technology-business-tax-certificate-transfer-(NOL).*

PhRMA urges the Court to uphold the requirement of sound science in New Jersey courtrooms because any lesser standard could threaten the availability of needed medicines that are, themselves, the result of rigorous scientific testing. The pharmaceutical industry spent almost $50 billion in 2013 on research and development on compounds that are potential new medicines. *See* Tufts Center for the Study of Drug Development, *Costs of Developing A New Drug*, at slide 6 (Nov. 18, 2004) (slides available at http://csdd.tufts.edu/news/complete_story/cost_study_press_event_webcast). The average cost of obtaining approval for a single, new prescription medicine is now almost $2.6 *billion*. *See id.* at 5. These costs have skyrocketed, increasing from $179 million in the 1970s for research and development of each approved new medicine (calculated in 2013

dollars). *See* R.W. Hansen, *The Pharmaceutical Development Process: Estimates of Current Development Costs and Times and the Effects of Regulatory Changes, in Issues in Pharmaceutical Economics* 151-91 (R.I. Chien & D.C. Heath, eds., 1979).

These enormous costs are driven, to a substantial degree, by the rigorous scientific standards followed by the pharmaceutical industry to ensure that new drugs are both safe and effective. Under federal law, pharmaceutical companies must expend significant resources on drug development, particularly to perform the massive amount of testing necessary to generate scientifically reliable evidence of safety and efficacy needed for FDA approval. After researchers develop a compound that they believe may be a therapy for a disease for which there are no or few effective treatments, they engage in preclinical testing. This involves testing the compound in vitro (i.e., in cells) and in animals to ensure that the drug is safe for testing in humans and that signs of efficacy exist, after which the drug's sponsor submits an investigational new drug application to the FDA for approval to begin human testing. *See* 21 U.S.C. § 355(i); 21 C.F.R. § 312.1 *et seq.*

Assuming the FDA agrees that the compound is safe and possibly effective, human clinical trials can commence, which will usually last many years, occur in several phases, and the results of which are subject to FDA review. *See Riegel v.*

Medtronic, Inc., 552 U.S. 312, 343 n.15 (2008) (Ginsburg, J., dissenting) (discussing new drug approval process); 21 C.F.R. § 321. The initial phase (Phase 1)[1] takes place with typically under 100 volunteers to determine the safety, tolerability, and effects of the compound. *See Riegel*, 552 U.S. at 343 n.15. Phase II trials enlist between 100 and 500 volunteers to determine the efficacy and dose response of the compound. *See id.* Phase III trials - usually involving thousands of patients - occur across the United States and possibly around the world. *See id.* These controlled trials ensure that the drug is safe and effective, and the results of all of these studies are submitted to FDA for approval. *See id.* The sponsor then files a New Drug Application, which contains, among other things, the results of double-blind randomized controlled trials and the proposed labeling. *See* 21 U.S.C. § 355(b)(1). Only after examining all of this data will the FDA approve a new medicine, assuming the sponsor can demonstrate safety and efficacy.

Even after a drug is approved, pharmaceutical companies continue to expend resources to ensure that the drug is safe. Post-approval trials (Phase IV) monitor safety and long-term side effects and whether the drug is effective in other

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[1] A Phase 0 now exists for exploratory studies involving limited human exposure to a compound with no therapeutic or diagnostic goals. *See, e.g.*, Margot J. Fromer, *FDA Introduces New Phase 0 for Clinical Trials*, Oncology Times 18 (Aug. 10, 2006).

settings. *See, e.g., Fuja v. Benefit Trust Life Ins. Co.*, 18 F.3d 1405, 1410 (7th Cir. 1994). These trials, among other things, enable pharmaceutical companies to ensure that side effects that were not seen in the pre-approval trials do not arise when the drug is introduced to a larger population.

In 2013, almost 6,200 clinical trials (Phase 0-IV) were active in the United States with almost 1.15 million patients enrolled. *See* Battelle Technology Partnership Practice, *Biopharmaceutical Indusry-Sponsored Clinical Trials: Impact on State Economies*, at i (Mar. 2015). The average cost of these trials is $36,500 *per patient*. *See id.* at 6. In New Jersey alone, there were 1,234 active clinical trials, involving more the 25,000 individuals, with a total economic impact of approximately $617 million. *See id.* at 10.

II. ARGUMENT

The trial court below conducted a thorough and appropriate analysis of the flawed methodologies of the plaintiffs' causation experts, and PhRMA fully supports the arguments set forth in Appellee's brief, which demonstrates why that gatekeeping analysis should be upheld. PhRMA will not repeat those arguments here. Rather, PhRMA presents this amicus brief to assist the court in understanding how scientists outside the courtroom would view the methodology applied by plaintiff's experts in reaching their causation opinions below.

A. A Primer On The Bradford Hill Methodology Purportedly Relied Upon By Plaintiffs' Experts.

Plaintiffs' experts purport to base their causation opinion below on the Bradford Hill methodology. In so doing, they seek to bring their opinion within the scope of the New Jersey Supreme Court's favorable discussion of Bradford Hill in *Landigran v. Celotex Corp.*, 127 N.J. 404, 415-16 (1992). However, an expert cannot invoke Bradford Hill as a basis for admissibility of his opinion unless he can show that he has faithfully applied that methodology to the facts in the case. *See Soldo v. Sandoz Pharm. Corp.*, 244 F. Supp.2d 434, 561 (W.D. Pa. 2003) (in assessing the reliability of expert testimony, a court "should be wary that the [expert's] method has not been faithfully applied" (quoting *Lust v. Merrell Dow Pharm., Inc.*, 89 F.3d 594, 598 (9th Cir. 1996)). Plaintiffs' experts have not done so here.

In their appellate brief, plaintiffs jump directly to nine considerations identified by Sir Austin Bradford Hill in assessing whether an association between an exposure and an outcome can be deemed causal. Pb6. But as Bradford Hill explained in setting forth his methodology, an expert should not turn to these considerations to reach an opinion on causation until he first observes a statistically-significant association in the epidemiologic literature: "Our observations reveal an association between two variables, perfectly clear-cut and beyond

what we would care to attribute to the play of chance. What aspects of that association should we especially consider before deciding that the most likely interpretation of it is causation?" Austin Bradford Hill, *The Environment and Disease: Association or Causation*, 58 Proc. Royal Soc'y Med. 295, 295 (1965).

In *Landigran*, the New Jersey Supreme Court thus explained that the Bradford Hill methodology is used to determine whether an expert has "some basis for deciding whether a statistical association derived from an observational study represents a cause-and effect relationship[.]" 127 N.J. at 415-16. The Bradford Hill criteria are used "to assess likelihood of causal relationship from statistical associations"; they are not used in the absence of such a threshold finding. *Id.* at 416. The Federal Judicial Center, Reference Manual on Scientific Evidence (3d. ed. 2011) agrees: "In a number of cases, experts attempted to use these [Bradford Hill] guidelines to support the existence of causation in the absence of any epidemiologic studies finding an association.... There may be some logic to that effort, but it does not reflect accepted epidemiologic methodology." *Id.* at 599 n.141; *see also Frischhertz v. SmithKline Beecham Corp.*, Civil Action No. 10-2125, 2012 WL 6697124, *3 (E.D. La. Dec. 21, 2012) (excluding expert testimony that purported to rely on Bradford Hill methodology without epidemiologic data showing a statistically significant association).

Here, not only are plaintiffs' experts seeking to rely on a single epidemiologic study that does not report a statistically significant increased association between Accutane and IBD or Crohn's disease, Pb 14, but the trial court's review of epidemiologic literature shows that all nine epidemiologic studies to examine the question have failed to identify a statistically significant association. *See* Opinion at 12-13. Accordingly, scientists outside the courtroom would recognize that the necessary precondition for the Bradford Hill criteria has not been met, and plaintiffs' experts cannot rely on the Bradford Hill methodology as support for their causation opinion in this case.

B. A Primer On The Categories of Scientific Evidence Proffered In Support Of Plaintiffs' Experts' Causation Opinion.

The New Jersey Supreme Court has held that a trial court cannot fulfill its gatekeeping responsibility against unreliable expert testimony without carefully reviewing the types of scientific evidence upon which the expert relies: "[W]hen an expert relies on such data as epidemiological studies, the trial court should review the studies, as well as other information proffered by the studies, to determine if they are of a kind on which such experts ordinarily rely." *Landigran*, 127 N.J. at 417; *see also Hisenaj v. Kuehner*, 194 N.J. 6, 14-15 (2008) (noting appellate division's review of seventeen studies upon which expert based his opinion). "[A]n expert must be able to identify the factual basis for his conclusion, explain his methodology, and demonstrate that both the factual basis and underlying methodology are scientifically reliable." *Kemp ex rel. Wright v. State*, 174 N.J. 412, 427 (2002).

In the face of a solid body of contrary epidemiologic evidence, Plaintiffs' experts purport to rely on various categories of scientific studies and other evidence in support of their expert causation opinion in this case. PhRMA will not speak to the specific scientific evidence presented to the trial court, which are discussed in the parties' respective merits briefing. However, plaintiffs' experts' treatment of the

various types of evidence presented demonstrate that they have not followed a scientifically reliable methodology. Scientists outside the courtroom properly place different weight on these different types of evidence because of the well understood limitations in extrapolating from such evidence to human health outcomes. PhRMA provides the following review of the scientific literature and judicial treatment of each of the general categories of evidence purportedly relied upon by plaintiffs' experts to assist the Court in its determination of whether and under what circumstances such evidence can provide a foundation for a reliable expert causation opinion.

1. Epidemiology

Epidemiological studies are generally considered the most reliable evidence for testing a hypothesis that a particular substance causes a particular injury in humans.[2] Epidemiological studies can be especially important in cases where the drug or substance at issue is widely used or where

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

there is a measurable background rate of the alleged injury regardless of exposure. While the absence of epidemiology may not be fatal to a plaintiff's case, numerous courts have held that a plaintiff seeking to establish causation without such evidence will face a high evidentiary hurdle.[3]

This is particularly the case where, as here, a plaintiffs' expert proffers a causation opinion that contradicts a solid body of epidemiological evidence failing to find an association between the drug and the outcome at issue. "[W]hile an expert's conclusion reached on the basis of other studies could be sufficiently reliable where no epidemiological studies have been conducted, no reliable scientific approach can simply ignore the epidemiology that exists."[4]

There are two categories of epidemiological studies: experimental studies and observational studies. The most scientifically reliable epidemiological studies are double-blind, randomized controlled clinical trials, the type of experimental studies that FDA requires before approving a drug

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

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

as safe and effective.[5] In a double-blind, randomized controlled clincal trial, scientists test a predetermined hypothesized association by exposing a group of randomly-assigned individuals in a clinical setting either to the studied treatment or a placebo and then following them prospectively without knowledge of the group in which the individuals belong and measuring any differences in the outcome at interest.

In the absence of such studies, the most scientifically reliable evidence of causation in humans comes from observational epidemiology. In observational studies, scientists seek to infer associations from exposures that occur in non-controlled settings, either by comparing the incidence of disease among individuals exposed to an agent with an unexposed group ("cohort studies") or by comparing the frequency of prior exposures in individuals who have a disease as compared to a group of individuals who do not have the disease ("case control studies").[6]

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

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

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

Epidemiologists attempt to account for the possibility of chance by calculating 95% "confidence intervals" around point estimates of potential increased risk derived from epidemiological studies. An epidemiological study is considered to show a statistically significant association with an increased risk if the confidence interval of upper and lower bound estimates of risk does not include the possibility of no increased risk in the exposed population. The possibility of no increased risk is referred to as the "null" hypothesis, which is

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[7] *See Reference Guide on Epidemiology*, at 552.

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

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

generally indicated by a relative risk or odds ratio of 1.0.[10] If an epidemiological study is not statistically significant, that is, if the confidence interval includes the number 1.0, it cannot provide scientifically reliable evidence of an association, let alone causation.[11]

Bias in epidemiology is any systematic error that makes the two groups being compared different in more ways than just the variable being studied.[12] Common sources of bias include confounding factors (other factors associated with the studied factor that might account for a perceived increased risk), selection bias (uncontrolled differences between the studied populations), and information bias (systematic error in measuring data that results in differential accuracy of information).[13] A court must consider each of these sources of

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

[11] *See Joiner*, 522 U.S. at 145; *see also Dunn v. Sandoz Pharms. Corp.*, 275 F. Supp. 2d 672, 681 (M.D.N.C. 2003) ("statistically insignificant results do not constitute proof" of causation); *Soldo*, 244 F. Supp. 2d at 533 ("Courts have emphasized that epidemiologic proof must be statistically significant") (citing cases); *Caraker*, 188 F. Supp. 2d at 1034 (rejecting experts' causation opinions "inasmuch as they rely on selective use of statistically insignificant data from epidemiological studies").

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

[13] *See Merrell Dow Pharms. v. Havner*, 953 S.W.2d 706, 719 (Tex. 1997); *see also* Bresnitz, *supra* note 8, at 1831-32; *Reference Guide on Epidemiology*, Reference Manual on Scientific Evidence at 583-97 (discussing sources of bias); David A. Grimes & Kenneth F. Schuls, *Bias and Causal Associations in Observational*

bias in interpreting an epidemiological study because bias can produce an erroneous association.[14] Thus, for example, courts have excluded expert causation testimony based on purported statistically significant epidemiologic evidence where the study failed to account for other confounding exposures that could have accounted for the apparent association.[15]

Even when investigators attempt to control for chance and bias, a finding of a small increased risk of 2.0 or 3.0 in an individual observational epidemiologic study does not provide reliable evidence of causation.[16] The scientific literature is replete with examples of associations in observational studies that were refuted by subsequent research. For example, "[b]y the late 1980s, epidemiologists had noted contradictory findings in published case-control studies on 56 different topics."[17]

Research, 359 The Lancet 248 (Jan. 19, 2002) (same, including real world examples of confounding errors).

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

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

[16] *See* David A. Grimes and Kenneth F. Schulz, *False Alarms and Pseudo-Epidemics: The limitations of Observational Epidemiology*, 120(4) Obstetrics & Gynecology 920, 920 (2012).

[17] *Id.*

"More recently, researchers identified 12 randomized controlled trials that tested 52 claims from observational studies. None of the claims could be corroborated and, ironically, for five of the 52 claims, the treatment effect was statistically significant in the opposite direction.[18]

Reliable scientists accordingly pay close attention to whether the results of an epidemiologic study have been replicated. As explained in the Reference Manual on Scientific Evidence: "Rarely, if ever does a single study persuasively demonstrate a cause-effect relationship. It is important that a study be replicated in different populations and by different investigators before a causal relationship is accepted by epidemiologists and other scientists."[19] "Consistency in these findings is an important factor in making a judgment about causation."[20] In the present case, the consistent findings of nine epidemiologic studies point away from causation.

Scientists outside the courtroom also recognize the impropriety of cherry picking isolated, statistical associations

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

[19] *Reference Guide on Epidemiology*, at 604.

[20] *Id.*

out of a larger data base of contrary findings.[21] Even if perfectly controlled and without bias, a finding that just reaches statistical significance has a 1 in 20 chance of being artificial. Accordingly, if one looks at a data base with 20 separate findings, one would expect to find a seemingly "significant" finding in the group by pure chance. (In mathematical terms, the likelihood of a finding a false, but statistically significant, result in a group of 20 studies is 1-$(0.95)^{20}$ or 64.15 percent.) Epidemiologists account for this statistical reality by making an adjustment for multiple comparisons, such as the Bonferroni correction, which require much higher levels of statistical confidence and power before a single "statistically-significant" result can be considered evidence of a true association.[22] As one scientist explained, "[i]f nonadjustments for multiple comparisons became acceptable [i]t would be a license to publish coincidences with pseudoscientific gloss."[23]

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

[22] *See* Donald Berry, *Multiplicities in Cancer Research: Ubiquitous and Necessary Evils*, 104(15) J. Nat. Cancer Inst. 1124 (2012).

[23] John R. Thompson, *Invited Commentary: Re: "Multiple Comparisons and Related Issues in the Interpretation of Epidemiologic Data,"* 147 Am. J. Epid. 801, 804 (1998).

Finally, scientists in the outside world do not base causation opinions on criticisms of contrary epidemiology. While such criticisms can play an important role in raising new hypotheses or pointing to the need for additional research, they do not provide any affirmative evidence in support of causation.[24]

2. Animal Research

Animal research may be a useful tool for raising suspicions that can then be tested in humans, but there are significant differences in humans and laboratory animals that limit the degree to which animal research can validate a causation hypothesis in humans.[25] There are numerous examples of apparent positive findings in animal studies that have subsequently been found inapplicable to humans. The most commonly cited example, perhaps, is saccharine, which was linked to bladder cancer in rats over 20 years ago but was removed from the National Toxicology Program list of potential human carcinogens after years of subsequent research failed to find any health risk in

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

[25] See, *e.g.*, Irva Hertz-Picciotto, *Epidemiology and Quantitative Risk Assessment: A Bridge from Science to Policy*, 85 Am. J. Public Health. 484, 485 (1995) ("The uncertainty stemming from interspecies extrapolation is far larger than the uncertainty resulting from uncontrolled bias or errors in exposure information in epidemiological studies").

humans.[26] Similarly, scientists have determined that a common insecticide, carbaryl, causes fetal abnormalities in dogs because dogs lack a specific enzyme involved in metabolizing carbaryl. Humans have the enzyme at issue and are accordingly not believed to be at risk.[27]

The sharp differences between findings in animals and humans are evident as well in scientific studies in drug development and safety testing. In 2004, for example, the FDA estimated that 92 percent of drugs that pass preclinical tests, including "pivotal" animal tests, fail to proceed to market."[28] Conversely, a number of extremely important medications that have been shown safe in humans have been reported to cause adverse effects in animals. For example, tomoxifen, one of the

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[26] *NTP Report on Carcinogens Background Document for Saccharin*, at 3 (March 1999), available at https://ntp.niehs.nih.gov/ntp/newhomeroc/other_background/saccharin1_3apps_508.pdf

[27] *See* Bernard D. Goldstein & Mary Sue Henifen, *Reference Guide on Toxicology*, Reference Manual on Scientific Evidence 662 n.78 (3d ed. 2011). For additional examples of the often dramatic differences in responses among animal species and between animals and humans, see Neil Shanks *et al.*, *Are Animal Models Predictive for Humans?*, Philosophy, Ethics and Humanities in Medicine 4:1 (2009); David L. Eaton & Curtis D. Klaassen, *Principles of Toxicology* in Casarett & Doull's Toxicology: The Basic Science of Poisons 25-26 (Curtis D. Klaassen ed., 6th ed. 2001).

[28] Aysha Akhtar, *The Flaws and Human Harms of Animal Experimentation*, 24 Cambridge Quarterly of HealthCare Ethics 407, 410 (2015).

most effective drugs for certain types of breast cancer, has been uniquely associated with liver tumors in rats.[29] Similarly, Gleevac, a revolutionary cancer drug used to treat chronic myelogenous leukemia, has been associated with severe liver damage in dogs but was shown through clinical trials to have no such effect in humans.[30]

Animal toxicology studies are not designed to establish whether a substance is safe in humans but rather to allow scientists to study the types of effects a substance can produce under specified conditions.[31] Accordingly, animal studies are often conducted with the goal of inducing the greatest number of adverse effects. This is accomplished in a number of ways, including the use of extremely high doses and exposures through special routes designed to deliver the substance directly to a particular organ without allowing for normal absorption and metabolization.[32] While these models are useful and appropriate in the laboratory as a means to generate hypotheses for further testing, they create additional problems for extrapolating study findings to humans.

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[29] *Id.* at 414.

[30] *Id.*

[31] *See* Eaton & Klaassen, *supra* note 27, at 27.

[32] *See id.*; Karl K. Rozman & Curtis D. Klaassen, *Absorption, Distribution, and Excretion of Toxicants*, in Casarett & Doull's Toxicology: The Basic Science of Poisons, at 111.

Because of numerous such problems of extrapolation, courts repeatedly have held that animal studies alone cannot prove causation in humans.[33] At a minimum, extrapolations from animal studies to humans are not considered reliable in the absence of a credible scientific explanation why such extrapolation is warranted.[34] And animal studies cannot support a reliable causation opinion where, as here, there is a body of contrary epidemiological evidence.[35]

3. Chemical Analogies

Causation opinions derived from chemical analogies rely on the hypothesis that a substance's effects can be predicted based on the established effects of similarly structured compounds. Trial courts should be very wary of such "guilt-by-association" evidence,[36] particularly where there is scientific research

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[33] *See Siharath*, 131 F. Supp. 2d at 1367 (quoting *Bell v. Swift Adhesives, Inc.*, 804 F. Supp. 1577, 1579-80 (S.D. Ga. 1992)); *Wade-Greaux v. Whitehall Labs., Inc.*, 874 F. Supp. 1441, 1483-84 (D.V.I. 1994), *aff'd without op.*, 46 F.3d 1120 (3d Cir. 1994).

[34] *See Soldo*, 244 F. Supp. 2d at 565; *Siharath*, 131 F. Supp. 2d at 1366-67 (citing cases).

[35] *See In re Silicone Gel Breast Implants Prod. Liab. Litig.*, 318 F. Supp. 2d 879, 891 (C.D. Cal. 2004) (*citing Richardson v. Richardson-Merrell, Inc.*, 857 F.2d 823, 839 (D.C. Cir. 1988)).

[36] *Caraker*, 188 F. Supp. 2d at 1038; *see also Soldo*, 244 F. Supp. 2d at 549 ("Other federal courts facing proffered expert testimony based on the effects of allegedly similar compounds have reached the same conclusion and rejected such contentions: these courts have found that consideration of the effects of *other* drugs can only lead away from the truth.") (citing cases).

involving the actual substance at issue that demonstrates differences between it and its purported chemical cousins. Because even small changes in molecular structure can radically change a particular substance's properties and propensities, research in analogous substances does not reliably test the causal hypothesis at issue.[37]

The difficulty in relying on chemical analogies has been demonstrated by attempts to create computerized programs to assess the toxicity of chemical agents based on structure-activity relationships ("SARs"). These computerized models are far more sophisticated than the simplistic chemical analogies often relied on by causation experts in toxic tort litigation and often rely on additional information regarding a substance beyond its chemical structure. Even so, while these models ultimately may prove helpful in setting research priorities or generating hypotheses, they have failed to provide reliable predictions as to a chemical's toxic effect.[38] As reported in

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[37] *See McClain v. Metabolife Int'l, Inc.*, 401 F.3d 1233, 1246 (11th Cir. 2005); *Rider v. Sandoz Pharms. Corp.*, 295 F.3d 1194 1200-01 (11th Cir. 2002); *Glastetter v. Novartis Pharms., Corp.*, 252 F.3d 986, 990 (8th Cir. 2001); *Schudel v. General Electric Co.*, 120 F.3d 991, 996-97 (9th Cir. 1997).

[38] *See, e.g.*, Faustman & Omenn, *supra* note [ADD], at 86-87; A.M. Richard & R. Benigni, *AI and SAR Approaches for Predicting Chemical Carcinogenicity: Survey and Status* Report, 13 SAR and QSAR in Environmental Research 1 (2002); J. Ashby & R.W. Tenant, *Prediction of Rodent Carcinogenicity for 44 Chemicals: Results*, 9 Mutagenisis 7 (1994).

one survey article, two prediction toxicity exercises conducted in recent years under the aegis of the National Toxicology Program have found that models that attempt to predict carcinogenicity "based solely on information derived from chemical structure" have been particularly unreliable, with the first exercise reporting that "overall accuracy in terms of positive or negative predictions was in the range 50-65%" and the ongoing second exercise reporting even higher error rates in preliminary results.[39] Moreover, "[a] clear limitation of almost all the prediction systems ... was their excessive sensitivity, *i.e.*, incorrectly predicting many non-carcinogens as positive."[40] Efforts to predict toxicity based on structure activity relationships have resulted in similar problems.[41]

4. Case Reports/Case series

Case reports and case series are anecdotal observations of adverse effects occurring in coincidence with exposure to a

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[39] *See* Richard & Benigni, *supra* note 38, at 8, 10.

[40] *Id.* at 8; *see also* Ashby & Tenant, *supra* note 38, at abstract ("carcinogenicity tends to be overpredicted by this integrated technique" of basing predictions on chemical structure, genotoxicity and rodent toxicity).

[41] *See* James D. McKinney, *et al.*, *Forum: The Practice of Structure Activity Relationships (SAR) in Toxicology*, 56 Toxicological Sciences 8, 15 (2000) ("Given the huge range and variability of possible interactions of chemicals in biological systems, it is highly unlikely that SAR models will ever achieve absolute certainty in predicting a toxicity outcome, particularly in a whole-animal system.").

given substance. If a sufficient body of similar case reports appear in the literature, they can spur epidemiological or other controlled research to test the hypothesis that a causal link exists.[42] However, as most courts have properly recognized, case reports themselves do not test the causal hypothesis and accordingly cannot support a reliable expert causation opinion.[43] And they certainly cannot be relied upon, as plaintiffs' experts seek to do here, when contrary to a solid body of epidemiologic research.[44]

Case reports are merely anecdotal accounts of observations in particular individuals; they are not controlled tests,

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[42] *See* Howard Hu & Frank E. Speizer, *Influence of Environmental and Occupational Hazards on Disease*, in Harrison's Principles of Internal Medicine 19 (Braunwald, *et al.* eds. 15th ed. 2001) ("Case reports either sent to local authorities or published in the literature often prompt follow-up studies that can lead to the identification of new hazards"); David A. Grimes & Kenneth F. Schulz, *Descriptive Studies: What They Can and Cannot Do*, 359 The Lancet 145 (Jan. 12, 2002) ("epidemiologists and clinicians generally use descriptive reports to search for clues of cause of disease - *i.e.*, generation of hypotheses."); J.A. Arnaiz *et al.*, *The use of evidence in pharmacovigilence: Case reports as the reference source for drug withdrawals*, 57 Eur. J. Clin. Pharmacol 89-91 (2001).

[43] *See McClain*, 401 F.3d at 1253-54; *Norris*, 397 F.3d at 885; *Rider*, 295 F.3d at 1199; *Hollander*, 289 F.3d at 1211; *Glastetter*, 252 F.3d at 989-90; *Soldo*, 244 F. Supp. 2d at 541; *Caraker*, 188 F. Supp. 2d at 1034-35; *Brumbaugh v. Sandoz Pharm. Corp.*, 77 F. Supp. 2d 1153, 1156 (D. Mont. 1999); *see also Siharath*, 131 F. Supp. 2d at 1361-62 (citing cases).

[44] *See Glastetter v. Novartis Pharms. Corp.*, 107 F. Supp. 2d 1015, 1030 (E.D. Mo. 2000) (citing *Allison v. McGhan Med. Corp.*,

frequently lack analyses, and frequently make little attempt to screen out alternative causes for a patient's condition.[45] When the substance at issue is widely used, it is statistically certain given general background rates of injury that there will be case reports in which an exposure and an injury coincidentally coincide. Accordingly, the existence of such case reports is of little scientific value.[46]

In drug product liability cases, causation experts may rely on so-called "causality assessments" of individual case reports. Causality assessments are algorithms used in some European pharmacovigilance regulatory schemes that seek to impose some structure on evaluation of individual case reports by creating standardized questions to be used in the review of such reports, such as:

- Was the adverse event a known consequence of the drug?

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184 F.3d 1300, 1316 (11th Cir. 1999)), *aff'd*, 252 F.3d 986 (8th Cir. 2001).

[45] *See Rider*, 295 F.3d at 1199; *Glastetter*, 252 F.3d at 989-90; *Soldo*, 244 F. Supp. 2d at 539-40; *see also* Ellenhorn's Medical Toxicology: Diagnosis and Treatment of Human Poisoning 1 (Ellenhorn ed. 2d ed. 1997) ("Case reports demonstrate a temporal but not necessarily causative relationship between exposure and health effects. This information is often confounded by the inability to exclude other causes of illness.").

[46] *See* Grimes & Schulz, *supra* note 42, at 148 (case reports, case series, and other descriptive studies "do not allow conclusions about cause of disease").

- Did the event occur in temporal proximity to the use of the drug?

- Did the symptoms disappear upon withdrawal of the drug ("dechallenge")?

- Did the symptoms reappear following reintroduction of the drug (rechallenge)?

- Are there alternative causes for the adverse event?

Reviewers then grade individual case reports using such terms as "not possible," "unlikely," "possible," and "probable." [47] Causality assessments are used by some regulatory agencies as a signaling tool, but "they have no objective reliability which would render them useful in a wider environment."[48] "None of the available causality assessment systems has been validated. ... In other words the uncertainty [inherent in case reports] is not reduced, but categorized (at best in a semiquantitative way)."[49] Studies of standardized causality assessments have repeatedly

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[47] *See* M.N.G. Dukes, *et al.*, *Responsibility for Drug-Induced Injury: A Reference Book for Lawyers, the Health Professionals and manufacturers* 45-46 (2d ed. 1998); Ronald H.B. Mayboom *et. al.*, *Causal or Casual? The Role of Causality Assessments in Pharmacovigilance*, 17 Drug Safety 374, 375-81 (1997).

[48] M.N.G. Dukes, *supra* note 47, at 46.

[49] Mayboom, *supra* note 47, at 382; *see also* Martin J. Doherty, *Algorithms for Assessing the Probability of an Adverse Drug Reaction*, Respiratory Medicine CME 2, 63, 64 (2009) (causality algorithms "cannot prove or disprove causality, nor give an accurate quantitative measurement of the likelihood of a relationship").

found significant disagreements between graders using the same assessment methodology.[50] Accordingly, causality assessments carry no greater scientific weight than other case reports and likewise cannot provide the type of evidence required under *Kemp*.[51]

Some case reports include information regarding purported dechallenges or rechallenges, *i.e.*, reports that a patient's condition improved when the substance was removed or worsened when the substance was reintroduced. Where the dechallenge/rechallenge report is merely an after-the-fact account of an anecdotal observation, it suffers from similar reliability problems as other case reports. Many medical conditions result in fluctuations in symptomology in the ordinary course, and apparent temporal associations with

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[50] *See* Niti Mittal & Mahesh C. Gupta, *Comparison of Agreement and Rational Uses of the WHO and Naranjo Adverse Event Causality Assessment Tools*, 6 J. Pharmacol. Pharmacother. 91-93 (2015); Doherty, *supra* note 49, at 64; *Mayboom*, *supra* note 47, at 381; G. Miremont *et al.*, *Adverse drug reactions: Physicians' Opinions Versus a Causality Assessment Method*, 46 Eur. J. Clin. Pharmacol. 285, 288 (1994).

[51] *See Glastetter v. Novartis Pharms. Corp.*, 107 F. Supp. 2d 1015, 1037 n.21 (E.D. Mo. 2000) ("like case reports ... a causality assessment involves only one individual, and, in any event, is not sufficient to establish causation"), *aff'd*, 252 F.3d 986 (8th Cir. 2001); *Soldo*, 244 F. Supp. 2d at 545 (plaintiff has failed to show that the causality assessment "methodology - adopted for foreign regulatory purposes - meets any of the *Daubert* criteria, nor has plaintiff shown any other indicia of reliability.").

exposure may be due to pure chance. Even if the dechallenge or rechallenge is conducted prospectively with the intent of testing a causal hypothesis, a perceived effect in one person has limited scientific value at best.[52] Because the data are limited to a single observation, a trial court must be particularly diligent in determining whether the dechallenge/rechallenge was conducted under strict controls to account for potential confounding influences. Prospective dechallenge/rechallenge experiements - sometimes referred to as "single subject" or "n of 1" experiments - have numerous limitations that preclude general causation conclusions.[53] "[W]ithout strong assumptions regarding how an intervention on one individual relates to its effects on others, the results from a single-subject design provide little useful information ... [and e]xamination of a single subject cannot verify those assumptions."[54] As courts have explained, a prospective

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[52] *See Dunn*, 275 F. Supp 2d at 683; *Soldo*, 244 F. Supp. 2d at 541-42; *Caraker*, 188 F. Supp. 2d at 1035-36; *see also Revels v. Novartis Pharms. Corp.*, No. 03-98-00231-CV, 1999 WL 644732, *5 (Tex. App. Aug. 26, 1999).

[53] *See* David M. Reboussin & Timothy M. Morgan, *Statistical Considerations in the Use and Analysis of Single-Subject Designs*, Medicine and Science in Sports and Exercise 639, 640-642 (1996) (discussing limitations).

[54] *Id.*, abstract.

dechallenge/rechallenge report "constitutes but one single, uncontrolled experiment."[55]

III. CONCLUSION

The trial court below properly exercised its gatekeeping responsibility in concluding that plaintiffs' experts failed to apply a reliable methodology in reaching their expert opinions. PhRMA urges the Court to affirm the trial court's ruling.

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[55] *Soldo*, 244 F. Supp. 2d at 541 (quoting *Revels*, 1999 WL 644732, at *5); *see also McClain*, 401 F.3d at 1254-55 ("de-challenge/re-challenge tests are still case reports and do not purport to offer definitive conclusions as to causation" (quoting *Rider*, 295 F.3d at 1200)).

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IN RE: ACCUTANE® LITIGATION	SUPERIOR COURT OF NEW JERSEY APPELLATE DIVISION DOCKET NO.: A-4698-14T1 On Appeal from Superior Court, Law Division, Atlantic County Case No. 271 Sat Below: Hon. Nelson C. Johnson, J.S.C.

CERTIFICATION OF SERVICE

On this day I caused two (2) copies of PhRMA's Notice of Motion For Leave to Appear as Amicus Curiae, Certification of Gregory S. Chernack, Proposed Amicus Brief, and the within Certification of Service to be sent via Federal Express to the following counsel of record:

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I also caused the original and five (5) copies of the aforementioned documents to be sent via Federal Express to Mark Joseph H. Orlando, Clerk of the Superior Court of New Jersey, Appellate Division, Hughes Justice Complex, P.O. Box 006, Trenton, New Jersey 08625.

I hereby certify that the foregoing statements are true. I am aware that if any of the foregoing statements are willfully false, I am subject to punishment.

Gregory S. Chernack

Dated: November 11, 2015