EFiled: Oct 01 2024 02:11PM EDT
Filing ID 74642543
Case Number 255,2024

IN THE
SUPREME COURT OF THE STATE OF DELAWARE

IN RE ZANTAC (RANITIDINE) LITIGATION

No. 255, 2024

CASE BELOW:

SUPERIOR COURT OF THE STATE OF DELAWARE,
C.A. NO. N22C-09-101

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Dated: October 1, 2024

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NATURE OF PROCEEDINGS

This appeal arises from coordinated proceedings in the Superior Court involving nearly 82,000 plaintiffs who allege that the medication ranitidine—sold for 35 years under the brand-name Zantac—caused them to develop cancer. Litigation commenced in 2019, when an online pharmacy claimed to have detected dangerous levels of the alleged carcinogen *N*-nitrosodimethylamine (NDMA) in ranitidine tablets, prompting the filing of tens of thousands of cases in state and federal courts around the country.

Over the last five years, however, the science has refuted plaintiffs' claims. The FDA criticized the online pharmacy's methodology and conducted its own testing of ranitidine, finding far lower levels of NDMA, with many samples containing levels below the FDA's acceptable daily intake. Sixteen epidemiological studies have now been published in peer-reviewed medical journals, and the overwhelming consensus is that there is no association between ranitidine and any type of cancer, especially when comparing ranitidine users to users of other heartburn medications. The FDA and its European counterpart have reviewed the literature and found *no evidence* of a causal relationship. After all this research, no regulatory body or medical organization has concluded that ranitidine causes cancer.

Accordingly, the federal MDL court, the first to apply the *Daubert* standard to general-causation experts opining that ranitidine use can cause cancer, granted

Defendants' motions to exclude. The court found that the plaintiffs' experts had employed unreliable methodologies and made unsubstantiated analytic leaps to reach conclusions at odds with the scientific consensus. *In re Zantac (Ranitidine) Prods. Liab. Litig.*, 644 F. Supp. 3d 1075 (S.D. Fla. 2022). Among other fatal flaws in the experts' analyses, they failed to identify a "threshold dose" at which they allege ranitidine or NDMA—the latter of which humans ingest in common foods, water, and air, and which the body naturally produces—can cause cancer, *id*. at 1275-76, and had relied disproportionately on studies involving NDMA exposures from food and rubber-factory fumes, while minimizing epidemiological studies of patients taking ranitidine, *id*. at 1217-18. A Florida state court applying *Daubert* excluded general-causation opinions by different experts applying the same flawed methodologies, for the same reasons, including that the expert "failed to identify a minimum dose of NDMA in ranitidine that could cause [the plaintiff's] cancer." *See* A-024632.

That leaves the Superior Court as the only court in the country applying *Daubert* to admit an opinion that ranitidine use can cause cancer. The Court denied Defendants' motions to exclude the opinions of Plaintiffs' general-causation experts, who opined that ranitidine can cause ten distinct types of cancers. Despite this Court's longstanding decision to follow the U.S. Supreme Court's interpretation of F.R.E. 702 in *Daubert*, *M.G. Bancorporation v. Le Beau*, 737 A.2d 513, 521 (Del.

1999), the Superior Court based its opinion on several purported "differences in Delaware law" as compared to the standard applied in federal court. Op.17. Three of those putative differences are subjects of this appeal.

First, the Superior Court held that "Delaware does not recognize a 'threshold dose' requirement as part of the general causation analysis," Op.16, and thus Plaintiffs' experts' failure to identify such a dose was not grounds for exclusion. That ruling contradicted a prior Superior Court decision, which this Court affirmed, and ample federal authority requiring a general-causation expert to identify a "dose required for human toxicity." *Tumlinson v. Advanced Micro Devices, Inc.*, 2013 WL 7084888, at *8 (Del. Super. Ct. Oct. 15, 2013), *aff'd*, 81 A.3d 1264 (Del. 2013). If Delaware did not require general-causation experts to identify a threshold range at which a substance becomes toxic, then plaintiffs could proceed on the untenable theory that "*any* amount of a carcinogen, no matter how small, is actionable because an infinitesimal risk can neither be proven nor disproven." *Zantac*, 644 F. Supp. 3d at 1109.

Second, the Superior Court determined that "general causation focuses on NDMA," Op. 18, rather than ranitidine, thereby permitting expert testimony that sidesteps the ranitidine epidemiology in favor of non-ranitidine studies involving exposure to NDMA through foods and inhalation of rubber fumes, all of which contain other carcinogens. That is inconsistent with prior Delaware decisions,

Daubert precedent (including the Zantac MDL and Florida state court holdings), and basic logic. The ruling would permit a plaintiff to reach a jury simply by producing evidence that a product contains trace levels of a substance that may cause injuries at high concentrations, notwithstanding peer-reviewed literature overwhelmingly indicating that exposure to the product itself—at levels involved in real-word use—does not cause the disease at issue.

Third, the Superior Court stated that Delaware courts "conduct their *Daubert* analyses 'with a liberal thrust favoring admission,'" Op.13 (quoting *Messick v. Novartis Pharms. Corp.*, 747 F.3d 1193, 1196 (9th Cir. 2014)), and will submit "[a]ny quarrel with the *application* of [a] methodology" to "the fact finder." Op.55 (emphasis added). But this Court has made clear that, under Rule 702, an expert's opinion must be the product of a reliable methodology "reliably *applied* to the facts of each case," and has affirmed experts' exclusions after rigorous review of their analyses. *Bowen v. E.I. DuPont de Nemours & Co.*, 906 A.2d 787, 797 (Del. 2006) (emphasis added); *see also Zayas v. State*, 273 A.3d 776, 788 (Del. 2022). Delaware law accords with federal precedent, which requires courts to "take a hard look" at an expert's methodology to ensure it is "reliable at every step of the way." *In re Mirena IUS Levonogorstrel-Related Prods. Liab. Litig.*, 982 F.3d 113, 123 (2d Cir. 2020) ("*Mirena II*").

This Court should reverse the Superior Court on all three issues and remand with instructions to grant Defendants' motions to exclude or at least to evaluate the motions using the appropriate principles. If not reversed, the Superior Court's decision would mark the beginning of a new era in Delaware's Rule 702 jurisprudence, in which Delaware courts would apply a far more lenient standard than their federal counterparts and stop enforcing the guardrails that prevent expert opinions based on unreliable methods from reaching juries. The predictable result of such a holding would be to transform Delaware into a mass-tort haven, especially given the many corporations incorporated and subject to general jurisdiction here.

SUMMARY OF ARGUMENT

1. The Superior Court erred by holding that Delaware law does not require general-causation experts in chemical-exposure cases to identify a threshold dose. Prior Superior Court decisions, and many federal appellate opinions, have recognized that an expert must identify a "dose required for human toxicity" to carry the plaintiff's burden on general causation. *Tumlinson v. Advanced Micro Devices, Inc.*, 2013 WL 7084888, at *8; *see McClain v. Metabolife Int'l, Inc.*, 401 F.3d 1233, 1241 (11th Cir. 2005) (collecting cases). Dispensing with the requirement would permit experts to testify that trace levels of alleged carcinogens—some of which, like NDMA, are present in food, water, and air—could have caused a plaintiff's cancer.

2. The Superior Court erred by holding that the general-causation analysis "focuses on NDMA" rather than ranitidine. Delaware and federal authority confirm that a reliable general-causation opinion must focus on the product at issue, not just an allegedly harmful component. *See, e.g.*, *In re Asbestos Litig.*, 911 A.2d 1176 (Del. Super. Ct. 2006); *Chapman v. Procter & Gamble*, 766 F.3d 1296, 1303-04 (11th Cir. 2014). An expert may rely on more general evidence concerning exposure to the same agent if the context is "indistinguishable," *Asbestos*, 911 A.2d at 1202, but the Superior Court did not even examine whether Plaintiffs' experts had shown that NDMA exposures assessed in studies of rubber fumes and certain foods (which

contain multiple carcinogens) were equivalent to Plaintiffs' alleged NDMA exposure from ranitidine.

3. The Superior Court erred by holding that courts should apply a "liberal thrust favoring admission" in their Rule 702 gatekeeping role and, rather than considering challenges to an expert's application of his methodology, treat all such challenges to the expert's reasoning merely as fodder for cross-examination. Op.13. Both Delaware and federal authority are clear that, far from applying a presumption in favor of admission, a court must rigorously review an expert's opinion to ensure his methodology has been "reliably applied to the facts of [the] case." *Bowen*, 906 A.2d at 797.

STATEMENT OF FACTS

A. History of Zantac

For more than 35 years, millions of patients used ranitidine to treat ulcers, heartburn, indigestion, and other conditions of the stomach and esophagus. A predecessor of Defendant GlaxoSmithKline LLC ("GSK") developed ranitidine in the early 1980s, and in 1983, the FDA approved its sale as a prescription drug under the trade name "Zantac." The FDA approved over-the-counter (OTC) Zantac in 1995. GSK, Pfizer, Boehringer Ingelheim, and Sanofi sold OTC Zantac at different times.

In 2019, an online pharmacy called Valisure submitted a citizen petition to the FDA with test results purporting to show that some ranitidine products contained high levels of NDMA. The EPA and the International Agency for Research on Cancer (IARC) classify NDMA as a "probable" carcinogen, *Zantac*, 644 F. Supp. 3d at 1095, meaning there is "[l]imited evidence of carcinogenicity in humans."[1] Valisure's headline-grabbing result stemmed, however, from badly flawed testing that *generated* NDMA through extreme heat and concentrations of salt, and thus did not measure NDMA levels in real-world ranitidine. *See id*.

[1] World Health Org., *IARC Monographs on the Identification of Carcinogenic Hazards to Humans: Preamble* 35.

The FDA, noting the obvious flaws in Valisure's testing, conducted its own testing of ranitidine products. The FDA testing found far lower levels of NDMA in ranitidine samples, with many results below its conservative, daily-intake guideline of 96 nanograms. *Id*. at 1093. The FDA estimates that, if one were to ingest 96 nanograms of NDMA every day for 70 years, one's risk of cancer would increase by 0.001%. *Id*. Even for the ranitidine samples that exceeded 96 nanograms, the FDA compared the level of NDMA detected to what "you would expect to be exposed to if you ate common foods like grilled or smoked meats" and stated that these "low levels" of NDMA "would not be expected to lead to an increase in the risk of cancer." *Id*. at 1191. Out of an abundance of caution, the FDA requested that manufacturers voluntarily withdraw ranitidine products from the market in April 2020. *Id*.

While the flawed Valisure test results prompted the hurried filing of tens of thousands of personal-injury lawsuits, independent scientists began working to determine whether ranitidine use (which by definition includes whatever NDMA might have been present in ranitidine) was associated with an increased risk of cancer. Sixteen published, peer-reviewed epidemiological studies have now investigated the question, and nearly all have found no association between ranitidine and the risk of cancer. The FDA and its European equivalent have

reviewed the epidemiological literature and concluded that it provides no evidence of a causal relationship between ranitidine use and cancer.

FDA	**"[N]o consistent signals emerged across studies, and studies with comparison to active controls found no association between ranitidine and overall or specific cancer risk."**
EUROPEAN MEDICINES AGENCY SCIENCE MEDICINES HEALTH	**"Based on a comprehensive review of epidemiological and post marketing data, it can be concluded that there is no evidence of a causal association between ranitidine therapy and the development of cancer in patients."**

Id. at 1107, 1191.

B. The MDL Court Excludes Plaintiffs' Experts' General-Causation Opinions.

Federal ranitidine lawsuits were consolidated in an MDL before Judge Robin Rosenberg in the Southern District of Florida in February 2020. The MDL plaintiffs' lead counsel hired experts to provide general-causation opinions, but those experts would only opine that ranitidine could cause five cancers: liver, stomach, esophagus, pancreas, and bladder. *Id*. at 1099. ***The MDL plaintiffs' epidemiologists affirmatively opined that the "evidence was not sufficient to support an opinion that use of ranitidine can cause breast, prostate, kidney, lung, or colorectal cancer."***[2]

[2] *Zantac*, No. 20-md-2924, ECF 6171-9, at 16 (McTiernan Rpt.); *see also* ECF 6179-6, at 6 (Moorman Rpt.).

Without an expert to support a significant proportion of their cases, in mid-2022, plaintiffs' attorneys withdrew thousands of claims alleging breast, colorectal, kidney, lung, or prostate cancers from the MDL claims registry and filed them in Delaware, where leadership counsel offered new general-causation experts. Of the nearly 75,000 Plaintiffs in Delaware at the time Defendants sought interlocutory review, ***88% alleged one of the five cancers for which the MDL plaintiffs' experts acknowledged there was insufficient evidence of causation*****,** and ***79%*** originally registered their claims in the MDL.

The MDL plaintiffs' experts supported their general-causation opinions by extrapolating from NDMA dietary and rubber-fume studies and minimizing studies directly investigating ranitidine use. 644 F. Supp. 3d at 1093. In December 2022, the MDL court issued an order excluding these opinions. Three of the MDL court's legal rulings are especially important here.

First, the court held that the experts "must identify a threshold dose range at which ranitidine can cause cancer," *id*. at 1109, applying ample precedent holding that "a plaintiff must demonstrate *the levels of exposure* that are hazardous to human beings generally." *Id*. (quoting *McClain*, 401 F.3d at 1241 (emphasis added)). If "an actionable exposure threshold dose cannot, as a matter of law, be merely *anything*, that means it must be *something provable*." *Id*.

Second, the MDL court held that a reliable general-causation inquiry must focus on the relevant product, ranitidine, not extrapolations from studies about the allegedly harmful component, NDMA. *See id*. at 1104-06. The court applied federal *Daubert* precedent, including an Eleventh Circuit decision concerning zinc exposure from the dental adhesive Fixodent, holding that "plaintiffs had to show Fixodent—not zinc, generally—could cause the injury at issue." *Id*. at 1106 (citing *Chapman*, 766 F.3d at 1303-04). Focusing on NDMA would be unreliable, the court noted, because the plaintiffs could not prevail just by showing that NDMA can cause cancer, but instead "must show that ranitidine consumption can result in sufficient NDMA ingestion to cause their alleged injuries." *Id*. Because "[t]he amount of NDMA in ranitidine is uncertain," "[a] critical, important benefit of the ranitidine epidemiology is that it removes this question from the estimate of cancer risk." *Id*. at 1218. "Regardless of how much NDMA was in ranitidine products at the time of manufacture, people consumed them," and no studies have shown that ranitidine consumption—with whatever NDMA exposure that entails—causes cancer. *Id*.

Third, the MDL court emphasized its gatekeeping obligation to ensure that "speculative and unreliable opinions do not reach the jury." *Id*. at 1102 (quoting *McClain*, 401 F.3d at 1237). To meet that obligation, a court must examine an expert's methodology and exclude the opinion when there is "too great an analytical gap between the data and the opinion proffered," or where the opinion "is connected

to existing data only by the *ipse dixit* of the expert." *Gen. Elec. v. Joiner*, 522 U.S. 136, 146 (1997). Applying that required scrutiny, the MDL court concluded that the plaintiffs' experts had "utilized unreliable methodologies" with "a lack of substantiation for analytical leaps" and "a lack of internally consistent, objective, science-based standards for the evenhanded evaluation of data." 644 F. Supp. 3d at 1094. The experts' unprincipled methodologies led them to dismiss the large body of epidemiological and experimental evidence indicating that ranitidine does not cause cancer.[3] The fact that the experts' conclusions lacked "any acceptance, let alone general acceptance, in the scientific community" was itself "an indication of an unreliable methodology." *Id*. at 1234.

On August 15, 2024, a Florida state court applying *Daubert* excluded general-causation opinions applying similar methodologies. The court found the same critical flaws that the MDL court had identified, holding that the experts had failed to identify the required "threshold dose" for NDMA or ranitidine, A-024637; A-024632, that the experts' attempt to base their opinions on studies of rubber workers

[3] The MDL court noted that two studies (Wang and Cardwell) had found statistically significant associations between ranitidine use and an increased risk of liver and bladder cancer, respectively, but concluded the experts unreliably cherry picked those findings while discounting contrary findings from studies with similar designs. 644 F. Supp. 3d at 1223-24, 1259-160. The Florida court held similarly. A-024623-24. Other studies, including a subsequent study of liver cancer, found that ranitidine use was significantly associated with a *decreased* risk of cancer. *See id*. at 1225; A-011506.

required "assumption piled upon assumption," A-024623 (quoting *Zantac*, F. Supp. 3d at 1217), and that they had engaged in impermissible "cherry picking" of the scientific literature, A-024624.

C. The Superior Court Declines to Exclude Opinions Nearly Identical to Those the MDL Court Found Unreliable and Inadmissible.

In Delaware, Plaintiffs proffered a new slate of experts, including eight who opined that ranitidine causes ten types of cancer. Those experts based their opinions on the same body of scientific evidence as the excluded MDL and Florida state court experts and made many of the same methodological errors.

On May 31, 2024, the Superior Court denied all Rule 702 motions. In describing the applicable standard, the Court stated that courts should "conduct their *Daubert* analyses 'with a liberal thrust favoring admission,'" Op.13 (quoting *Messick*, 747 F.3d at 1196), relying on decades-old, discredited authority holding that scientific critiques of an expert's application of a methodology "go to the weight, not the admissibility" of his opinion. *Kennedy v. Collagen Corp.*, 161 F.3d 1226, 1231 (9th Cir. 1998) (quoting *McCullock v. H.B. Fuller Co.*, 61 F.3d 1038, 1044 (2d Cir. 1998)).

The Court further claimed that "the evidentiary law governing some of the salient issues differs" between Delaware and federal courts, including that "Delaware does not recognize a 'threshold dose' requirement as part of the general causation analysis." Op.16. The Court also stated that "Delaware courts are loath

to step into the heart of technical debate between opposing scientists" and that, "[i]n that regard, the jurisprudence reflected in the Floridian *Zantac* differs from Delaware's." Op.17. Because of those supposed legal differences, the Court concluded that "Defendants' praise of the MDL court's rationale breathes not a whisper to the difference in Delaware law." *Id*.

The Court rejected Defendants' argument that its analysis should concentrate on ranitidine and concluded that "general causation focuses on NDMA." Op.18. The Court acknowledged Defendants' argument that "studies of ranitidine *necessarily account* for any exposure to NDMA contained in ranitidine products," but countered that "Defendants do not dilate on" why that is true. Op.19. Ultimately, the Court concluded it could not "turn a blind eye to the focus on NDMA, especially where the record suggests that Defendants acknowledged the dangers of it." Op.21.

Before considering Plaintiffs' experts' individual opinions, the Court addressed "Plaintiffs' alleged failure to offer satisfactory proof of a threshold dose." Op.29. The Court read *Tumlinson* as holding that any requirement to identify a threshold dose is "excus[ed]" when "the substance in question is known to be harmful at some level and the plaintiff suffered the precise harm connected to that exposure." *Id*. (quoting *Tumlinson*, 2013 WL 7084888, at *7). The Court dismissed Defendants' argument that the sort of "precise harm" that might excuse the need to identify a threshold dose must be far more specific than ten different types of cancer,

citing GSK's 2019 "Hazard Assessment" regarding NDMA's carcinogenicity. Op.30.

The Court then proceeded to evaluate the individual experts' opinions. It dismissed Defendants' methodological critiques, which Defendants set forth at length in their briefing, *see* A-000107-275, in cursory fashion. Addressing the first expert, for example, the Court noted that Defendants raised several "challenges to the reliability of Dr Jameson's methodology," including that "he cherry picked evidence" and "did not rank or weigh his studies," and that the tests on which he relied "do not imitate conditions in humans" and were "non-peer reviewed." Op.38. The Court then asserted, without further explanation, that "[t]hese challenges are for the jury" and that "the Court finds that [Dr. Jameson] utilized sound scientific methodology in formulating his opinions." *Id*.

The Court repeated this refrain for expert after expert, finding that Defendants' arguments that the experts "cherry picked" favorable evidence and applied their methodologies in a "result-oriented" manner, among many other flaws, were matters for the jury to consider. *See, e.g.*, Op.46-47 (Neugut; bladder cancer), Op.49-50 (Rustgi; liver), Op.51-52 (Hatzaras; colorectal, esophageal, stomach), Op.54-55 (Raz; lung), Op.60 (Leone; breast), Op.63-64 (Margulis; kidney), Op.67-68 (Miller; pancreatic), Op.72 (Trock; prostate). For the Court, it was enough that the experts possessed the requisite qualifications and purported to apply an accepted

methodology. "Any quarrel with the *application* of [a] methodology," in the Court's view, "[wa]s for the fact finder." Op.55 (emphasis added). The Court's ruling even found that Plaintiffs' expert who opined that ranitidine can cause kidney cancer employed reliable methods, even though he later admitted in peer-reviewed literature that ***the available scientific evidence is insufficient to conclude that ranitidine causes kidney cancer***.[4]

In conclusion, the Court opined that "[d]ifferences in jurisprudence" and "interpretation of the law" could alter *Daubert*'s application in different jurisdictions, but that "[i]n Delaware, our jurisprudence counsels that, subject to earnest deliberation, trial courts entrust questions of science to the scientists." Op.102. Defendants' methodological criticisms of Plaintiffs' experts' opinions would thus have to "be made at trial via cross-examination and introduction of counter evidence." *Id*.

[4] *See* Gold & Margulis, Reply by Authors, JU OPEN PLUS (2023) ("We believe preclinical data and limited population data demonstrate an association between [ranitidine] and kidney cancer but not causation.") (A-011428).

ARGUMENT

I. THE SUPERIOR COURT ERRED IN HOLDING THAT PLAINTIFFS' EXPERTS NEED NOT IDENTIFY THE THRESHOLD DOSE REQUIRED TO CAUSE THE CANCERS AT ISSUE.

A. Question Presented

Whether a general-causation expert must identify a threshold dose required to cause the disease at issue in cases where there is neither a "signature harm" known to result from the substance nor an established causal relationship between the substance and the disease. Op. 29-32.

B. Scope of Review

This Court reviews legal conclusions *de novo*. *Kahn v. Kolberg Kravis Roberts & Co.*, 23 A.3d 831, 836 (Del. 2011). The Court reviews "a trial court's decision to admit or exclude expert evidence for abuse of discretion." *Tumlinson*, 81 A.3d at 1268.

C. Merits of Argument

1. A general-causation expert typically must identify the dose required to cause the disease at issue.

This appeal presents the question of whether Plaintiffs' experts reliably opined that ranitidine use can cause ten different cancers—*i.e.*, "general causation." A "hallmark" of general-causation analysis is "[t]he relationship between dose and effect (dose-response relationship)." *McClain*, 401 F.3d at 1242. "One of the central tenets of toxicology is that 'the dose makes the poison,' such 'that all chemical

agents are intrinsically hazardous' and 'whether they cause harm is only a question of dose.'" *In re Lipitor (Atorvastin Calcium) Mktg., Sales Pracs., & Prods. Liab. Litig.*, 892 F.3d 624, 639 (4th Cir. 2018) (citation omitted).

Because "dose matters," *id*., an essential element of a general-causation opinion is "how much" of a given substance "must be used for how long" to cause a given disease, *Chapman*, 766 F.3d at 1307. Courts around the country, including in Delaware, typically require general-causation experts to identify the "threshold dose" required to cause the disease at issue—in other words, "the minimum amount of a substance below which the substance would not cause the disease or effect, even where exposure occurs repeatedly over the long-term." *Zantac*, 644 F. Supp. 3d at 1265-66. "[M]ore than thirty … federal courts and state courts" have rejected as unreliable opinions lacking such an identification. *Krik v. Exxon Mobil Corp.*, 870 F.3d 669, 677 (7th Cir. 2017).

A "range" of doses may suffice, *Zantac*, 644 F. Supp. 3d at 1109, so long as the expert reliably supports the proffered range. But it is vital that an expert identify *some* minimum level at which a substance presents a risk of harm, rather than simply asserting that the substance "*sometimes* causes the [alleged] harm." *Wright v. Willamette Indus.*, 91 F.3d 1105, 1107 (8th Cir. 1996) (emphasis added).

Two Delaware cases apply this requirement. In *Tumlinson*, the plaintiffs alleged that exposure to factory chemicals produced birth defects. 2013 WL

7084888 at *1. Unlike in other Rule 702 decisions in Delaware, the chemicals' "toxicity" was not "established." *Id.* at *3. The court explained that a general-causation expert's opinion must address a testable question, such as whether "exposure to X chemical(s) in Y dose for Z time" is likely to cause a certain birth defect. *Id.* at *7. The plaintiffs' expert, however, had failed to specify the "dose element" necessary to make a general-causation hypothesis testable. *Id.* The court acknowledged cases excusing imprecision in "the specific dose required for human toxicity," but explained that they concerned substances "known to be harmful at some exposure level and the plaintiff suffered the precise harm connected to that exposure." *Id.* at *8. By contrast, *Tumlinson* involved "neither scientific consensus that" the chemicals at issue were "toxic to humans nor a signature harm." *Id.* Because the expert did not supply a threshold dose, among other flaws in his analysis, the court excluded the opinion under Rule 702. *Id*. This Court affirmed. 81 A.3d at 1267.

Wilant v. BNSF Railway Co., 2020 WL 2467076 (Del. Super. Ct. May 13, 2020), involved a claim that diesel exhaust caused bladder cancer. *Id.* at *1. Although "many scientific studies demonstrat[ed] the positive epidemiological relationship between diesel exhaust and lung cancer," the science regarding bladder cancer was "less certain." *Id.* at *2. The court held that the plaintiff's expert's failure to specify the dose of diesel exhaust "that might cause or even elevate the risk of

bladder cancer generally further weakens the reliability of this testimony." *Id.* at *5 n.43 (citing *McLaughlin v. BNSF Railway*, 439 F. Supp. 3d 1173, 1177-78 (D. Neb. 2020)). The court noted that, when "[p]ressed on the lack of dosage data in the literature, [the expert] suggested that a proposed 'threshold limit value' based on the known risk for lung cancer was 'a reasonable place to start' in assigning one for bladder cancer." *Id.* at *5. The court rejected this unsupported suggestion, noting that it could not know whether this was true "without evidence." *Id.*

Many cases in other *Daubert* jurisdictions have also excluded general-causation opinions that failed to identify a threshold dose. *See, e.g.*, *McClain*, 401 F.3d at 1241 ("[A] plaintiff must demonstrate the levels of exposure that are hazardous to human beings generally[.]"); *Mitchell v. Gencorp*, 165 F.3d 778, 781 (10th Cir. 1999) (same); *Wright*, 91 F.3d at 1106 (same); *Wills v. Amerada Hess Corp.*, 379 F.3d 32, 49-50 (2d Cir. 2004) (explaining that threshold dose must be reliably determined); *Allen v. Pa. Eng'g Corp.*, 102 F.3d 194, 199 (5th Cir. 1996) ("Scientific knowledge of the harmful level of exposure to a chemical, plus knowledge that the plaintiff was exposed to such quantities, are minimal facts necessary to sustain the plaintiffs' burden in a toxic tort case.").

These cases reject expert assertions that "any level is too much." *McClain*, 401 F.3d at 1241; *see also Krik*, 870 F.3d at 677; *Cano v. Everest Minerals Corp.*, 362 F. Supp. 2d 814, 849 (W.D. Tex. 2005) (collecting cases). To survive scrutiny

under Rule 702, a general-causation expert "must be able to say more than" that the plaintiff was exposed to an agent, "some unknown amount of [that agent] can cause cancer," and therefore the exposure caused the cancer. *McLaughlin*, 439 F. Supp. 3d at 1183. "This is just the type of opinion that is connected to the data only by the *ipse dixit* of the expert[.]" *Id.* (citing *Joiner*, 522 U.S. at 146).

2. The Superior Court erred when it excused plaintiffs' experts from establishing a threshold dose.

In rejecting the argument that *Tumlinson* required Plaintiffs' experts to identify a threshold dose, the Superior Court interpreted *Tumlinson* to excuse the threshold-dose requirement in cases where "the substance in question is known to be harmful." Op. 29-30 (quoting *Tumlinson*, 2013 WL 7084888, at *8). *Tumlinson* acknowledged only that "imprecision" regarding threshold dose may be "excused" in cases involving a "scientific consensus that these causation chemicals are toxic" and/or "a signature harm." *Tumlinson*, 2013 WL 7084888, at *3, *8. Asbestos and cigarette cases are prototypical examples. For example, as this Court has remarked, "the general association" between asbestos and the "very rare" "'signature' disease" of mesothelioma "is well established in the scientific community." *Gen. Motors Co. v. Grenier ("Grenier II")*, 981 A.2d 531, 537 (Del. 2009).

This case presents the opposite situation. It is not established in the scientific community that ranitidine causes *any* form of cancer, let alone ten, at any dose. The Superior Court ignored this point in attempting to distinguish *Tumlinson*. Regulators

have concluded that evidence of a causal association between ranitidine use and cancer is lacking. Nor could ten distinct varieties of cancer, many of which are very common in the general population, possibly be a "signature harm" of ranitidine. In this context, the failure to present any reliable scientific evidence establishing the threshold dose of ranitidine allegedly required to cause the ten cancers is fatal.

Below Plaintiffs noted that IARC classifies NDMA as a "probable" carcinogen, but that determination means there is "[l]imited evidence of carcinogenicity in humans" and says nothing about *how much* NDMA is needed to cause cancer in humans, which is the essential question for general causation. *See McLaughlin*, 439 F. Supp. 2d at 1182-83 (expert cannot rely merely on IARC determination that "diesel exhaust causes lung cancer" because the expert did not "know *how much* diesel exhaust exposure the IARC found to cause lung cancer").

Even if NDMA can be a carcinogen at some level, it is Plaintiffs' burden to establish that level, as well as how much ranitidine one must ingest to consume that level, with reliable expert opinions. Otherwise, plaintiffs could advance the untenable theory that "*any* amount of a carcinogen, no matter how small, is actionable." *Zantac*, 644 F. Supp. 3d at 1109. That theory would be especially dubious in the case of NDMA, which is present in air, water, and common foods. *Id.* at 1106. Surely, an expert cannot reliably base an opinion that water causes

cancer on the syllogism that (1) NDMA is a probable carcinogen, (2) water can contain trace amounts of NDMA, therefore (3) water causes cancer. *Id.* at 1106.

In rejecting a threshold-dose requirement, the Superior Court also mentioned that the FDA's "acceptable daily intake" level and GSK's internal assessment recognized the carcinogenic potential of NDMA. Op. 30-31 (citing A-015224, A-018371). But the FDA has been clear that its "acceptable daily intake" "is a highly hypothetical concept that should not be regarded as a realistic indication of the actual risk" to humans. A-011810. And the GSK assessment merely acknowledged that "it is considered highly likely that NDMA is carcinogenic to humans, potentially at relatively low levels of exposure." A-015263. As the MDL court understood, "potentially . . . low levels of exposure" "do not equate to 'no threshold.'" *Zantac*, 644 F. Supp. 3d at 1275.

The Court also cited a truncated excerpt of testimony from one of Defendants' experts, whom it characterized as stating that "threshold dose is a 'somewhat meaningless statement [] scientifically.'" Op. 30-31; *see* A-017120-21. But in fact, the expert explained that, at the "population" level, there "will be some level at which there is no known associate[d] increase in risk." A-017119-20. In other words, the expert confirmed that some threshold dose must exist.

Finally, the Court suggested that Plaintiffs should be permitted to argue to the jury that "collective delays by all Defendants forestalled development of the science

of NDMA exposure," Op. 31—in other words, to attempt to explain why Plaintiffs' experts lack reliable scientific evidence of threshold dose. That suggestion turns Rule 702 on its head. No Delaware authority permits a court to admit an unreliable expert opinion just because the party proffering the opinion has a (supposed) explanation for why the science does not yet reliably support the opinion. To the contrary, "[t]he law is not an arena to test scientific theory." *Minner v. Am. Mortg. & Guar. Co.*, 791 A.2d 826, 854 (Del. Super. Ct. Apr. 17, 2000).

3. Application of these principles requires exclusion of Plaintiffs' experts.

Plaintiffs' experts either failed to provide any opinion on threshold dose, or simply asserted that NDMA is unsafe at any level:

- *Breast cancer*: Dr. Leone characterized NDMA as "not considered safe at any threshold or dose." A-000807.
- *Colorectal, gastric, and esophageal cancers*: Dr. Hatzaras testified that "[i]t would be imprudent" to "just pull a number off" when asked for a dose at which NDMA induces cancer. A-003793.
- *Kidney cancer*: Dr. Margulis conceded that he is not "offering an opinion on the minimum dose and duration of exposure to ranitidine [or NDMA] that is necessary to cause kidney cancer." A-007399.

- *Prostate cancer*: Dr. Trock testified that the "data" do not establish the minimum dose of ranitidine necessary to cause prostate cancer. A-011141-44.
- *Liver cancer*: Dr. Rustgi declined to offer "a number at which there's no risk." A-009970.
- *Lung cancer*: Dr. Raz testified that "I don't have an answer for a specific dose" that causes lung cancer. A-009744.
- *Pancreatic cancer*: Dr. Miller declined to identify "how much NDMA in ranitidine is needed to cause pancreatic cancer." A-007782.
- *Bladder cancer*: Dr. Neugut (unlike the other experts) purported to derive a conclusion on threshold dose from the Cardwell study, but Cardwell's comparison of ranitidine users to similarly situated individuals taking medications of the same class, which Dr. Neugut conceded is generally more appropriate, did not show any association or dose response. A-011377; A-009070. The MDL court rejected as unreliable a similar opinion. *Zantac*, 644 F. Supp. 3d at 1275-76.

Without any reliable opinions on threshold dose to bridge the "analytical gap" between ranitidine consumption and the ten cancers, Plaintiffs' experts' opinions are unsupported "*ipse dixit*" and must be excluded. *Joiner*, 522 U.S. at 146.

* * *

This Court should hold that, where there is neither a "signature harm" known to result from a substance nor an established causal relationship between a given dose of the substance and the disease, a general-causation expert's failure to identify a threshold dose renders his methodology unreliable. Because Plaintiffs' general-causation experts failed to reliably identify a threshold dose or range, the Court should reverse and exclude those experts' opinions.

II. THE SUPERIOR COURT ERRED IN FOCUSING THE GENERAL-CAUSATION ANALYSIS ON NDMA, RATHER THAN RANITIDINE.

A. Question Presented

Whether a general-causation analysis must focus on the product at issue, rather than an allegedly harmful component of the product to which individuals are exposed in other contexts. Op.18-23.

B. Scope of Review

The Court reviews legal conclusions *de novo* and a decision to admit or exclude expert evidence for abuse of discretion. *See supra*, at 18.

C. Merits of Argument

1. A reliable general-causation analysis must focus on the product at issue, not the allegedly toxic agent.

Plaintiffs' burden is to prove that use of Defendants' ranitidine products can cause the alleged cancers. Yet the Superior Court held that "general causation focuses on NDMA," not on ranitidine itself. Op.18. The Court gave no tenable justification for that holding, which takes an approach contrary to that of every independent scientist who has investigated whether there is a relationship between ranitidine and cancer. While the Court acknowledged Defendants' argument that "studies of ranitidine necessarily account for any exposure to NDMA contained in ranitidine products," it apparently found the argument insufficiently explained, remarking that "Defendants do not dilate on" why the ranitidine epidemiology necessarily accounts for NDMA exposure. Op.19. But the point is a straightforward

one: the epidemiologic studies of ranitidine investigate whether people ingesting ranitidine products have an increased risk of cancer, and thus the studies necessarily evaluate any effects of whatever amount of NDMA those products contained.

Ranitidine-focused studies thus have the "critical, important benefit" of removing any uncertainty about the levels of NDMA in ranitidine. *Zantac*, 644 F. Supp. 3d at 1218. "Regardless of how much NDMA was in ranitidine products at the time of manufacture, people consumed them," and the ranitidine epidemiology assesses any effect of that consumption on cancer risks. *Id*. As one study noted, the consistent finding that ranitidine use is not associated with any cancer, much less that it causes cancer, suggests "that few people were exposed to a high enough level of NDMA to increase the risk of cancer."[5] In contrast, Plaintiffs' experts cannot accurately compare NDMA exposures in food or rubber fumes to the alleged NDMA exposures from ranitidine, nor account for the fact that food and rubber fumes contain other chemicals that—unlike NDMA—are established carcinogens.

The Superior Court's other reasons for focusing on NDMA are likewise erroneous. The Court cited ranitidine's withdrawal from the market, Op.19-20, the fact that Zantac was marketed to individuals with gastrointestinal disorders and allegedly promoted off-label for long-term use, Op.21, and GSK's acknowledgment

[5] Masao Iwagami, et al., "Risk of Cancer in Association with Ranitidine and Nizatidine vs. Other H2 Blockers," *Drug Safety* 44:369 (2021) (A-011481).

in one document that NDMA is a probable human carcinogen, Op.21-22. But none of those facts is relevant to whether general-causation opinions should focus on ranitidine or NDMA.[6] The Court said it could not "turn a blind eye to the focus on NDMA, especially where the record suggests that Defendants acknowledged the dangers of it," Op.21, but the Court seems to have misunderstood why a reliable causation opinion must focus on ranitidine. The point is not that general causation should focus on ranitidine because NDMA is always harmless. Rather, a reliable analysis must focus on ranitidine because, regardless of the risks NDMA may pose, studying ranitidine use necessarily accounts for whatever amount of NDMA was in the ranitidine products consumed.

The Court's reliance on *Asbestos* is especially misplaced because that decision expressly rejects the Court's approach. The *Asbestos* plaintiffs alleged they contracted mesothelioma and other asbestos-related diseases from working with "automotive friction products"—brakes and clutches—that contained chrysotile asbestos. 911 A.2d at 1180. The plaintiffs argued there was adequate evidence of general causation because "friction products contain chrysotile, chrysotile causes disease and, therefore, friction products cause disease." *Id*. at 1201. "In other words," plaintiffs argued that the defendant's "admission that its products contain a

[6] It is, moreover, well-settled that "regulatory thresholds" are not reliable evidence of causation. *Zantac*, 644 F. Supp. 3d at 1285.

known carcinogen ends the inquiry." *Id*. at 1202. The court "rejected this approach" and "found that plaintiffs must establish that their experts can reliably conclude that exposure to *friction products* increases the risk of contracting an asbestos-related disease." *Id*. The court recognized that the parties "were litigating the reliability of plaintiffs' medical and scientific evidence that exposure to *friction products* (not just chrysotile) increases the risk of contracting an asbestos-related disease." *Id*. at 1179.

When this Court reviewed *Asbestos*, it endorsed the trial court's view that the general-causation analysis must focus on the product, stating that the plaintiff "was required to prove that Ford's *friction products* are capable of causing mesothelioma." *Grenier II*, 981 A.2d at 538 (emphasis added). That approach is also consistent with federal caselaw. In *Chapman*, the plaintiffs argued they satisfied their burden on general causation because the product at issue contained zinc, and there was a "general consensus in the medical community that ingestion of zinc causes [myelopathy]." 766 F.3d at 1304. The Eleventh Circuit rejected that position, holding that plaintiffs' burden was not to prove that zinc causes myelopathy, but to "prov[e] the zinc *in Fixodent* causes myelopathy." *Id*. at 1308 (emphasis added). Similarly, although gasoline contains benzene, a plaintiffs' expert cannot rely on literature about benzene concentrate to conclude that gasoline causes leukemia. *See Burst v. Shell Oil Co.*, 2015 WL 3755953, at *9 (E.D. La. June 16, 2015) (the issue "is whether exposure to gasoline containing benzene can cause

[leukemia], not whether exposure to benzene generally can cause [leukemia]"), *aff'd*, 650 F. Appx. 170 (5th Cir. 2016); *Henricksen v. ConocoPhillips Co.*, 605 F. Supp. 2d 1142, 1156 (E.D. Wash. 2009) ("[T]he court cannot simply presume that the qualitative toxic and carcinogenic effects of benzene from any source are the same.").

In litigation where Plaintiffs allege that ranitidine use caused them to develop cancer, a reliable causation analysis must focus on ranitidine. The Superior Court erred when it determined that the focus should, instead, be on NDMA and its effects in distinct, non-ranitidine contexts.

2. The Superior Court did not require Plaintiffs' experts to demonstrate that non-ranitidine studies involved identical NDMA exposures, nor did any expert reliably do so.

Although the general-causation analysis must always focus on the product at issue, that does not imply that experts can never base an opinion on evidence of a toxic agent's effects in other circumstances. Yet to provide such an opinion reliably, Delaware precedent requires an expert to establish that the exposures examined in the non-product studies are "indistinguishable" from exposure to the product at issue. *Asbestos*, 911 A.2d at 1202; *see Grenier II*, 981 A.2d at 536-37 (affirming *Asbestos*). The Superior Court did not require Plaintiffs' experts to make that showing, nor could they do so.

The Court found support for its focus on NDMA in a truncated quotation from *Asbestos*, stating that the plaintiffs could attempt to prove general causation "by presenting competent evidence that friction products, in certain circumstances, release respirable products [that cause cancer]." Op.23 (quoting *Asbestos*, 911 A.2d at 1202). But, as discussed above, *Asbestos* did not permit the plaintiffs to rest their case on evidence that the friction products released allegedly carcinogenic components. The required showing was more specific: that the friction products "release respirable chrysotile fibers that are *indistinguishable* in size and other characteristics from [the] unrefined chrysotile fibers" that other asbestos-containing products release. 911 A.2d at 1202 (emphasis added). With that "evidentiary predicate in hand," the plaintiffs' experts could turn to the "undisputed" evidence that unrefined chrysotile fibers can cause mesothelioma when inhaled. *Id*. at 1202. Thus, to rely on evidence concerning other asbestos-containing products, the plaintiffs' experts had to show that the exposures from those products were *materially identical* to exposures from the defendants' products.

This Court enforced that requirement vigorously when it reviewed the *Asbestos* decision. The trial court originally found that the experts had appropriately relied on studies concerning other asbestos exposures because, in part, one expert reviewed fibers from friction products using an electron microscope and found "no basis to distinguish the surface characteristics of friction fibers from those of other

chrysotile fibers." *Id*. at 1203. But this Court found that the expert's testimony did not support that conclusion and remanded for reconsideration. *Gen. Motors Corp. v. Grenier ("Grenier I")*, 981 A.2d 524, 528-30 (Del. 2009). The trial court then clarified its decision, and this Court affirmed. The expert had "provide[d] the necessary scientific basis" to conclude "the two forms of chrysotile are equally carcinogenic" by submitting published research comparing "the morphology, size and shape" of the fibers, which are the "primary factors that explain the carcinogenicity of asbestos." *Grenier II*, 981 A.2d at 536-37.

The Superior Court did not require Plaintiffs' experts to make any similar showing of equivalence between exposure to NDMA in ranitidine and exposure to NDMA in food and rubber dust and fumes. Nor could they have made that showing. Plaintiffs' general-causation experts did not undertake the sort of painstaking, peer-reviewed analysis that this Court found sufficient in *Grenier II*. ***No independent scientist has ever relied on dietary and occupational studies to conclude that ranitidine causes cancer.*** *See, e.g.*, A-0113333 (study authors noting that "analyses of cancer risk following ranitidine use *per se*—rather than studies based on debatable estimates of NDMA exposure—are more informative"). The lack of "general acceptance" of Plaintiffs' experts' methodology in the scientific community is an important factor indicating their approaches are unreliable, yet the Superior Court did not even consider that factor. *See Zantac*, 644 F. Supp. 3d at 1234.

Plaintiffs' experts conceded that they did not know whether the levels of NDMA in ranitidine were comparable to the levels of NDMA that subjects in the dietary and occupational studies ingested or inhaled. *See* A-007814-16 (Dr. Miller acknowledging that he did not "attempt[] to correlate the doses observed" in the non-ranitidine studies "to the doses in ranitidine").[7] And they acknowledged that those studies did not isolate any effect of NDMA from the effects of the established carcinogens in the foods and rubber fumes studied, *see* A-003147-49 (Dr. Hatzaras conceding that rubber-worker study "was not able to isolate NDMA exposure, as opposed to other nitrosamine exposures"), and in some cases did not even collect data on the cancer at issue, *see* A-007499-500 (Dr. Margulis admitting that "none of those rubber worker studies reported an increased risk of kidney cancer"). The Court did not address those enormous gaps between the experts' opinions and the studies on which they relied, and instead declared that the experts could reliably focus on

[7] Plaintiffs offered an expert, Dr. Sawyer, to "convert the inhalation doses of NDMA" from one rubber-worker study "into an equivalent oral dose," Op.39, but the general-causation experts did not rely on Dr. Sawyer's opinion to establish a threshold dose (which they declined to provide) or to bridge the gap between ranitidine and non-ranitidine studies. Nor did the Court mention Dr. Sawyer's opinion as a basis for permitting Plaintiffs' general-causation experts to focus on the non-ranitidine studies.

NDMA studies, while minimizing ranitidine studies for inconsistent reasons, because of evidence that NDMA can be hazardous in other contexts.[8]

* * *

The Superior Court erred, and contravened Delaware precedent, when it held that a reliable general-causation analysis in this litigation could focus on NDMA rather than ranitidine. This Court's *Grenier* decisions confirm that in Delaware, as in federal courts, general causation must focus on the product at issue, not the allegedly toxic agent that the product contains. A general-causation expert may rely on non-product studies of the agent only if the expert has reliably shown that exposure to the product and the exposures to the agent in the other contexts would be "equally carcinogenic." *Grenier II*, 981 A.2d at 537. The Superior Court did not require Plaintiffs' experts to make that showing here, nor could they have done so.

Were this Court to affirm the Superior Court's ruling, a general-causation expert could base an opinion on studies of an alleged carcinogen unrelated to the product at issue, even when peer-reviewed epidemiological studies of the product and the relevant regulatory authority's conclusion do not support their opinion. While this Court should hold that all the experts' opinions are subject to exclusion

[8] Plaintiffs' experts' failure to identify a threshold dose for ranitidine or NDMA, discussed above, amplifies the unreliability of their extrapolation from non-ranitidine data.

for failure to identify a threshold dose, if it does not, then it should remand to the Superior Court to conduct a new Rule 702 analysis where the general-causation analysis focuses on ranitidine rather than NDMA.

III. THE SUPERIOR COURT APPLIED AN UNDULY LENIENT STANDARD AND WRONGLY HELD THAT ALL METHODOLOGICAL CRITIQUES WENT TO WEIGHT, NOT ADMISSIBILITY.

A. Question Presented

Whether Delaware courts apply a "liberal thrust favoring admission" in their Rule 702 analyses, Op.13, and consider faults in an expert's application of his methodology to go "to the weight, not the admissibility" of his opinion. Op.14.

B. Scope of Review

The Court reviews legal conclusions *de novo* and a decision to admit or exclude expert evidence for abuse of discretion. *See supra*, at 18.

C. Merits of Argument

1. Rule 702 analyses should not be conducted with a "liberal thrust favoring admission."

The Superior Court's assertion that Rule 702 analyses should be conducted with a "liberal thrust favoring admission" is unprecedented in Delaware caselaw and misinterprets the original *Daubert* decision. The Supreme Court used that phrase in *Daubert* only to explain that "a rigid 'general acceptance' requirement," like that imposed by the *Frye* test, "would be at odds with the 'liberal thrust' of the Federal Rules." 509 U.S. 579, 588 (1993). The Supreme Court never suggested that the *Daubert* standard *itself*—which requires a trial court to assess the "scientific validity and thus the evidentiary relevance and reliability" of the methodology underlying an expert's opinion—should be approached with a "thrust" one way or the other. *Id*. at

594-95. Rather, to fulfill its "gatekeeping role" under Rule 702, a trial court should undertake the *Daubert* inquiry objectively, without a thumb on the scale. Indeed, it is "[t]he party seeking to introduce the expert testimony" who "bears the burden of establishing its admissibility by a preponderance of the evidence." *Bowen*, 906 A.2d at 795. That burden is especially heavy when, as here, the experts' conclusions are at odds with those of independent scientists, regulators, and the medical community. *See* F.R.E. 702, note to 2000 amendment (adopted by Delaware) (when an expert "reaches a conclusion that other experts in the field would not reach, the trial court may fairly suspect that the principles and methods have not been faithfully applied").

The Court drew the erroneous idea that Rule 702 should be applied with a "liberal thrust favoring admission" from a Ninth Circuit opinion decided 21 years after *Daubert*. *See Messick*, 747 F.3d at 1196. The phrase has since taken on a life of its own in the Ninth Circuit, producing a bias toward admission that has made the Circuit a recognized outlier. The Court relied extensively on a federal district court decision that *expressly acknowledged* it was applying a lenient standard, explaining that the Ninth Circuit's "great emphasis" on the "liberal thrust" language had produced "more room for deference to experts in close cases than might be

appropriate in some other Circuits." *In re Roundup Prods. Liab. Litig.*, 390 F. Supp. 3d 1102, 1112-13 (N.D. Cal. 2018).[9]

Delaware should not adopt an outlier standard that misinterprets *Daubert*. This Court should, instead, make clear that Delaware courts will assess the reliability of experts' methodologies objectively, without any presumption of admission or exclusion.

2. A trial court must ensure that an expert applies his methodology reliably.

Because it applied a "liberal thrust favoring admission," the Superior Court repeatedly held that criticism of how Plaintiffs' experts applied their methodologies went to "the weight, not the admissibility" of their opinions. Op.13-14. As a result, the Court did not consider most of the flaws Defendants identified in the experts' methodologies, including that they cherry-picked favorable evidence to avoid

[9] In affirming that decision, the Ninth Circuit denied that it was "an outlier following a more flexible *Daubert* approach than other circuits." *Hardeman v. Monsanto Co.*, 997 F.3d 941, 961 (9th Cir. 2021). Even if that is correct, *but see* Thomas D. Schroeder, *Toward A More Apparent Approach to Considering the Admission of Expert Testimony*, 95 NOTRE DAME L. REV. 2039, 2050 (2020) ("Ninth Circuit caselaw appears to interpret *Daubert* as liberalizing the admission of expert testimony, which may explain decisions from that circuit that set it apart from most others."), the point here is that the federal district court expressly acknowledged it was applying a lenient standard and the Superior Court relied heavily on that decision.

grappling with the totality of the ranitidine epidemiology and weighed the studies they considered in a result-driven manner.

The Court's approach to its gatekeeping responsibility is inconsistent with Rule 702's text, this Court's precedent, and robust federal authority. A trial court cannot simply send "[a]ny quarrel with the application of [the expert's] methodology" to the jury. Op.55. Rule 702 renders opinion testimony admissible only if "the expert has reliably *applied* [his] principles and methods to the facts of the case," D.R.E. 702(d) (emphasis added), and entrusts the trial court with making that determination. Many federal appellate decisions, applying the identically worded version of the federal rule, have "required" a trial judge to "take a hard look" at an expert's opinion to ensure that his analysis is "reliable at every step of the way." *Mirena II*, 982 F.3d at 123; *see, e.g.*, *Amorgianos v. Nat'l R.R. Passenger Corp.*, 303 F.3d 256, 267 (2d Cir. 2002) (trial court must "undertake a rigorous examination of the facts on which the expert relies . . . and how the expert applies the facts and methods to the case at hand"); *In re Zoloft (Sertraline Hydrochloride) Prods. Liab. Litig.*, 858 F.3d 787, 797 (3d Cir. 2017) ("*any* step that renders the analysis unreliable under the *Daubert* factors *renders the expert's testimony inadmissible*"); F.R.E. 702, note to 2000 amendment ("[T]he trial court must scrutinize not only the principles and methods used by the expert, but also whether those principles and methods have been properly applied to the facts of the case."). Without such

scrutiny, there is a substantial risk that unreliable opinions will "exert[] undue influence on the jury." *United States v. Hall*, 93 F.3d 1337, 1343 (7th Cir. 1996).

Accordingly, it is not sufficient that a general-causation expert purport to employ an established methodology. Plaintiffs' experts referred to the Bradford Hill framework, a set of criteria used by epidemiologists to determine whether an association between an alleged toxin and a disease is causal, but invoking that framework is not some magic incantation that opens the Rule 702 gate. The trial court has "an independent duty to ensure that all experts 'reliably applied' Bradford Hill" to the evidence before them. *In re Onglyza (Saxagliptin) & Kombiglyze (Saxagliptin & Metformin) Prods. Liab. Litig.*, 93 F.4th 339, 347 (6th Cir. 2024) (quoting F.R.E. 702(d)); *accord* A-024624 (Florida decision) (finding expert's "'particular method' of applying Bradford Hill criteria was unreliable" for failure to engage with "the published epidemiological studies"). Here, Plaintiffs' experts inconsistently applied Bradford Hill's criteria across the entire body of the ranitidine epidemiological literature, minimizing the lack of consistent findings of an association, for example, and the absence of a demonstrated dose-response relationship—*i.e.*, greater ranitidine consumption leading to a greater risk of cancer.

Courts in multiple mass-tort litigations have found that the same flaws that Defendants identified in Plaintiffs' experts' application of Bradford Hill render causation opinions inadmissible. "[C]herry-picking" favorable evidence, for

example, requires exclusion of an expert's opinion because it "undermines the principles of the scientific method and is a quintessential example of applying methodologies (valid or otherwise) in an unreliable fashion." *Onglyza*, 93 F.4th at 347 (quoting *Lipitor*, 892 F.3d at 634); *In re Acetaminophen – ASD-ADHD Prods. Liab. Litig.*, 707 F. Supp. 3d 309, 336 (S.D.N.Y. 2023) (same); *see Daniels-Feasel v. Forest Pharms., Inc.*, 2023 WL 4837521, at *3 (2d Cir. July 28, 2023) (affirming exclusion where expert "cherry-picked only favorable studies to support his causal conclusion"). So too with the failure to consistently and objectively weigh the evidence and studies under consideration. To ensure that Bradford Hill "is truly a methodology, rather than a mere conclusion-oriented selection process . . . there must be a scientific method of weighting that is used and explained." *Zoloft*, 858 F.3d at 796. Otherwise, multi-criteria frameworks like Bradford Hill are "virtually standardless and their applications to a particular problem can prove unacceptably manipulable." *In re Acetaminophen*, 707 F. Supp. 3d at 357.

This Court likewise has recognized that Rule 702 requires not only that experts identify a reliable methodology, but that they apply that methodology reliably to the facts of the case. In *Bowen*, for example, a plaintiffs' expert applied an established model for estimating the amount of a substance that human skin will absorb, and the plaintiffs argued his opinion was admissible simply because he employed a "widely accepted methodology." 906 A.2d at 797. But this Court noted

that "the issue" was "not whether the [] model is ever a reliable tool," but whether it was applied reliably there. *Id*. The expert's decision to "rely exclusively upon the [] model and to ignore or discard 'more favorable' methodologies"—in other words, cherry-picking—"directly undermine[d] the reliability of his methodology." *Id*. Other Delaware decisions have similarly scrutinized the factual and analytic bases for experts' opinions, and excluded opinions that lack adequate support. *See, e.g.*, *Zayas*, 273 A.3d at 788 (reversing admission of opinion that "was based upon an incomplete factual predicate"); *Scaife v. Astrazeneca LP*, 2009 WL 1610575, at *18 (Del. Super. Ct. June 9, 2009) (excluding opinion because "the expert cannot accept some but reject other data from the medical literature without explaining the bases for her acceptance or rejection"). That is the type of rigorous review of an expert's analysis that Rule 702 requires, and which the Court declined to undertake here.

In holding that criticisms of how an expert applies his methodology go to weight, rather than admissibility, the Superior Court relied on outdated authority that has been effectively overruled. The Court's principal support for its approach was *McCullock v. H.B. Fuller Co.*, 61 F.3d 1038 (2d Cir. 1998), which held that "fault in [an expert's] use of differential etiology as a methodology, or lack of textual authority for his opinion, go to the weight, not the admissibility, of his testimony." *Id*. at 1044. The Court cited *McCullock* six times, as it repeatedly declined to consider Defendants' methodological critiques. *See* Op.14 & n.59, 39, 40, 42, 46,

47. But the Second Circuit restricted *McCullock* to its facts in *Ruggiero v. Warner-Lambert Co.*, 424 F.3d 249 (2d Cir. 2005), emphasizing that the case only addressed the expert opinion "*in that case*." *Id*. at 255. *Ruggiero* made clear that a liberal application of *McCullock* was untenable under *Joiner* and held that "when an expert opinion is based on data, a methodology, or studies that are simply inadequate to support the conclusions reached, *Daubert* and Rule 702 *mandate* the exclusion of the unreliable opinion testimony." *Id*. (quoting *Amorgianos*, 303 F.3d at 266) (emphasis added). Even the Ninth Circuit has held that dismissing an argument as "'going to the weight, not admissibility, of [the expert's] testimony' is *not* a reliability determination." *United States v. Valencia-Lopez*, 971 F.3d 891, 899 (9th Cir. 2020) (quoting *Nease v. Ford Motor Co.*, 848 F.3d 219, 230 (4th Cir. 2017)).

The Court's refusal to scrutinize Plaintiffs' experts' reasoning led it to bless opinions with significant hallmarks of unreliability, including:

- Dr. Neugut's reliance on non-statistically significant results to support his opinion, even though in his professional work he does not "conclude that there's an association between an exposure and an outcome unless the findings are statistically significant." A-009046-47.
- Dr. Rustgi declining to provide any explanation of how he weighed the diverse set of studies he considered. *See* A-010044. ("I think they're all important. I can't say that I emphasize one over the other.").

- Dr. Miller prioritizing studies that compare ranitidine users to the general population, despite acknowledging that studies comparing ranitidine users to users of other heartburn medications better control for confounders and thus deliver "stronger, more reliable results." A-007841-42.
- Dr. Trock admitting that the exact probability that NDMA is responsible for the outcomes observed in the occupational studies is "really speculation" that he "can't put a number on." A-011011, A-010973.
- Dr. Margulis opining that ranitidine can cause kidney cancer while conceding in peer-reviewed literature that the data demonstrate association "but not causation." *Supra*, at 17 n.5.

* * *

Were this Court to embrace the Superior Court's lenient Rule 702 standard, Delaware would become an outlier among state and federal courts, and Delaware-based defendants would be forced to try cases predicated on flimsy expert opinions that would be excluded under *Daubert* in other jurisdictions. That is what occurred here, where Plaintiffs fled from the proper application of *Daubert* in federal court. Since the Court's ruling, approximately 7,000 additional Zantac lawsuits have been filed in Delaware.

The Superior Court authorized the introduction of opinions that no scientist or medical body outside this litigation holds, that contradict the conclusions of the

FDA and its European equivalent, and that two other courts applying *Daubert* have excluded. Among many other flaws, the experts apply inconsistent methods and discount the overwhelming body of epidemiological data showing no evidence of a causal association between ranitidine and any type of cancer. Delaware law requires more of experts, and the application of the proper standard would result in their exclusion under Rule 702.

CONCLUSION

The decision below should be reversed.

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IN THE SUPREME COURT OF THE STATE OF DELAWARE

IN RE ZANTAC (RANITIDINE) LITIGATION	**No. 255, 2024** CASE BELOW: SUPERIOR COURT OF THE STATE OF DELAWARE, C.A. NO. N22C-09-101

CERTIFICATE OF COMPLIANCE WITH TYPEFACE REQUIREMENT AND TYPE-VOLUME LIMITATION

This brief complies with the typeface requirement of Rule 13(a)(1) because it has been prepared in Times New Roman 14-point typeface using Microsoft Word.

This brief complies with the type-volume limitation of Rule 14(d)(i) because it contains 9,959 words, which were counted by Microsoft Word.

DATED: October 1, 2024

/s/ Patrick M. Brannigan
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CERTIFICATE OF SERVICE

I, Patrick M. Brannigan, hereby certify that on this 1st day of October, 2024, I caused to be served a true and correct copy of the foregoing **APPELLANTS' OPENING BRIEF** upon the following counsel of record via email and File & Serve*Xpress*:

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Opinion of the Superior Court

Omnibus Order on Motions to Exclude Expert Opinions
In re Zantac (Ranitidine) Litigation, C.A. No. N22C-09-101 ZAN
May 31, 2024 (corrected June 3, 2024)

IN THE SUPERIOR COURT OF THE STATE OF DELAWARE

IN RE ZANTAC (RANITIDINE) LITIGATION	)	C.A. NO. N22C-09-101 ZAN

Submitted: March 7, 2024
Decided: May 31, 2024
Corrected: June 3, 2024

OMNIBUS ORDER
ON MOTIONS TO EXCLUDE EXPERT OPINIONS

I. INTRODUCTION

Nearly 75,000 Plaintiffs seek to be heard in Delaware for claims alleging that their cancer was caused due to the ingestion of a heartburn medication commonly known as Zantac. In this early stage of these proceedings, before the Court for disposition are the parties' competing motions to exclude expert testimony pursuant to Rule 702 of the Delaware Rules of Evidence and *Daubert v. Merrell Dow Pharm. Inc.*,[1] (the "Motions").

The Motions were the subject of discovery, a three-day "*Daubert*" hearing, multiple layers of briefing, and post-hearing submissions all supported by more than

[1] 509 U.S. 579 (1993).

forty volumes of exhibits. Having considered the pleadings, oral arguments, supplemental submissions, and the full record herein, for the reasons now stated, the parties' Motions are **DENIED.**

II. FACTUAL AND PROCEDURAL HISTORY[2]

This case involves a molecule known as ranitidine. Ranitidine is marketed under the label name of Zantac. N-Nitrosodimethylamine ("NDMA") is found in ranitidine.[3] NDMA causes cancer.[4]

Zantac is a part of a class of medications known as Histamine-2 Receptor Antagonists ("H2Ras").[5] Ranitidine is a histamine-2 receptor blocker used to "treat heartburn and many other gastro-intestinal disorders, including duodenal ulcers, gastroesophageal reflux disease ("GERD") and esophagitis."[6]

In 1983, based on extensive testing, including humans, the FDA approved ranitidine for prescription use to treat ulcers and later approved it to treat other

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2 The recitation of the history and facts in this section are for context only.

3 *See* Plaintiffs' Opposition to Defendants' Motion to Exclude General Causation Experts' Opinions at 14, Trans. ID 71670509 (Dec. 20, 2023) (herein "Pls.' Opp'n to Defs.' Mot. to Exclude Gen. Causation Experts' Op.").

4 *Id.*

5 Defendants' Brief in Support of Brand Defendants' and Patheon's Motion to Exclude Plaintiffs' General Causation Experts' Opinions at 3, Trans. ID 71408977 (Nov. 15, 2023) (herein "Defs.' Br. in Supp. of Brand Defs.' & Patheon's Mot. to Exclude Pls.' Gen. Causation Experts' Op.").

6 *In re Zantac*, 644 F. Supp.3d 1075, 1095 (S.D. Fla. 2022).

stomach and esophageal conditions.[7] In 1995, the FDA authorized ranitidine for over-the-counter ("OTC") use.[8] By 2004, the FDA had further approved higher dosages of ranitidine for OTC use.[9]

Zantac was on the market for more than 35 years.[10] During approximately four decades of marketing, there were four brand pharmaceutical companies and generic manufacturers that sold versions of the product.[11] GlaxoSmithKline ("GSK") developed the medication and initially marketed it in prescription form.[12] In 1995, GSK marketed it as an OTC in a joint venture with a predecessor of Pfizer.[13] In 1998, GSK transferred its rights to sell OTC Zantac in the U.S. to that Pfizer predecessor.[14] In 2006, Defendant Boehringer Ingelheim ("BI") acquired the rights to sell OTC Zantac.[15] In 2017, Defendant Sanofi began selling OTC Zantac after acquiring the brand from BI.[16]

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7 Defs.' Br. in Supp. of Brand Defs.' & Patheon's Mot. to Exclude Pls.' Gen. Causation Experts' Op. at 4.

8 *Id.*

9 *Id.*

10 *Id.*

11 *Id.*

12 Defs.' Br. in Supp. of Brand Defs.' & Patheon's Mot. to Exclude Pls.' Gen. Causation Experts' Op. at 4, n1.

13 *Id.*

14 *Id.*

15 *Id.*

16 *Id.*

In September of 2019, Valisure, an online pharmacy submitted a citizen petition to the FDA claiming detection of "extremely high levels of N-Nitrosodimethylamine (NDMA)" in ranitidine.[17] Valisure reported NDMA at levels in excess of three million nanograms per tablet. This far exceeded the limit of 96 nanograms per day that the FDA had set for NDMA ingestion in the context of an unrelated class of medications.[18]

After reviewing Valisure's petition, the FDA raised concerns about the testing methodology.[19] FDA and ranitidine manufacturers studied NDMA in ranitidine and examined whether ranitidine use increases cancer risks in patients.[20] Over the next month, some tests revealed amounts lower than what Valisure reported, and some lots tested revealed amounts below the acceptable daily intake (ADI).[21]

In September and October of 2019, then-existing ranitidine manufacturers recalled their products. And by April 2020—after further testing confirmed NDMA levels in some samples continued to exceed ADI—the FDA requested manufacturers initiate a market withdrawal of all remaining batches then remaining on the market.[22] After the recall of ranitidine-containing Zantac, litigation ensued around the country.

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[17] Defs.' Br. in Supp. of Brand Defs.' & Patheon's Mot. to Exclude Pls.' Gen. Causation Experts' Op. at 5.

[18] *Id.*

[19] *Id.*

[20] *Id.*

[21] *Id.* (citing FDA, *FDA Statement: Statement on new Testing Results, Including Low Levels of Impurities in Ranitidine Drugs* (2019) (Brown Decl. Ex. 89) at 1).

[22] *Id.* at 8.

A. NATIONAL PROCEDURAL HISTORY - THE "MDL"[23]

To address these claims, on February 6, 2020, the United States Judicial Panel on Multidistrict Litigation established a multidistrict litigation process (the "MDL") in the U.S. District Court for the Southern District of Florida in West Palm Beach for all pretrial purposes. The Panel ordered federal lawsuits for personal injury and economic damages from the purchase or use of Zantac to be transferred to the MDL.

As part of MDL management, a Census Registry ("The Registry") was created to allow the parties and the Court to "understand the nature of the unfiled claims that are a part" of the MDL.[24] The MDL Court held a *Daubert* hearing in early 2022.

On December 6, 2022, the MDL Court issued its opinion on *Daubert* and summary judgment motions ("MDL Order").[25] In its 200-page opinion, the MDL Court, in pertinent part, excluded those plaintiffs' experts' general causation opinions and granted summary judgment for Defendants.[26]

B. LITIGATION IN OTHER STATES

Similar suits were also proceeding in state courts throughout the United States. The largest one, other than here, was a coordinated proceeding in California, the

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[23] *See generally, In re Zantac*, 644 F.Supp.3d at 1095.

[24] *Id.* at 1096.

[25] As of the date of this ruling, it appears that the MDL decision is on appeal in the Eleventh Circuit Court of Appeals.

[26] *See generally, id.*

Judicial Council Coordinated Proceeding ("JCCP"). In the California state court, several thousand cases were being coordinated in the JCCP, with sixteen bellwether trials scheduled for 2024. The JCCP Plaintiffs were pursuing their claims for the same cancers claimed here. Those cases advanced beyond the general causation phase.[27]

C. THE PARTIES AND PROCEDURAL HISTORY HERE

Plaintiffs in this litigation were not before the federal MDL Court. Nor are the experts the same. Plaintiffs here are pursuing ten cancers—bladder, esophageal, gastric, liver, pancreatic, breast, colorectal, kidney, lung and prostate. Notably, in the MDL, Plaintiffs' Leadership (also not present here) notified that Court that it had decided not to pursue general causation expert reports for breast and kidney cancers and initially narrowed their list from ten to eight cancers.[28] In January of 2022, they again notified the MDL Court that they were not moving forward with certain cancers, and again, narrowed the list to five cancers. Thus, five of the cancer claims here were not before the MDL Court.[29]

In September of 2022, nearly 75,000 complaints were filed in this Court.

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[27] *See* Pls.' Opp'n to Defs.' Mot. to Exclude Gen. Causation Experts' Op. Ex 75.

[28] *In re Zantac*, 644 F.Supp.3d at 1098.

[29] *Id*. (The MDL noted in its final disclosure that the plaintiffs in the MDL intended to "prove that ranitidine causes bladder, esophageal, gastric, liver, and pancreatic cancers (the 'Designated Cancers'), as opposed to other cancers ('Non-Designated Cancers.'). The Defendants do not address Non-Designated Cancers in the *Daubert* motions, so individual cases in which Plaintiffs allege their ranitidine use caused their Non-Designated Cancers remain pending at this time and are not the subject of this Order.").

Plaintiffs allege Defendants collectively bear responsibility for their cancer diagnoses, and the related injuries or deaths caused from their ingestion of the medication known as Zantac.

The Defendants are GlaxoSmithKline LLC ("GSK"), Boehringer Ingelheim Pharmaceuticals, Inc., Boehringer Ingelheim Corporation, and Ingelheim U.S.A. Corporation (collectively, B.I.), Sanofi US Services Inc., Sanofi-Aventis U.S. LLC, and Chattem, Inc. (collectively, "Sanofi), Pfizer Inc. ("Pfizer") (together with all those just mentioned are referred to as the "Brand Defendants") and Patheon, (all collectively "Defendants").[30]

In these initial proceedings, the first phase addresses "general causation," which involves the question of whether the ingestion of this product is capable of causing cancer as alleged. To carry their burden at this stage, Plaintiffs have retained ten experts to offer opinions on general causation for the ten mentioned cancers. Defendants move to exclude them all.[31] Plaintiffs also move to exclude certain opinions proffered by Defendants' sole General Causation Expert, William C.

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[30] Brand Defendants' and Patheon's Motion to Exclude Plaintiffs' Expert Dr. Charles Jameson, Trans. ID 71409144 (Nov. 15, 2023) (herein "Brand Defs.' & Patheon's Mot. to Exclude Pls.' Expert Dr. Jameson").

[31] Defendants move to exclude all of Plaintiffs' General Causation Experts: Drs. Charles William Jameson, PhD; William Sawyer, PhD; Alfred I. Neugut, M.D., PhD; Vinod K. Rustgi M.D., MBA; Ioannis Hatzaras, M.D. MPH, PhD, F.A.C.S.; Dan J. Raz, M.D.; Bruce J. Trock, MPH, PhD; George Miller, M.D.; Pablo Leone, M.D.; and Vitaly Margulis, M.D. (collectively "Plaintiffs' General Causation Experts").

Zamboni, Pharm.D., PhD.

III. APPLICABLE LEGAL STANDARDS

As in any products liability case, each party bears the burden of proof on the admissibility of their expert opinion testimony.[32] Delaware Rule of Evidence 702 addresses the admissibility of expert testimony. It provides:

> A witness who is qualified as an expert by knowledge, skill, experience, training, or education may testify in the form of an opinion or otherwise if:
>
> (a) the expert's scientific, technical, or other specialized knowledge will help the trier of fact to understand the evidence or to determine a fact in issue;
>
> (b) the testimony is based on sufficient facts or data;
>
> (c) the testimony is the product of reliable principles and methods; and
>
> (d) the expert has reliably applied the principles and methods to the facts of the case.[33]

This rule is nearly identical to Federal Rule of Evidence 702.[34] Our Supreme Court has interpreted Federal Rule of Evidence 702, addressed the admissibility of expert testimony,[35] and adopted the holdings of *Daubert v. Merrell Dow Pharm.*,

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[32] *Minner v. Amer. Mort. & Guar. Co.*, 791 A.2d 826, 843 (Del. Super. 2000).

[33] D.R.E. 702.

[34] *Barrera v. Monsanto Co.*, 2019 WL 2331090, at *3 (Del. Super. May 31, 2019).; *see also Minner*, 791 A.2d at 833 n.2.

[35] *See Tumlinson v. Advanced Micro Devices, Inc.*, 81 A.3d 1264, 1269 (Del. 2013) (herein "*Tumlinson*").

Inc. ("*Daubert*") and its progeny as the correct interpretation of Delaware Rule of Evidence 702.[36]

A. THE *DAUBERT* STANDARD

Decided in 1993 by the United States Supreme Court, *Daubert* is a name well-known to most lawyers. Even so, the Court has urged litigants to appreciate "the perspective from which this Court will view so-called *Daubert* motions, and the process by which such motions will be addressed."[37] This encouragement merits respect, as *Daubert* at first blush may seem contradictory, expanding the power of the trial court by rejecting the "general acceptance" requirement for admissibility while at the same time emphasizing the limitations on the court's role in deference to the role of the jury.[38] And although *Daubert* rejected the exclusivity of the "general acceptance" requirement, an expert's "access to the courtroom is not unfettered."[39]

A few factors can be implicated in *Daubert* reviews. Some are enumerated in Rule 702; others, some identified *in Daubert*, are deemed nonexclusive.[40] But even the expanded list is not exclusive. None of the *Daubert* factors, specific or

[36] *See M.G. Bancorporation, Inc. v. LeBeau*, 737 A.2d 513, 522 (Del. 1999).

[37] *In re Asbestos Litig.*, 911 A.2d 1176, 1197 (Del. Super. 2006).

[38] *Minner*, 791 A.2d at 841.

[39] *In re Asbestos Litig.*, 911 A.2d at 1197.

[40] *Daubert*, 509 U.S. at 590.

otherwise, is binding on the trial court.[41] The trial court also has broad discretion to consider factors not articulated by *Daubert*.[42]

B. THE GATEKEEPER AND THE JURY

Predominant among *Daubert's* holdings is the recognition of the trial court's role as gatekeeper. In that role, the "Trial Judge…insure[s] that the scientific testimony is not only relevant but reliable."[43] While *Daubert* may require trial courts to dive deeper into certain preliminary facts than had historically been the case, it was not intended to abrogate the jury's constitutionally protected role as the ultimate fact-finder; a role the courts of this State defend vigorously.[44] *Daubert* and its progeny have repeatedly emphasized the importance of the trial system and the role of juries as the ultimate arbiters in expert evidentiary issues.

Therefore, "[a]s a threshold matter, *Daubert* neither requires nor empowers Trial Courts to determine which of . . . competing scientific theories has the best performance."[45] *Daubert* "requires only that the trial court determine whether the

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[41] *Tumlinson*, 81 A.3d at 1269.

[42] *Id.* at 1272–73; *Long v. Weider Nutrition Group*, 2004 WL 1543226, at *5 (Del. Super. June 25, 2004) (citing *Kumho Tire Co., Ltd. v. Carmichael*, 526 U.S. 137, 150 (1999)).

[43] *Minner*, 791 A.2d at 843 (citations omitted).

[44] *In re Asbestos Litig.*, 911 A.2d at 1199; *see. e.g., Kaur v. Bos. Sci. Corp.*, 2022 WL 1486178, at *3 (Del. Super. May 11, 2022) (an expert's investigations and assumptions "are readily subject to cross examination and to evaluation by the fact finder . . .").

[45] *Minner*, 791 A.2d at 848 (citation omitted).

proponent of the evidence has demonstrated that scientific conclusions have been generated using sound and reliable approaches."[46] But "the judge is not a scientist and the courtroom is not a science laboratory."[47] Indeed,

> "[i]t would be unreasonable to conclude that the subject of scientific testimony must be 'known' to a certainty . . . . [N]ot knowing the mechanism whereby a particular agent causes a particular effect is not always fatal to a plaintiff's claim. Causation can be proved even where we do not know precisely *how* the damage occurred if there is sufficiently compelling proof that the agent must have caused the damage *somehow*."[48]

As such, to determine the admissibility of scientific evidence consistent with *Daubert*, the trial judge must determine whether:

> (1) the witness is qualified as an expert by knowledge, skill, experience, training or education;
>
> (2) the evidence is relevant;
>
> (3) the expert's opinion is based upon information reasonably relied upon by the experts in the particular field;
>
> (4) the expert testimony will assist the trier of fact to understand the evidence or to determine a fact in

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[46] *In re Asbestos*, 911 A.2d at 1201; *see also Minner*, 791 A.2d at 842 (citations omitted).

[47] *Daubert*, 509 U.S. at 596–97 (quoting "Introduction to Reference Manual on Scientific Evidence", Fed. Jud. Ctr. at 2 (2000)).

[48] *Daubert v. Merrell Dow Pharms., Inc.*, 43 F.3d 1311, 1314 (9th Cir. 1995) (emphasis in original); *accord, Bowen v. E.I. Du Pont de Nemours and Co*., 2005 WL 1952859, at *9 (Del. Super. June 23, 2005) (herein "*Bowen*"), *aff'd* 906 A.2d 787 (Del. 2006) (explaining that the trial court need not "decide the admissibility of scientific evidence with the degree of certainty required in scientific circles").

issue; and

(5) the expert will not create unfair prejudice or confuse or mislead the jury.[49]

The gatekeeper must apply these particular "factors in a flexible manner that takes into account the particular specialty of the expert under review and the particular facts of the underlying case."[50] "Where the question of admissibility is a close one, exclusion of the evidence is not appropriate where cross examination, the presentation of contrary evidence and careful instruction regarding the burden of proof will insure that the jury is not misled or confused."[51] Restated, "[t]he reliability requirement is not a tool for the Court to use to exclude questionably reliable evidence."[52] This Court's refusal to establish a bright line rule for proving causality has previously been considered.[53] And no doubt, "the requisite proof necessary to establish causation will vary greatly case by case."[54]

The Supreme Court in *Daubert* was more direct: "Vigorous cross-examination, presentation of contrary evidence, and careful instruction on the burden of proof are the traditional and appropriate means of attacking shaky but admissible

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[49] *Bowen v. E.I. DuPont de Nemours & Co., Inc.,* 906 A2d 787, 795 (Del. 2006) (herein "*Bowen I*").

[50] *Id.*; *Scaife v. Astrazeneca LP*, 2009 WL 1610575, at *14 (Del. Super. June 9, 2009).

[51] *Bowen,* 2005 WL 1952859, at *8, *aff'd sub nom. Bowen II*, 906 A.2d at 787.

[52] *Barrera*, 2019 WL 2331090, at *10.

[53] *Id.* at *5 (citing *In re Zoloft*, 858 F.3d 787, 783 (3d Cir. 2017)).

[54] *In re Zoloft*, 858 F.3d at 787.

evidence."[55] Thus guided, courts confronted by "shaky but admissible evidence" conduct their *Daubert* analyses "with a 'liberal thrust' favoring admission."[56]

C. *DAUBERT* AND GENERAL CAUSATION CONSIDERATIONS

As the preliminary question concerns *general causation*, this Court finds the federal district court's approach in *In re Roundup Products Liability Litigation*[57] instructive:

> The question at this early phase in the proceedings - the 'general causation phase - is whether a reasonable jury could conclude that glyphosate . . . can cause Non Hodgkins Lymphoma ("NHL") . . . . There are two significant problems with the plaintiffs' presentation, which combine to make this a very close question.
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> * * *
>
> The evidence, viewed in its totality, seems too equivocal to support any firm conclusion that glyphosate causes NHL. This calls into question the credibility of some of the plaintiffs' experts, who have confidently identified a causal link.
>
> However, the question at this phase is not whether the plaintiffs' experts are right. The question is whether they have offered opinions that would be admissible at a jury trial. And the case law - particularly Ninth Circuit case law - emphasizes that a trial judge should not exclude an expert opinion merely because he thinks it's shaky, or

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[55] *Daubert*, 509 U.S. at 596.

[56] *Messick v. Novartis Pharmaceuticals Corp.*, 747 F.3d 1193, 1196 (9th Cir. 2014) (quoting *Daubert*, 509. U.S. at 588); *M.G. Bancorporation, Inc.*, 737 A.2d at 522.

[57] 390 F.Supp.3d 1102 (N.D. CA 2018) (herein "*In re Roundup*").

> because he thinks the jury will have cause to question the expert's credibility. So long as an opinion is premised on reliable science principles, it should not be excluded by the trial judge; instead, the weaknesses in an unpersuasive expert opinion can be exposed at trial, through cross-examination or testimony by opposing experts.[58]

In *Kennedy v. Collagen Corp.*, the Ninth Circuit emphasized that, while competing experts, science, experiments, and publications "may increase or lessen the value of the expert's testimony . . . their presence should not preclude the admission of the expert's testimony—they go to the weight, not the admissibility."[59]

Also important in *Daubert* proceedings is the gravity of the decision to be made. This Court in *In re Asbestos Litig.* placed particular emphasis on the risks attending expert opinion decisions:

> In the products liability context, an incorrect decision can either deprive a plaintiff of warranted compensation while discouraging other similarly situated individuals from trying to obtain compensation, or it can improperly impose liability in a manner that will cause the abandonment of an important product or technology. Either result is unacceptable. The Court must tread carefully.[60]

Notably, in *Long v. Weider Nutrition Group, Inc.*,[61] this Court likewise counseled judicial restraint from a different, but equally compelling, perspective:

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[58] *Id.* at 1108–09; *see also Kennedy v. Collagen Corp.*, 161 F.3d 1226, 1229–31 (9th Cir. 1998).

[59] 161 F.3d at 1230–31 (italics in original) (quoting *McCullock v. H.B. Fuller Co.*, 61 F.3d 1038, 1044 (2d Cir. 1995). *Accord*, *In re Asbestos Litig.*, 911 A.2d at 1180.

[60] *In re Asbestos Litig.*, 911 A.2d at 1200.

[61] 2004 WL 1543226, at *1.

> The first of several victims of a new toxic tort should not be barred from having their day in court simply because the medical literature, which will eventually show the connection between the victims' condition and the toxic substance, has not yet been completed.[62]

The cautions urged in *In re Asbestos* and *Long* seem self-evident even where the plaintiffs are few. Here, where there are nearly 75,000 plaintiffs, the implications are much more profound. Therefore, this Court proceeds cautiously.

IV. DISCUSSION

A. THE DISCRETIONARY MDL ORDER

Defendants extol the MDL Court's decision with great fervor.[63] Several issues confound that reliance. First, the Delaware Supreme Court has made plain that issues of admissibility, as procedural questions, are governed by Delaware law.[64] Therefore, Delaware evidentiary decisions control here.[65]

For example:

- that an expert may change her opinion goes to the weight, not the admissibility, of the expert opinion;[66]

- the use of animal studies in the course of an expert

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[62] *Id*. at 6 (quoting *Turner v. Iowa Fire Equip. Co*., 229 F.3d 1202, 1208–09 (8th Cir. 2000)).

[63] Defs.' Br. in Supp. of Brand Defs.' & Patheon's Mot. to Exclude Pls.' Gen. Causation Experts' Op. at 13–37.

[64] *Tumlinson*, 81 A.3d at 1270.

[65] *Id*. at 1273 (stating that it is improper to consider the law of a foreign forum when the admissibility of evidence is a Delaware issue).

[66] *Barrera*, 2019 WL 2331090, at *11.

analysis does not bar admissibility of the expert opinion on human disease;[67]

- Delaware law holds that statistical significance is "not necessary to prove causality";[68]

- Delaware does not recognize a "threshold dose" requirement as part of the general causation analysis; an issue discussed below;[69]

- epidemiological studies are not required as a threshold for the admission of an expert opinion on general causation.[70]

Second, the MDL Order concerned the exclusion of different experts; none of whom are designated nor challenged here.[71]

Third, similar to other state courts that considered and opted not to be bound by the MDL Order (e.g., the California JCCP Court) so, too, here, this Court views the MDL Order as a "discretionary decision on the exclusion of evidence."[72] "Two different trial judges can review the same evidence, weigh the evidence differently,

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[67] *Id.* at *14.

[68] *Id.* at *4; *see In re Zoloft*, 858 F.3d at 793.

[69] *Barrera*, 2019 WL 2331090, at *5.

[70] *Long*, 2004 WL 1543226, at *6; *see also Tumlinson v. Advanced Micro Devices, Inc.*, 2013 WL 7084888, at *9 (Del. Super. Oct. 15, 2013) (herein "*Tumlinson II*"), *aff'd*, 81 A.3d 1264 (Del. 2013) (stating that the Bradford Hill factors are not all-inclusive and only establish a framework to establish causation).

[71] *See* Index of Exhibits in Support of Plaintiffs' Opposition to Defendants' Motion to Exclude Plaintiffs' General Causation Experts' Opinions, Trans. ID 71666233 (Dec. 20, 2023) (herein the exhibits will be cited in reference to the corresponding motion, such as "Pls.' Opp'n to Defs.' Mot. to Exclude Gen. Causation Experts' Op., Ex. _") Ex. 75 at 8.

[72] *Id.* at 6.

and make different decisions . . . ."[73] This is especially true where the evidentiary law governing some of the salient issues differs. Defendants' praise of the MDL Court's rationale breathes not a whisper to the differences in Delaware law implicated here.

Fourth, as the preceding discussion reflects, Delaware courts approach *Daubert* decisions cautiously and with deep deference for the role of juries as the ultimate fact finders. To that end, our trial courts need not definitely "resolve" every expert query posed, even those that might present "close calls" or "shaky opinions." When experts disagree, or credibility or other questions confound the reliability issue, resolution of those issues rests with the jurors.[74] Delaware courts are loath to step into the heart of technical debate between opposing scientists. In that regard, the jurisprudence reflected in the Floridian *Zantac* differs from Delaware's. This Court—with great respect for the hard judicial work done there—distinguishes that ruling from what was presented here.[75]

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[73] *See* Pls.' Opp'n to Defs.' Mot. to Exclude Gen. Causation Experts' Op. at 34; Ex. 75, at 6.

[74] *In re Asbestos Litig.*, 911 A.2d at 1207.

[75] The post-*Daubert* briefing here followed adjournment of the three-day *Daubert* hearing. Defendants' submissions are noteworthy only for their zealous endorsement yet again of *In Re Zantac* and ask this Court to agree that "[the] MDL Decision is a Roadmap for this Court." Of the 18 pages of argument in their Opening Post-*Daubert* brief, 14 pages are devoted to the MDL Order, which this Court has already addressed. Defendants also again cite to *Long v. Weider Nutrition*, 2004 WL 1543226 (Del. Super. June 25, 2004). *See id*., at 5. This Court affords great deference to the *Long* decision: in a case of this legal and medical gravity, the Court should proceed cautiously. *See Long*, 2004 WL 1543226, at *6; *see also In re Asbestos*, 911 A.2d at 1200.

B. GENERAL CAUSATION FOCUSES ON NDMA

The discrete issue before the Court at this stage is whether NDMA can cause cancer. Both sides disagree as to how to frame the general causation question. Plaintiffs cast the issue directly:

> It is undisputed that N-Nitrosodimethylamine ("NDMA") is found in ranitidine *and* that NDMA causes cancer. That is why the U.S. Food and Drug Administration ordered an immediate recall after independent testing showed unacceptable levels of NDMA in the drug. In turn, it would seem obvious then, that if a person ingested ranitidine with NDMA, they could develop cancer.[76]

Plaintiffs maintain that the issue is not whether ranitidine, untethered to NDMA, can cause cancer because *the cancer-causing agent is* NDMA, and its route of exposure to NDMA is through the ingestion of ranitidine.[77]

Conversely, Defendants frame the general causation question as turning on "the consensus of the scientific community that *ranitidine* use does not increase the risk of cancer, and the unreliable methodologies employed by Plaintiffs' experts [] to avoid that reality."[78] In support, Defendants cite the "largest and highest quality healthcare databases," "leading medical journals," "40 medical institutions, research

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[76] Pls.' Opp'n to Defs.' Mot. to Exclude Gen. Causation Experts' Op. at 14 (emphasis in original).

[77] *Id.* at 40 (emphasis in original).

[78] Brand Defendants' Opposition to Plaintiffs' Motion to Exclude Certain Opinions of Defendants' Expert William C. Zamboni at 1–2, Trans. ID 71683862 (Dec. 22, 2023) (herein "Brand Defs.' Opp'n to Pls.' Mot. to Exclude Certain Op. of Defs.' Expert Zamboni") (emphasis added).

topics" and "15 peer-reviewed studies" addressing "whether *ranitidine* causes cancer."[79] Defendants add that these "studies of ranitidine *necessarily account* for any exposure to NDMA contained in ranitidine products."[80]

Yet, Defendants do not dilate on how the studies "necessarily account" for any exposure to NDMA contained in ranitidine products. Whether describing source documents, like those above, or setting the predicate for a point of advocacy, Defendants speak in terms of ranitidine: "patients who took ranitidine,"[81] "whether ranitidine causes cancer,"[82] "studies of ranitidine,"[83] "exposure to NDMA contained in ranitidine,"[84] "'no demonstrable association' between ranitidine use and any cancer types[,] ranitidine patients,"[85] and "real-world ranitidine data in humans."[86]

At the same time, Defendants concede that in September and October of 2019, "as a precautionary public health measure, then-existing ranitidine manufacturers voluntarily recalled their ranitidine products *pending further investigation into the*

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[79] Defs.' Br. in Supp. of Brand Defs.' & Patheon's Mot. to Exclude Pls.' Gen. Causation Experts' Op. at 9–13 (emphasis added).

[80] *Id.* at 10 (emphasis added).

[81] *Id.* at 9.

[82] *Id.* at 10.

[83] *Id.*

[84] Defs.' Br. in Supp. of Brand Defs.' & Patheon's Mot. to Exclude Pls.' Gen. Causation Experts' Op.

[85] *Id.*

[86] *Id.* at 11 (quotation marks in original); *see also id.* at 12 ("[N]o evidence of a causal association between ranitidine therapy and . . . cancer . . . none of these organizations has concluded that ranitidine use increases the risk of any type of cancer.").

potential root-causes of NDMA found in some lots" of ranitidine.[87] Defendants likewise acknowledge that, in April 2020, *after* "further investigation" confirmed that NDMA levels in some samples *continued to exceed* the ADI, the "FDA requested that *manufacturers initiate a market withdrawal of any batches remaining in the market.*"[88] The recall was based on the FDA's conclusion that NDMA is a "substance that can cause cancer."[89]

Since the FDA recall, ranitidine is no longer sold in the United States and many other parts of the world.[90] Plaintiffs emphasize that no evidence has been offered that the FDA ever stated that ranitidine is safe to be returned to the market or that any Defendant has sought to do so.[91] And although Defendants place little significance on the recall, they also do not challenge that assertion.

Instead, they rely on an FDA July 2021 study (Florian) to suggest that its findings "do not support that ranitidine is converted to NDMA in a *general, healthy population*."[92] This does little to advance their arguments. If that were the only

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87 *Id.* at 8 (emphasis added).

88 *Id.* (emphasis added); *In re Zantac*, 644 F.Supp.3d at 1095–96.

89 Plaintiffs' Brief in Support of Plaintiffs' Motion to Exclude Certain Opinions of Defendants' Expert Dr. William C. Zamboni, Trans. ID 71466806 (Nov. 21, 2023) (herein "Pls.' Br. in Supp. of Pls.' Mot. to Exclude Certain Op. of Defs.' Expert Dr. Zamboni") at 2.

90 *In re Zantac*, 644 F.Supp.3d at 1091–92; *see also* Pls.' Br. in Supp. of Pls.' Mot. to Exclude Certain Op. of Defs.' Expert Dr. Zamboni at 4.

91 Pls.' Opp'n to Defs.' Mot. to Exclude Gen. Causation Experts' Op. at 19.

92 *Id.* at 11 (emphasis added) (referring to the Florian study).

issue here, that study might have some utility.

Zantac was not marketed to serve a generally healthy population. It was intended to treat persons with heartburn, and many other gastro-intestinal disorders, including duodenal ulcers, gastroesophageal reflux disease ("GERD") and esophagitis. Notably, the record suggests that at least one defendant understood the importance of marketing it to this population. The record suggests that Defendant GSK's marketing efforts, from day one, focused on the off-label promotion of Zantac for long-term use, despite the drug's approved indication only for short-term use. One GSK executive expressed that very sentiment in 1983.[93]

Nevertheless, Defendants insist that the inquiry should focus on ranitidine, not NDMA.[94] That focus is understandable, but the Court cannot turn a blind eye to the focus on NDMA, especially where the record suggests that Defendants acknowledged the dangers of it:

> On September 25, 2019, GSK's scientists prepared a Hazard Assessment Report on NDMA ("Hazard Assessment") to "protect the *scientists and anybody handling*" NDMA in the laboratory.[95] Some of its

[93] Pls.' Opp'n to Defs.' Mot. to Exclude Gen. Causation Experts' Op. Ex. 33, at 2 ("The sheer size of this opportunity and the potential rewards from it dwarf anything we've done so far. It's not just that Zantac is bigger than all our other products put together . . . It's bigger than the whole company. You've all heard the numbers. My mind finds it difficult to absorb all those zeroes . . .").

[94] Defs.' Br. in Supp. of Brand Defs.' & Patheon's Mot. to Exclude Pls.' Gen. Causation Experts' Op. at 9–10.

[95] Pls.' Opp'n to Defs.' Mot. to Exclude Gen. Causation Experts' Op. Ex. 12, at 16:1–17 (emphasis added).

conclusions:

> [NDMA] is reasonably anticipated to be a human carcinogen based on sufficient evidence of carcinogenicity from studies in experimental animals.
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> * * *
>
> There is overwhelming evidence that NDMA is mutagenic and clastogenic . . . Positive results have been observed in *human* as well as rodent cells.
>
> * * *
>
> Qualitatively, the metabolism of NDMA appears to be similar in humans and animals; as a result, *it is considered highly likely that NDMA is carcinogenic to humans*, potentially at relatively low levels of exposure.
>
> * * *
>
> *NDMA is a genotoxic carcinogen, and exposure should be reduced to the extent possible*.
>
> N-nitrosamines such as NDMA [] are considered carcinogens and have been implicated in human cancers such as bladder, esophagus, stomach and naso-pharynx.[96]

This fundamental dispute of whether the science should focus on ranitidine versus NDMA lies at the heart of every challenge mounted in the Motions. This Court was confronted with a similar issue in *In re Asbestos Litig*. The Court's ruling there speaks to Defendants' ranitidine premise:

> Plaintiffs must establish that their experts can reliably conclude that exposure to friction products increases the risk of contracting an asbestos-related disease. *This does*

[96] Pls.' Opp'n to Defs.' Mot. to Exclude Gen. Causation Experts' Op. at 19–20; Ex. 13, at 2.

> *not, however, preclude the plaintiffs from attempting to carry this burden by presenting competent evidence that friction products, in certain circumstances, release respirable products* [that can cause cancer].[97]

Similarly, in *Kennedy*, the Ninth Circuit rejected the trial court's refusal to consider collagen in a general causation analysis, emphasizing that "the body breaks down the collagen into amino acids, *which are then absorbed into the body*."[98] The *Kennedy* court reversed the trial court's ruling, finding that such evidence will assist the trier of fact and is therefore admissible under *Daubert* and Rule 702.[99] At this stage, the particular facts here compel the same conclusion.

For these reasons, this Court cannot constrain its gatekeeping function solely to the studies related to ranitidine. NDMA's dangers, the science, the studies, and the opinions therein must be given due consideration.

The Court now considers the specific challenges as to each expert.

C. PLAINTIFFS' *DAUBERT* CHALLENGE

Defendants have disclosed William C. Zamboni as their sole causation expert. Dr. Zamboni will opine, in part, that Defendant GSK's Tanner study, discussed below, is the type of study "often not submitted to FDA nor requested by the

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[97] *In re Asbestos Litig*., 911 A.2d at 1202 (emphasis added); *see also Kennedy*, 161 F.3d at 1229.

[98] *Kennedy*, 161 F.3d at 1229 (emphasis added).

[99] *Id*. at 1231; *see also* Pls.' Opp'n to Defs.' Mot. to Exclude Gen. Causation Experts' Op. Ex. 75 at 33–34 (holding that cases in California "do not suggest that experts cannot consider studies on NDMA and must rely on epidemiology studies regarding ranitidine.").

FDA."[100] Dr. Zamboni bases that conclusion on his "experience with drug development."[101] Plaintiffs move to exclude that one sentence opinion as wholly speculative, citing, *inter alia*, Dr. Zamboni's lack of relevant experience in FDA drug applications and his failure to review or consider documents relevant to the FDA's request of GSK for data on ranitidine studies.[102] Plaintiffs do not move to exclude the "majority" of Dr. Zamboni's opinions.[103]

Instead, they urge that "an expert is not permitted to opine on the FDA's state of mind," which, they claim, is exactly what Dr. Zamboni is doing.[104] Defendants do not quarrel with that proposition.

The Court is constrained to pause on the context in which Plaintiffs' Motion arises. Plaintiffs dedicate considerable argument to what it characterizes as GSK's concealment of material science pertaining to NDMA beginning in 1982. Plaintiffs'

[100] Brand Defs.' Opp'n to Pls.' Mot. to Exclude Certain Op. of Defs.' Expert Dr. Zamboni at 3 (citing Pls.' Br. in Supp. of Pls.' Mot. to Exclude Certain Op. of Defs.' Expert Dr. Zamboni Ex. 2, at 28).

[101] Pls.' Br. in Supp. of Pls.' Mot. to Exclude Certain Op. of Defs.' Expert Dr. Zamboni at 28; Ex. 2 at 1–2.

[102] Pls.' Br. in Supp. of Pls.' Mot. to Exclude Certain Op. of Defs.' Expert Dr. Zamboni at 29 ("Dr. Zamboni's opinion regarding what the FDA would not want to know was rendered without reference to the very document summarizing what [information] the FDA requested.").

[103] *Id.* at 2 n.1.

[104] Plaintiffs' Reply in Support of Plaintiffs' Motion to Exclude Certain Opinions of Defendants' Expert Dr. William C. Zamboni, Trans. ID 71806319 (Jan. 12, 2024) (herein "Pls.' Reply in Supp. of Pls.' Mot. to Exclude Certain Op. of Defs.' Expert Dr. Zamboni") at 1.

effort is detailed and grounded in quotations from GSK and FDA documents.[105]

By way of background, Plaintiffs allege that as early as 1982, before Zantac was approved by the FDA, GSK conducted tests that directly linked ranitidine to NDMA formation. A 1982 series of tests, called the Tanner study, named for the scientist who performed and reported on the tests, has become a focus of the parties here.[106] Plaintiffs assert that the Tanner study found that "molecules . . . like ranitidine, can react with nitrite under certain conditions to yield [NDMA]."[107] Therefore, NDMA "was already a well-established genotoxic and mutagenic nitrosamine."[108]

The Tanner Study was only "circulated internally at GSK."[109] Beginning in 1980, prior to FDA Approval of Zantac, the FDA had voiced concerns about the nitrosation potential of ranitidine.[110] It is alleged that GSK met with the FDA in May 1982, to discuss ranitidine's mutagenicity and nitrosation. Neither the Tanner Study nor NDMA was raised by GSK.[111] The meeting never reached those topics

[105] *See* Pls.' Br. in Supp. of Pls.' Mot. to Exclude Certain Op. of Defs.' Expert Dr. Zamboni at 4–24.

[106] *Id.* at 11.

[107] *Id.* (internal quotes omitted).

[108] *Id.* (emphasis omitted).

[109] *Id.*

[110] *Id.* at 5 (quotation omitted).

[111] Pls.' Br. in Supp. of Pls.' Mot. to Exclude Certain Op. of Defs.' Expert Dr. Zamboni at 12–13.

and the Tanner Study was not made public until 2019.[112]

In the intervening years, Zantac went through the FDA pre-approval process. The FDA requested of GSK specific information relative to nitrosation and ranitidine. Despite various interactions with the FDA, and additional internal testing and reports, GSK did not disclose the Tanner Study until 2019.

Plaintiffs allege that for almost four decades GSK "concealed the fact that ranitidine degrades into NDMA."[113] Defendants dispute Plaintiffs' allegations, emphasizing both that 1) substantively, that the Tanner Study addresses whether ranitidine "reacts with nitrite within the human stomach to form NDMA", that is, endogenously;[114] and 2) procedurally, that the Tanner study was a type of study "often not submitted to FDA nor requested by the FDA."[115] Dr. Zamboni bases that conclusion on his "experience with drug development."[116]

The potential implications of the Tanner Study were compounded by a 1984 report—the Preliminary Results of an Investigation into the Thermal Degradation of Ranitidine Hydrochloride ("Preliminary Results")—where GSK reported that

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[112] *Id.* at 2, 23.

[113] Brand Defs.' Opp'n to Pls.' Mot. to Exclude Certain Op. of Defs.' Expert Zamboni at 2; 2 n.5.

[114] *Id.*

[115] *Id.* at 1 (quoting Pls.' Br. in Supp. of Pls.' Mot. to Exclude Certain Op. of Defs.' Expert Dr. Zamboni Ex. 2, at 28).

[116] Pls.' Br. in Supp. of Pls.' Mot. to Exclude Certain Op. of Defs.' Expert Dr. Zamboni Ex. 2, at 28.

ranitidine would rapidly degrade in the presence of moisture and heat, yielding "unidentified, breakdown products . . . within the liquid mass formed as a result."[117] Plaintiffs allege that, despite the Tanner Study, the Preliminary Results report and numerous other inquiries and opportunities to do so, GSK did not test the unidentified breakdown products for NDMA.[118] The Tanner Study remained internal.

Furthermore, when ranitidine breaks down to NDMA, discoloration can indicate that this degradation process has begun.[119] It is alleged that after concluding that discoloration could not be avoided, GSK scientists recommended changing the color of the tablets to "mask any potential discoloration."[120] That recommendation was accepted.[121] Plaintiffs point to these issues to support the notion that GSK had knowledge of the dangers associated with NDMA as early as 1982.[122]

Defendants devote the majority of their opposition contesting Plaintiffs' history.[123] The one sentence in Dr. Zamboni's opinion which Plaintiffs move to

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[117] *Id*. at 19; Ex. 27, at 2.

[118] *Id.*

[119] *Id.* at 20–21 (responding to the discoloration problem, one GSK scientist asked, "surely [the discoloration] begs the question, 'if it changes with time, is it safe to use?' . . . which we do not have sufficient information on.") (quoting Ex. 33 at 5); Ex. 28–31.

[120] Pls.' Br. in Supp. of Pls.' Mot. to Exclude Certain Op. of Defs.' Expert Dr. Zamboni at 20; Ex. 28, at 1; Ex. 29, at 1; Ex. 30, at 6.

[121] *Id.*

[122] Pls.' Br. in Supp. of Pls.' Mot. to Exclude Certain Op. of Defs.' Expert Dr. Zamboni at 2–3.

[123] Brand Defs.' Opp'n to Pls.' Mot. to Exclude Certain Op. of Defs.' Expert Zamboni at 6–15.

exclude seems intended to support Defendants' challenge of GSK's failure to disclose the Tanner Report, and any other data, until 2019. The potential implications of Plaintiffs' history are disturbing. But it is not for the Court to plumb their depths at this time.

It may be more than generous to call Dr. Zamboni's opinion "shaky."[124] But, as *Daubert* and progeny teach us, "[t]he reliability requirement is not a tool for the Court to use to exclude questionably reliable evidence."[125] The one sentence opinion of Dr. Tanner targeted by Plaintiffs' Motion will not be excluded. Dr. Zamboni can testify to that assertion, though his testimony on that issue should be limited to the discrete issue which Plaintiffs move to exclude. Plaintiffs are not without recourse. His opinion can be properly measured by cross examination.[126] Plaintiffs' Motion to Exclude Certain Opinions of Defendants' Expert William C. Zamboni is **DENIED**.

D. DEFENDANTS' BROAD *DAUBERT* CHALLENGES

Defendants muster several broad challenges to general causation. Most of these are asserted in the context of Defendants' Motion to exclude certain experts

[124] *In re Roundup*, 390 F.Supp.3d at 1109.

[125] *Barrera*, 2019 WL 2331090, at *10.

[126] *In re Roundup*, 390 F.Supp.3d at 1109 ("[T]he weaknesses [in an] unpersuasive expert opinion can be exposed at trial, through cross-examination or testimony by opposing experts"); *see also Kaur*, 2022 WL 1486178, at *3 ("[C]hallenges to the 'factual basis of an expert opinion go to the credibility of the testimony, not the admissibility, and it is for the opposing party to challenge . . . the expert opinion on cross-examination.'").

and are addressed below.

One challenge merits discussion at the outset: Plaintiffs' alleged failure to offer satisfactory proof of threshold dose.[127] Plaintiffs rely on *In re TMI Litig.*,[128] where the Third Circuit Court recognized that "it is currently believed that there is no threshold dose below which the probability of cancer induction is zero."[129] Defendants point to *Tumlinson II*[130] in support.[131]

In *Tumlinson II*, this Court was confronted with a causation question involving ten possible airborne, causative agents. Plaintiffs' expert did not rely on a dosage in her causative analysis "but instead on atmospheric concentration ranges as a surrogate."[132] *Tumlinson* recognized that no black letter requirement for threshold dose exists. To the contrary, the Court discussed those cases excusing threshold dose, emphasizing that "[i]n each case, however, *the substance in question*

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[127] Defs.' Br. in Supp. of Brand Defs.' & Patheon's Mot. to Exclude Pls.' Gen. Causation Experts' Op. at 32; *see* Pls.' Opp'n to Defs.' Mot. to Exclude Gen. Causation Experts' Op. at 79–84; *see also* Reply Brief in Support of Brand Defendants' and Patheon's Motions to Exclude: (1) Plaintiffs' General Causation Experts' Opinions; and (2) Dr. Charles Jameson, Trans. ID 71797654 (Jan. 12, 2024) (herein "Reply Br. in Supp. of Defs.' Mot. to Exclude Pls.' Gen. Causation Experts' Op. & Dr. Jameson") at 32–35.

[128] 193 F.3d 613 (3d Cir. 1999), *amended*, 199 F.3d 158 (3rd Cir. 2000).

[129] *Id.* at 642. *In re TMI* is not mentioned in Defendants' Opening or Reply brief, and Defendants do not discuss threshold dose in their Reply.

[130] *Tumlinson II*, 2013 WL 7084888, at *7.

[131] *See* Defs.' Br. in Supp. of Brand Defs.' & Patheon's Mot. to Exclude Pls.' Gen. Causation Experts' Op. at 32–36; Reply Br. in Supp. of Defs.' Mot. to Exclude Pls.' Gen. Causation Experts' Op. & Dr. Jameson at 32–35.

[132] *Tumlinson II*, 2013 WL 7084888, at *7.

is known to be harmful at some level and the plaintiff suffered the precise harm connected to that exposure."[133]

The first prong of *Tumlinson II*'s comment goes to general causation; the second to specific causation.[134] Ostensibly, Defendants' focus on "precise harm" is intended to require something more than cancer.[135] The Court rejects such a precious reading, at least at the general causation phase, especially given the conclusions of GSK's 2019 Hazard Assessment, quoted at length above. *Daubert* counsels against black letter standards. Like general acceptance and statistical significance, threshold dose is another factor to be considered in the *Daubert* analysis, but its presence or absence is not outcome determinative.

Moreover, the record suggests that Defendants, particularly GSK, have been on notice of the harm that can result from NDMA in their product since the Tanner Study in 1982. The Hazard Assessment reflects GSK's own conclusions about carcinogenicity and NDMA.[136] Defendants' expert testified that threshold dose is a

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[133] *Id.*

[134] *See id.* at *5, 8 ("General causation does not consider the likelihood that a certain exposure caused a certain harm. Rather, it only considers the possibility."); *see also* Pls.' Opp'n to Defs.' Mot. to Exclude Gen. Causation Experts' Op. at 84 nn.271–273; Reply Br. in Supp. of Defs.' Mot. to Exclude Pls.' Gen. Causation Experts' Op. & Dr. Jameson at 33.

[135] *See* Reply Br. in Supp. of Defs.' Mot. to Exclude Pls.' Gen. Causation Experts' Op. & Dr. Jameson at 33.

[136] *See* Pls.' Opp'n to Defs.' Mot. to Exclude Gen. Causation Experts' Op. Ex. 12, at 16:1–17.

"somewhat meaningless statement [] scientifically."[137] Defendants debate the meaning of that concession.[138] Resolution of that debate awaits the jury's attention. But *Daubert* supports broad, flexible consideration at this stage.

Also, the parties do not dispute that the FDA has established an ADI limit for NDMA based on cancer risk.[139] Plaintiffs maintain the testing evidence shows "that ranitidine products expose consumers to levels in excess of that ADI."[140] The Hazard Assessment provides strong evidence that GSK admits the carcinogenic threat in NDMA.[141]

Notwithstanding Defendants' vigorous quarrel with the implications drawn from the Tanner history, it can fairly be inferred that GSK delayed revealing the cancer-causing potential of NDMA into the science marketplace. Plaintiffs should also be able to argue inferences that the collective delays by all Defendants forestalled development of the science of NDMA exposure.[142] At this stage, it does

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[137] *Id.* at 81; *id.* at 81 n.264.

[138] Reply Br. in Supp. of Defs.' Mot. to Exclude Pls.' Gen. Causation Experts' Op. & Dr. Jameson at 32.

[139] Pls.' Opp'n to Defs.' Mot. to Exclude Gen. Causation Experts' Op. at 83, 83 n.265; Ex. 84, at 8 (stating that the ADI "is a level that approximates an increased cancer risk").

[140] *See id.* at 83, 92.

[141] *Id.* Ex. 11 (e.g., "There is overwhelming evidence that NDMA is mutagenic and clastogenic . . . Qualitatively, the metabolism of NDMA appears to be similar in humans and animals; as a result, *it is considered highly likely that NDMA is carcinogenic to humans*, potentially at relatively low levels of exposure.").

[142] *See Long*, 2004 WL 1543226, at *6 ("[V]ictims of a new toxic tort should not be barred from having their day in court simply because the medical literature, which will eventually show the connection between the victims' condition and the toxic substance, has not yet been completed.").

not lie in the mouths of Defendants to assert a defense based on lack of threshold dose. That issue awaits a specific causation finding by the jury.

This is not a case where the imposition of a bright line rule is appropriate. That is not to suggest that [threshold dose] is irrelevant."[143] It remains, like general acceptance and statistical significance, one of the factors enumerated by *Daubert* and its progeny to be considered in the general causation analysis. But it is not, and should not, be deemed, alone, outcome determinative. That consideration belongs to the jury.

The Court now considers the specific challenges against Plaintiffs' experts.

E. DEFENDANTS' SPECIFIC *DAUBERT* CHALLENGES

1. Dr. Charles Jameson

Dr. Jameson has been asked to provide expert testimony on ranitidine's ability to form NDMA endogenously and exogenously and to provide "background information about the mechanism through which NDMA causes cancer."[144]

Dr. Jameson is a chemist and toxicologist specializing in carcinogenesis. He began his career as a senior chemist at the National Institute of Health ("NIH")'s National Cancer Institute. Later, Dr. Jameson was responsible for the National Institute of Health's Environmental Health Services division of Toxicology

[143] *In re Zoloft*, 858 F.3d at 793.

[144] Pls.' Opp'n to Defs.' Mot. to Exclude Gen. Causation Experts' Op. at 90.

Research and Testing. For 18 years, he served as a director on the National Toxicology Program's Report on Carcinogens.[145] He has authored or co-authored over 80 peer-reviewed scientific publications.[146] Dr. Jameson's methodology, when called upon to provide expert testimony, has been upheld by this Court,[147] as well as the California court overseeing the JCCP, where he provided expert testimony on NDMA and ranitidine.[148] In both cases, Dr. Jameson's testimony was admitted. Defendants do not challenge Dr. Jameson's qualifications to consider and opine on the questions before him. Dr. Jameson offers four opinions here:[149]

- ranitidine produces NDMA exogenously (outside the body);
- ranitidine produces NDMA endogenously (inside the body);
- NDMA "meets 5 characteristics of the generally accepted characteristics of a carcinogen; and,

[145] Pls.' Opp'n to Defs.' Mot. to Exclude Gen. Causation Experts' Op. Ex. 19.

[146] *Id.*, *see also id.* at 88–90 (providing a complete summary of Dr. Jameson's qualifications).

[147] *See Barrera*, 2019 WL 2331090, at *14.

[148] Pls.' Opp'n to Defs.' Mot. to Exclude Gen. Causation Experts' Op. at 88; Ex. 75.

[149] The scope of Dr. Jameson's opinion is specifically defined. Yet defendants challenge his failure to opine "that NDMA in ranitidine can cause cancer in any of the ten cancers at issue," a topic on which he is *not* offering an opinion. Reply Br. in Supp. of Defs.' Mot. to Exclude Pls.' Gen. Causation Experts' Op. & Dr. Jameson at 5. Calling that the "central issue at this stage" of the case, defendants argue that Dr. Jameson's expert testimony is "irrelevant." *Id.* at 6. The Court rejects that conclusion. Endogenous and exogenous formation of NDMA are a part of plaintiffs' case, as are the carcinogenic characteristics of NDMA and the generally accepted opinion among science researchers that NDMA is capable of causing cancer in animals, and humans; topics on which Dr. Jameson has been proffered, based on his review of scientific, chemical and medical data.

- "It is generally accepted among cancer science researchers that NDMA is capable of causing cancer in animals, including cancer in humans."[150]

In support of his expert opinion, Dr. Jameson opines that "the level of NDMA found in ranitidine *upon its storage* reaches levels that *exceed the daily intake limit*."[151] In its root cause analysis, GSK likewise concludes that degradation of ranitidine, which begins from the point of manufacture, increases NDMA levels, a point confirmed by the FDA.[152] This conclusion was also confirmed by independent, peer-reviewed testing.[153]

In preparing his opinions, Dr. Jameson reviewed data about "exogenous NDMA formation from ranitidine," including testing by FDA, Australia's TGA, GSK, Sanofi, and Emery Pharma, among others.[154] He considered GSK's root cause analysis which "concludes, definitively, that ranitidine decomposes into NDMA on

[150] Pls.' Opp'n to Defs.' Mot. to Exclude Gen. Causation Experts' Op. Ex. 19, at 3; *see id*. at 90–91.

[151] Pls.' Opp'n to Defs.' Mot. to Exclude Gen. Causation Experts' Op. Ex. 19, at 11–12 (emphasis added).

[152] Pls.' Opp'n to Defs.' Mot. to Exclude Gen. Causation Experts' Op. Ex. 15, at 9 ("NDMA levels in drug substances start to increase at a slow rate *from the point of manufacture*; both elevated temperatures and RH contribute to an increase in the rate of degradation") (emphasis added); *id.* Ex. 19, at 7; *id.* Ex. 8, at 2 ("NDMA levels increase in ranitidine even *under normal storage conditions*…and may *raise the level of NDMA in the ranitidine product above the acceptable daily intake limit*") (emphasis added); *see also id.* Ex. 19 at 7.

[153] *See id.* Ex. 30, at 1.

[154] Pls.' Opp'n to Defs.' Mot. to Exclude Gen. Causation Experts' Op. at 91, 91 nn.292–93.

standing, exacerbated by heat and humidity."[155] Dr. Jameson holds a PhD in organic chemistry, and opines as to the molecular reaction beneath the instability of the ranitidine molecules.[156] His opinion, which is confirmed by independent, peer-reviewed testing, "strongly suggest[s] that environmental factors such as heat and oxygen are involved in the formation of NDMA."[157]

Dr. Jameson concludes that the "evidence is very strong that ranitidine decomposes to NDMA which is formed because of an intermolecular degradation reaction of the ranitidine molecules that occurs primarily in ranitidine formations" and that the "level of NDMA formed in ranitidine upon its storage reaches levels that exceed the daily intake limit."[158] This is the same conclusion reached in GSK's root cause analysis and by the FDA, as evidenced by Defendants' recalling their products from the market.[159]

Dr. Jameson reviewed *in vitro* and *in vivo* data, including numerous *in vitro* studies prepared by Defendants and independent laboratories, and peer-reviewed literature that, *inter alia*, support the formation of NDMA from ranitidine within the

[155] *Id.* at 91–92, 92 n.294.

[156] *Id.* at 92, 92 n.295.

[157] *Id.*, 92 n.296.

[158] *Id.*, 92 n.297.

[159] *Id.* at 92–93, 92 nn.298–99.

human stomach when exposed to sodium nitrite.[160] The *in vitro* data "demonstrates that NDMA forms in conditions found in the human stomach."[161] Dr. Jameson also relied on an Emery Pharma simulated food study designed to explore how ranitidine interacted with nitrite to form NDMA.[162] Using the food tests, Emery was able to show that in simulated gastric fluid ranitidine reacts to form NDMA.[163] In his opinion and in his deposition, he explained his acceptance of or disagreement with literature he reviewed or pressed upon him by Defendants' counsel.[164]

Dr. Jameson also considered conclusions and recommendations from a litany of federal and international agencies, as well as GSK's internal studies, that NDMA "should be regarded *for practical purposes* as if it were carcinogenic to humans."[165] Conclusions with which he agrees. Some of the agencies reaching that conclusion include the FDA, the EPA, The Department of Health and Human Services' Report on Carcinogens, the U.S. Department Health and Human Services' Agency for Toxic

[160] Pls.' Opp'n to Defs.' Mot. to Exclude Gen. Causation Experts' Op. Ex. 19, at 7–9, 10–18; *see id*. at 93–94, 93–94 nn.300–311.

[161] *Id.*

[162] *See* Pls.' Opp'n to Defs.' Mot. to Exclude Gen. Causation Experts' Op. at 95, 95 nn.315–18.

[163] *See id.* at 95–100.

[164] *See id.* at 115–21. Beyond the ranitidine issue, Defendants challenge the science of the Hidajat study: the duration of the study, measurements of "actual NDMA" available, and estimates and imputations of NDMA detected and to which workers were exposed. These critiques go to weight and, as a consequence, fail to support the Motion.

[165] *See id.* at 16–22 (quoting Pls.' Opp'n to Defs.' Mot. to Exclude Gen. Causation Experts' Op. Ex. 1, at 36).

Substances and Disease Registry ("ATSDR"), and the World Health Organization ("WHO").[166] It cannot be suggested that Dr. Jameson "neglected the core facts of the case."[167] Upon completion of his review, he performed a Bradford Hill analysis.[168] Plaintiffs offer a brief comment on Bradford Hill analysis, none of which is remarkable or cause for debate, but three points merit repetition:

> (1) methods used by experts in forming opinions as to causation substantially rely on the expert's judgment in selecting and weighing their sources;
>
> (2) *Daubert* does not prescribe a specific weight that evidence should be given; and,
>
> (3) it is not the Court's role to weigh that evidence, second guess researchers or pass judgment on substantive issues.[169]

Dr. Jameson's review supports his conclusion that ranitidine produces NDMA endogenously and exogenously, meets five characteristics of the generally accepted characteristics of a carcinogen, and is generally accepted among cancer science researchers that NDMA is capable of causing cancer in animals, including cancer in

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[166] *Id.* at 16–19.

[167] *Kaur*, 2022 WL 1486178, at *3.

[168] Defendants do not voice challenges to Dr. Jameson's Bradford Hill analysis, either in their Opening Brief (filed separately) in support of their Motion to Exclude certain of his opinions, or in their Reply Brief. Defendants include three pages on alleged failings they ascribe to Defendants' Bradford Hill analyses, collectively, referring in that argument to "Plaintiffs' experts" and "some" of them. This does not give fair notice of specific challenges to Plaintiffs, their experts, or the Court. Defendants in their arguments directed at specific experts do raise Bradford Hill, which arguments are addressed later in this ruling.

[169] *See* Pls.' Opp'n to Defs.' Mot. to Exclude Gen. Causation Experts' Op. at 67–68.

humans.[170]

Defendants' challenges to the reliability of Dr. Jameson's methodology are as follows: he cherry picked his evidence;[171] did not rank or weigh his studies;[172] the tests do not imitate conditions in humans;[173] his reliance on non-peer reviewed studies;[174] reliance on bad science and improperly rejecting or favoring unreliable studies;[175] and, generally, relying on unreliable exogenous studies.[176] These challenges are for the jury.

The Court finds he utilized sound scientific methodology in formulating his opinions. His opinion is generally admissible.[177] The science with which Dr. Jameson approached his task here, detailed in Plaintiffs' Opposition, commends that

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[170] *Id.* at 90–91.

[171] Brief in Support of Brand Defendants' and Patheon's Motion to Exclude Plaintiffs' Expert Dr. Charles Jameson, Trans. ID 71409144 (Nov. 15, 2023) (herein "Defs.' Br. in Supp. of Brand Defs.' & Patheon's Mot. to Exclude Pls.' Expert Dr. Jameson") at 15.

[172] *Id.* at 16; *see* Pls.' Opp'n to Defs.' Mot. to Exclude Gen. Causation Experts' Op. at 100, 100 n.321 (stating that regulatory and scientific bodies do not rank studies but simply assess their strengths and weaknesses); *see also id*. at 116–117 (responding to questions from counsel, Dr. Jameson explains his methodology and explains the strengths and weaknesses of pertinent studies).

[173] *Id.* at 16; *but see id*. at 101, 101 nn.323–326 (rebutting the assertion that the tests do not imitate conditions in humans and relying in part on the Braunstein study).

[174] Defs.' Br. in Supp. of Brand Defs.' & Patheon's Mot. to Exclude Pls.' Expert Dr. Jameson at 16.

[175] *Id.* at 17; *but see* Pls.' Opp'n to Defs.' Mot. to Exclude Gen. Causation Experts' Op. at 103–20.

[176] *Id.* at 18.

[177] *In re Asbestos Litig*., 911 A.2d at 1204–06; *In re Roundup,* 390 F.Supp.3d at 1150–51 (admitting expert opinion where the expert "conducted a literature review and evaluated the quality of each of the studies"); *See Barrera,* 2019 WL 2331090, at *14, 17.

methodology.[178] Defendants may reject that science and the conclusions Dr. Jameson derives from it. But that makes for a battle of the experts; it does not make Dr. Jameson's opinion inadmissible.[179] This dispute presents a classic battle of the experts.[180] Defendants' Motion to exclude the expert opinions of Dr. Charles Jameson is **DENIED**.

2. <u>William Sawyer, PhD</u>

Plaintiffs offer Dr. William Sawyer for one purpose: to "convert the inhalation doses of NDMA observed in the Hidajat study into an equivalent oral dose."[181] Dr. Sawyer was not proffered, and will not offer, an opinion on causation; similarly he does not intend to discuss the "merits or demerits of any epidemiological study."[182] The express limits of Dr. Sawyer's opinion notwithstanding, Defendants criticize Sawyer for *not opining* on issues *not within* his specific task.[183]

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[178] Pls.' Opp'n to Defs.' Mot. to Exclude Gen. Causation Experts' Op. at 103–120.

[179] *McCullock*, 61 F.3d at 1044 ("Disputes as to the strength of [an expert's] credentials, faults in his use of [a particular] methodology, or lack of textual authority for his opinion, go to the weight, not the admissibility of his testimony") (parentheticals added); *see also Karlo v. Pittsburgh Glass Works, LLC*, 849 F.3d 61, 83 (3d Cir. 2017) ("The question of whether a study's results were properly calculated or interpreted ordinarily goes to the weight of the evidence, not to its admissibility") (citation omitted).

[180] *Long*, 2004 WL 1543226, at *6.

[181] Pls.' Opp'n to Defs.' Mot. to Exclude Gen. Causation Experts' Op. at 121.

[182] *Id.* at 122; Reply Br. in Supp. of Defs.' Mot. to Exclude Pls.' Gen. Causation Experts' Op. & Dr. Charles Jameson at 87, 89 ("Plaintiffs acknowledge Dr. Sawyer is not offering a general causation opinion").

[183] Defs.' Br. in Supp. of Brand Defs.' & Patheon's Mot. to Exclude Pls.' Gen. Causation Experts' Op. at 126–127; Reply Br. in Supp. of Defs.' Mot. to Exclude Pls.' Gen. Causation Experts' Op.

Defendants' challenges are several, but they focus on one primary issue: Dr. Sawyer's reliance on the 2019 Hidajat study. Defendants attack the Hidajat study because, they say, it "did not involve ranitidine at all,"[184] and stand on the limiting, mechanistic distinction they draw on ranitidine's role. But Dr. Hidajat did testify that "[her] study provided important evidence of. . . the association between NDMA exposure and cancer."[185] Thus, at this juncture, her study "fits" the facts of the case.

The science behind the Hidajat study, and Dr. Sawyer's use of it, merits pause. Beyond the ranitidine issue, Defendants challenge the science of the Hidajat study:[186] the duration of the study,[187] measurements of "actual NDMA" available,[188] and estimates and imputations of NDMA detected and to which workers were exposed.[189] These critiques go to weight and, as a consequence, fail to support the Motion.[190]

The Hidajat study "followed 36,441 rubber workers for 49 years—the longest

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& Dr. Charles Jameson at 89 (stating that Dr. Sawyer's analysis "could not bridge the analytical gap" on cancer causation).

[184] Defs.' Br. in Supp. of Brand Defs.' & Patheon's Mot. to Exclude Pls.' Gen. Causation Experts' Op. at 124, 126.

[185] Pls.' Opp'n to Defs.' Mot. to Exclude Gen. Causation Experts' Op. at 78–79.

[186] *Id.* at 124–126.

[187] *Id.* at 125.

[188] *Id.*

[189] *Id.* at 125–26.

[190] *Kaur*, 2022 WL 1486178, at *4; *Bowen*, 2005 WL 1952859, at *8; *McCullock*, 61 F.3d at 1038.

follow-up (by 25 years) of any other study in this case."[191] The length of the follow-up period allowed "near-complete dataset, with 94% of the cohort diseased."[192] To estimate exposure to NDMA, the authors "developed a peer-reviewed matrix based on the fumes at various locations in the rubber factories…[where workers were] 'divided into quartiles of exposure,' each quartile being compared to the first to see whether greater NDMA exposure was associated with specific cancers."[193] The Hidajat study documented a "clear dose-response relationship between NDMA exposure and the development of bladder, esophageal, liver, lung, pancreatic, prostate, and stomach cancer."[194] Because exposure in that study "was through inhalation," Dr. Sawyer "calculated what the equivalent lifetime oral dose would be in each quartile."[195]

Defendants protest that Dr. Sawyer's method is "flawed because the amount of bioavailable NDMA can depend on dose."[196] When challenged at his deposition, he explained that "this was the appropriate method used by forensic

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[191] Pls.' Opp'n to Defs.' Mot. to Exclude Gen. Causation Experts' Op. at 74, 74 nn.242–247.

[192] *Id.*

[193] *Id.*

[194] *Id.* at 74–77 (noting Dr. Sawyer offers no opinions on these findings. His opinion is limited to "convert[ing] the inhalation doses of NDMA observed in the Hidajat study into an equivalent oral dose."

[195] Pls.' Opp'n to Defs.' Mot. to Exclude Gen. Causation Experts' Op. at 74, 74 n.247.

[196] *Id.* at 121–122; *see* Defs.' Br. in Supp. of Brand Defs.' & Patheon's Mot. to Exclude Pls.' Gen. Causation Experts' Op. at 124–26.

toxicologists."[197] He further stated that "by using bioavailable data based on higher doses, he actually made a more conservative estimate of how much NDMA exposure is occurring in the Hidajat study."[198] That is, that he was erring "on the side of caution," as, Plaintiffs note, is "customarily done in toxicological dose assessments."[199] This challenge, like the various challenges Defendants assert against the Hidajat study, fails under *Daubert* and its progeny.

Dr. Sawyer's opinion is limited, plainly so. He is not testifying on causation, but instead on his conversion of inhalation dose to oral dose.[200] Defendants reject his science. Perhaps, as presented during oral arguments, his science may be a bridge too far. But at this juncture, the criticisms go to weight and do not preclude admission.[201] Defendants' Motion to exclude Dr. Sawyer is **DENIED**.

3. <u>Alfred I. Neugut, M.D., PhD.</u>

As his CV makes plain,[202] Dr. Neugut is an accomplished epidemiologist at Columbia University. Dr. Neugut received his MD and PhD from Columbia

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[197] *Id*. at 122, 122 n.409.

[198] *Id.*

[199] *Id.*, 122 nn.409–411 (citing to deposition testimony); Pls.' Opp'n to Defs.' Mot. to Exclude Gen. Causation Experts' Op. Ex. 136.

[200] Reply Br. in Supp. of Defs.' Mot. to Exclude Pls.' Gen. Causation Experts' Op. & Dr. Jameson at 89.

[201] *See Kaur*, 2022 WL 1486178, at *4; *see also Bowen*, 2005 WL 1952859, at *8; *see also McCullock*, 61 F.3d at 1038.

[202] *See* Pls.' Opp'n to Defs.' Mot. to Exclude Gen. Causation Experts' Op. Ex. 54.

University and a fellowship in Medical Oncology at Sloan-Kettering Cancer Center as well as Columbia. Dr. Neugut has published over 800 peer reviewed chapters and papers and received over $60 million in funding from the National Cancer Institute, American Cancer Society, Department of Defense, and various foundations. Dr. Neugut has taught cancer epidemiology at Columbia for over 40 years.[203]

Here, he was tasked to "assess whether the ingestion of ranitidine, contaminated with NDMA, is causally associated with the development of urinary bladder cancer."[204] Dr. Neugut was disclosed by plaintiffs in the JCCP litigation to offer general causation opinions on carcinogenicity and ranitidine.[205] The JCCP Court reviewed his methodology, found it to be reliable and denied defendants' motion to exclude his opinions.[206] The California Court of Appeals has also acknowledged Dr. Neugut as "an expert in the areas of medical oncology and cancer epidemiology."[207]

His opinions were excluded in *In re Roundup Products Liability Litig.*,[208] and the *Barrera* Court—then relying on *In re Roundup*—also excluded his opinions.[209]

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[203] *Id.*

[204] *Id.* at 5.

[205] *See id.* Ex. 75, at 34–38.

[206] *See id.*

[207] *Johnson*, 266 Cal.Rptr.3d at 118, *modified on denial of reh'g* (Aug. 18, 2020).

[208] 390 F.3d at 1144–46.

[209] *Barrera*, 2019 WL 2331090, at *15, 15 nn.199–200.

The *Roundup* court noted that Dr. Neugut was "eminently qualified and refreshingly candid," and lauded his reports as "high quality."[210] But that court was disturbed by Dr. Neugut's presentation, commenting on issues with his testimony, not reflected in the written transcript.[211] The *Roundup* Court quite correctly noted that "[e]ach problem with Dr. Neugut's testimony is not sufficient, on its own, to justify exclusion."[212] The cases discussed cited herein confirm that point. As to statistical significance, neither Delaware nor the Third Circuit requires "statistical significance to prove causality."[213]

In preparing his opinion on the question before him here, Dr. Neugut looked at peer-reviewed literature on NDMA, ranitidine, and bladder cancer, and considered the strengths and weaknesses of each study.[214] He then prepared a forest plot synthesizing the studies,[215] which revealed a consistent increased risk of cancer.[216] Dr. Neugut's approach "reflects a sound methodology consistent with *Daubert*'s

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[210] *In re Roundup,* 390 F.Supp.3d at 1144.

[211] *Id.* (The *Roundup* Court listed its reasons for its findings that Dr. Neugut's opinion was not sufficiently reliable to be admissible. Two related to his conclusions: one to his characterization of glyphosate as something other than a hazard assessment, the other about an IARC conclusion as to the meaning of "a probable carcinogen," and Dr. Neugut's agreement in his deposition regarding associations between glyphosate and NHL). None of those issues present here.

[212] *Id.* at 1146.

[213] *Barrera,* 2019 WL 2331090, at *5, 5 n.56 (citing *In re Zoloft*, 858 F.3d at 793).

[214] Pls.' Opp'n to Defs.' Mot. to Exclude Gen. Causation Experts' Op. Ex. 54, at 15–26; *compare In re Roundup,* 390 F.Supp.3d at 1144.

[215] Pls.' Opp'n to Defs.' Mot. to Exclude Gen. Causation Experts' Op. Ex. 54, at 33.

[216] *Id.*; *see also id*. at 126.

'reliability' component."[217] Dr. Neugut's review and synthesis of the data and his creation of the forest plot make his opinion generally admissible.

Dr. Neugut then synthesized the literature using the Bradford Hill factors:

> After reviewing the data and studies described above with regard to the association between ranitidine and bladder cancer and weighing the evidence in the light of the Bradford Hill criteria, it is my expert opinion, within a reasonable degree of medical certainty, that there is a causal association between ranitidine and urinary bladder cancer.
>
> Again, there is good biological plausibility that supports this conclusion. Human epidemiologic studies address this finding, and many are large, well done, and present reasonable strong associations for the finding. Also, several studies of NDMA exposure support an association with bladder cancer.[218]

In response to Dr. Neugut's review and opinion, Defendants pursue an "unreliable methodology" analysis, which they begin with the suggestion that Dr. Neugut applies a lower standard of proof in litigation than in his professional work.[219] Defendants do not make clear if they mean to say that Dr. Neugut's opinion

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[217] *In re Asbestos Litig.*, 911 A.2d at 1206. *Accord*, *In re Roundup*, 390 F.Supp.3d at 1150–51 (admitting expert opinion where the expert "conducted a literature review and evaluated the quality of each of the studies"). *Compare id*. at 1148 (excluding expert where the expert report "did not demonstrate that he engaged in his own objective analysis" of the medical literature on which he relied).

[218] Pls.' Opp'n to Defs.' Mot. to Exclude Gen. Causation Experts' Op. at 126.

[219] Defs.' Br. in Supp. of Brand Defs.' & Patheon's Mot. to Exclude Pls.' Gen. Causation Experts' Op. at 105; Pls.' Opp'n to Defs.' Mot. to Exclude Gen. Causation Experts' Op. at 126–27.

is not made to a "reasonable degree of medical certainty."[220] If so, Dr. Neugut declares directly that his opinion *is* provided to that degree of certainty.[221]

If Defendants' challenge goes to Dr. Neugut's call of the question, it is still not a proper basis for excluding his opinions. "Disputes as to the strength of [an expert's] credentials, faults in his use of [a particular] methodology, or lack of textual authority for his opinion, go to the weight, not the admissibility of his testimony."[222] That notwithstanding, Dr. Neugut applied the same "generally accepted scientific and medical principles and methodologies" used by cancer epidemiologists.[223] Any challenge to his application of those methodologies goes to the jury.

Defendants also charge that Dr. Neugut's analysis is "blatantly results-oriented,"[224] uses "cherry picked" data,[225] "outcome driven reasoning,"[226] and is "flatly contradict[ed] by his prior [deposition] testimony."[227] These criticisms attack the expert's credibility, the bases and calculations underlying his opinion, or seek to

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[220] *See* Defs.' Br. in Supp. of Brand Defs.' & Patheon's Mot. to Exclude Pls.' Gen. Causation Experts' Op. at 105.

[221] Pls.' Opp'n to Defs.' Mot. to Exclude Gen. Causation Experts' Op. at 127; *see id*. Ex. 54, at 35; Ex. 193, at 143:17–25, 144:2–19.

[222] *McCullock*, 61 F.3d at 1044 (parentheticals added).

[223] Pls.' Opp'n to Defs.' Mot. to Exclude Gen. Causation Experts' Op. at 127.

[224] Defs.' Br. in Supp. of Brand Defs.' & Patheon's Mot. to Exclude Pls.' Gen. Causation Experts' Op. at 110.

[225] *Id*. at 109.

[226] *Id.*

[227] *Id.* at 107–08.

elevate Defendants' science over that of Dr. Neugut.[228] These are all arguments that *Daubert* and its progeny reserve to the jury.[229]

As the gatekeeper, the Court has spent considerable effort in considering Dr. Neugut's opinion and Delaware's jurisprudence on point. The Court is not bound by the rulings made in *RoundUp* and *Barrera* excluding him, particularly given the comments of the Court on the merits of his opinion, and the presentation of the science presented here.

Every case is different. In this early phase of the litigation, the Court is more compelled to its conclusion by the legal concepts that animate *Daubert* proceedings, especially as they recognize and uphold the distinct roles of the Court as gatekeeper and that of the jury as the ultimate fact finder, and by the encouragement of *In re Asbestos Litig*. and *Long* to allow the jury to consider debatable scientific approaches. Defendants can take up their challenges before the jury on cross examination. Defendants' Motion to exclude Dr. Neugut's expert testimony is **DENIED**.

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[228] *Id.* at 101–13.

[229] *See McCullock*, 61 F.3d at 1038; *see also Karlo*, 849 F.3d at 83 ("The question of whether a study's results were properly calculated or interpreted ordinarily goes to the weight of the evidence, not to its admissibility.") (citation omitted); *see also In re Roundup*, 390 F.Supp.3d at 1150–51 ("different interpretations of [carcinogenicity] studies are not necessarily evidence of unreliability . . . plaintiffs may raise their concerns via cross-examination . . .").

4. Dr. Vinod K. Rustgi

Plaintiffs ask Dr. Vinod Rustgi to provide "an expert opinion regarding the role of high levels of NDMA found in ranitidine products in the risk of development of Hepatocellular carcinoma" ("HCC").[230] Defendants do not challenge his qualifications or his actual methodology of conducting a review of peer-reviewed literature and applying the Bradford Hill factors.[231]

In conducting his analysis, Dr. Rustgi relied on i*n vitro* data, *in vivo* data, tissue culture and animal models, as well as epidemiological evidence in humans.[232] Following a review of this data, and a Bradford Hill analysis, Dr. Rustgi concluded that "NDMA-contaminated Ranitidine can cause the development of HCC."[233] This base of analysis supports admissibility of Dr. Rustgi's opinion.[234]

Yet Defendants challenge Dr. Rustgi's opinion on several fronts. As predicate, they argue that Dr. Rustgi concedes that "ranitidine or NDMA" is not generally accepted by the community of liver specialists as a cause of liver cancer.[235]

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[230] Pls.' Opp'n to Defs.' Mot. to Exclude Gen. Causation Experts' Op. at 138.

[231] *Id.*

[232] *Id.*

[233] *Id.* (quoting Ex. 62, at 1).

[234] *In re Asbestos Litig.*, 911 A.2d at 1205–06*; In re Roundup*, 390 F.Supp.3d at 1150–51 (admitting expert opinion where the expert "conducted a literature review and evaluated the quality of each of the studies.").

[235] Defs.' Br. in Supp. of Brand Defs.' & Patheon's Mot. to Exclude Pls.' Gen. Causation Experts' Op. at 117.

But *Daubert* disposed of the general acceptance requirement for admissibility.[236]

Defendants urge that only one of seven epidemiological studies reported a significant association between ranitidine and cancer. But Defendants note that those "*results have not been replicated in subsequent studies*, and so could be due to change."[237] Defendants cite the MDL Order from *In re Zantac*[238] in support of these arguments. For the reasons discussed above, this Court is not guided by that ruling on these issues. Defendants' qualification undermines the value of this point.

More directly, the record reflects that Defendants' assertion misses the mark. Dr. Rustgi testified that it is generally accepted that NDMA causes liver damage and liver tumors, and that this is the "preponderance of the evidence going back decades."[239] With respect to ranitidine, Dr. Rustgi opines that "exposure to NDMA from ranitidine can cause the development of liver cancer."[240] Dr. Rustgi's Bradford Hill analysis, which he conducted, supports this opinion.[241]

This Court will not inject itself into a dispute over which party has the better

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[236] *Minner*, 791 A.2d at 841.

[237] Defs.' Br. in Supp. of Brand Defs.' & Patheon's Mot. to Exclude Pls.' Gen. Causation Experts' Op. at 117 (emphasis added).

[238] 644 F.Supp.3d at 1258–59.

[239] Pls.' Opp'n to Defs.' Mot. to Exclude Gen. Causation Experts' Op. at 139 (citing Ex. 141, at 332:1–10, 331:1–2).

[240] *Id.* (citing Ex. 53, at 35).

[241] *Id.* (citing Ex. 141, at 331:9–18); *In re Roundup*, 390 F.Supp.3d at 1150–51.

science.[242] Defendants' quarrel with Dr. Rustgi's reading of the Wang study is also unavailing, as the balance of Defendants' challenges to admissibility sound in areas reserved in the first instance to the expert witness's discretion and, ultimately, the jury's wisdom (i.e., cherry picking evidence, improper rejection of relevant data, vagueness in describing methodology, inconsistent testimony, etc.)[243] These issues present a classic battle of the experts. Resolution of those disputes lies with the jury.

Defendants have failed to satisfy the *Daubert* requirements to exclude Dr. Rustgi. The Motion is **DENIED**.

5. <u>Dr. Ioannis Hatzaras</u>

Plaintiffs identified Dr. Ioannis Hatzaras to evaluate whether NDMA exposure from ranitidine can cause esophageal, stomach and colorectal cancer.[244] In conducting his evaluation, Dr. Hatzaras reviewed studies "demonstrating that NDMA is a carcinogen" and reviewed "clinical studies looking into the relationship between ranitidine containing NDMA. . . and development of foregut/colorectal

[242] *See McCullock*, 61 F.3d at 1038; *Karlo*, 849 F.3d at 83 ("The question of whether a study's results were properly calculated or interpreted ordinarily goes to the weight of the evidence, not to its admissibility") (citation omitted); *In re Roundup*, 390 F.Supp.3d at 1150–51 ("different interpretations of [carcinogenicity] studies are not necessarily evidence of unreliability…plaintiffs may raise their concerns via cross-examination.").

[243] *See* Defs.' Br. in Supp. of Brand Defs.' & Patheon's Mot. to Exclude Pls.' Gen. Causation Experts' Op. at 116–22; *compare* Pls.' Opp'n to Defs.' Mot. to Exclude Gen. Causation Experts' Op. at 139–46.

[244] Pls.' Opp'n to Defs.' Mot. to Exclude Gen. Causation Experts' Op. at 149; Ex. 194, at 1.

cancer."[245] Dr. Hatzaras "examined 36 particular studies in detail in his report. . . and catalogued [their] strengths and weaknesses over 30 pages."[246] His report "dissect[s] each study's merits and drawbacks" to understand whether any association is, in fact, causal.[247]

Upon completing his review of the literature, Dr. Hatzaras performed a Bradford Hill analysis.[248] He then conducted a separate Bradford Hill analysis for esophageal, gastric, and colorectal cancer.[249] Based on his review, evaluation and analyses, Dr. Hatzaras concludes to a "reasonable degree of scientific certainty" that "NDMA in ranitidine causes foregut/colorectal carcinoma."[250] His Bradford Hill analysis confirms that opinion. Dr. Hatzaras' analysis supports admissibility of his opinion.[251] Defendants present several challenges, notwithstanding.

Relying again on the MDL Order, Defendants contend that Dr. Hatzaras employed "an inconsistent, results-driven approach" that "turn[s] science on its head," cherry picked his data, altered his opinion "mid-way through his deposition,"

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[245] *Id.*

[246] *Id.*

[247] *Id.* at 149–50.

[248] *Id.* at 150.

[249] *Id.*

[250] *Id.*

[251] *In re Asbestos Litig.*, 911 A.2d at 1204–06; *see In re Roundup*, 390 F.Supp.3d at 1150–51 (admitting expert opinion where the expert "conducted a literature review and evaluated the quality of each of the studies.").

and applied flawed methods, or none through a "standardless" approach.[252] For the reasons previously stated, the Court is not bound by that ruling.

Moreover, Plaintiffs' comprehensive presentation of Dr. Hatzaras' testimony sufficiently addresses Defendants' challenges,[253] including but not limited to an explanation of the science behind Dr. Hatzaras' rejection of the "binary approach to statistical significance extolled" by Defendants.[254] Defendants' arguments may undermine Dr. Hatzaras' opinion and be fodder for cross examination, but they cannot exclude that opinion. These expert battles are to be fought before the factfinders. This Motion is **DENIED**.

6. <u>Dr. Dan J. Raz</u>

Dr. Dan J. Raz, a thoracic surgeon and scientist specializing in lung cancer, was asked by Plaintiffs to give opinions as to the causal relationship between ranitidine and lung cancer.[255] As with all of Plaintiffs experts, Defendants do not challenge Dr. Raz' qualifications to offer the opinion sought.[256]

Dr. Raz used a "comprehensive review of electronic databases to provide sources for his opinions. He also looked to public health authorities, including the

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[252] Defs.' Br. in Supp. of Brand Defs.' & Patheon's Mot. to Exclude Pls.' Gen. Causation Experts' Op. at 76–78.

[253] *See* Pls.' Opp'n to Defs.' Mot. to Exclude Gen. Causation Experts' Op. at 150–62.

[254] *Id.* at 151–52.

[255] *Id.* at 163.

[256] *See id.* at 163–64 (detailing recitation of Dr. Raz' CV).

FDA, WHO, and IARC. He carefully considered the strengths and weaknesses of each source."[257] Upon completing his review, Dr. Raz performed a Bradford Hill analysis to determine whether ranitidine causes lung cancer. He opined that "NDMA exposure from ranitidine use is capable of causing lung cancer."[258]

Dr. Raz' methodology supports admission of his opinion.[259] His methodology appears to mirror that of Defendants' lung cancer expert, Anil Vachani, M.D., M.S.[260] Though they reach different conclusions, "different interpretations of these [sources] are not necessarily evidence of unreliability[.]"[261] This is, literally, a battle of the experts.

Nonetheless, Defendants advance several challenges to Dr. Raz' opinion. They begin with the charge that his opinions are not generally accepted.[262] Defendants conflate acceptance of methodology with acceptance of expert conclusions.[263] As noted above, while *Daubert* gives great latitude to the gatekeeper in evaluating what factors may be implicated in these disputes, none of those factors—including general acceptance of medical conclusions—is determinative in

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[257] *Id.* at 165.

[258] *Id.* at 164–65.

[259] *See In re Asbestos Litig*., 911 A.2d at 1205–06; *In re Roundup,* 390 F.Supp.3d at 1102.

[260] Pls.' Opp'n to Defs.' Mot. to Exclude Gen. Causation Experts' Op. at 165 n.614.

[261] *In re Roundup,* 390 F.Supp.3d at 1150.

[262] Pls.' Opp'n to Defs.' Mot. to Exclude Gen. Causation Experts' Op. at 166.

[263] *See Daubert*, 509 U.S. at 580; Pls.' Opp'n to Defs.' Mot. to Exclude Gen. Causation Experts' Op. at 166.

the trial court's analysis. Indeed, *Daubert* holds that methods, not conclusions, are to be tested.[264] Each factor is but one among many that this Court may consider.

Importantly, Plaintiffs' experts point to several public, private, and governmental medical and regulatory entities that have studied NDMA and concluded that NDMA *is* capable of causing cancer in humans. The record suggests that GSK conceded as much in 2019.[265] Also, the Wang study specifically showed a "statistically significant association between exposure to ranitidine and lung cancer."[266] The Habel study found an "overall increased cancer risk," but fell just short of statistical significance for lung cancer. But a positive association may still be relied upon by experts; *Daubert* does not preclude it. It permits it.[267]

Defendants' remaining challenges echo those cited in other expert challenges discussed above, such as improper weighing/cherry picking studies on which to rely, reliance on NDMA dietary studies, failing to consider/elevating Defendants' science over the witnesses. For example, Defendants complain that Dr. Raz' opinion should

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[264] *Daubert*, 509 U.S. at 580; *see Tumlinson*, 81 A.3d at 1272 (noting that "an expert *may* also rely on techniques that have gained widespread acceptance in the scientific community.") (emphasis added).

[265] *See* Pls.' Opp'n to Defs.' Mot. to Exclude Gen. Causation Experts' Op. Ex. 12, at 16:1–17 ("[P]rotect the *scientists and anybody handling*" NDMA in the laboratory.) (emphasis added); *see also* Pls.' Opp'n to Defs.' Mot. to Exclude Gen. Causation Experts' Op. Ex. 11.

[266] Pls.' Opp'n to Defs.' Mot. to Exclude Gen. Causation Experts' Op. at 169; Ex. 146, at 119:7–8.

[267] *Barrera*, 2019 WL 2331090, at *5 (permitting expert to testify where opinions were based on some studies showing statistically significant associations or positive associations).

be excluded because he improperly weighed seven epidemiological studies on ranitidine and lung cancer, and that his analysis of the studies was flawed.[268] In his report and deposition, Dr. Raz went into detail explaining that he considered all seven of the studies and his reasons for giving more weight to two of them: Wang and Habel.[269]

Yet, Defendants offer a one-page challenge to Dr. Raz' Bradford Hill analysis on three points: consistency, temporality, and strength of association.[270] Defendants claim that the analysis is "unreliable' because he relied upon only two data points cited in those two studies of Wang and Habel. As discussed previously, Dr. Raz' reliance upon these studies is reasonable. Any quarrel with the application of his methodology is for the fact finder.[271]

Evaluation of Bradford Hill factors turns on the "expert's judgment in selecting and weighing her sources."[272] "[E]xperts operating on reliable scientific

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[268] Defs.' Br. in Supp. of Brand Defs.' & Patheon's Mot. to Exclude Pls.' Gen. Causation Experts' Op. at 59–62.

[269] Pls.' Opp'n to Defs.' Mot. to Exclude Gen. Causation Experts' Op. at 167–71.

[270] Defs.' Br. in Supp. of Brand Defs.' & Patheon's Mot. to Exclude Pls.' Gen. Causation Experts' Op. at 62–63.

[271] *Karlo*, 849 F.3d at 83 ("The question of whether a study's results were properly calculated or interpreted ordinarily goes to the weight of the evidence, not to its admissibility"); *see also In re Roundup*, 390 F.Supp.3d at 1150–51 ("different interpretations of [carcinogenicity] studies are not necessarily evidence of unreliability…plaintiffs may raise their concerns via cross-examination.").

[272] *Barrera*, 2019 WL 2331090, at *4.

principles could weigh the studies differently[.]"[273] Any disputes about those judgments are not for the Court to resolve. These decisions, made within the framework constructed by *Daubert* and progeny, are reserved to the jury. Therefore, Defendants' Motion as to Dr. Raz is **DENIED**.

7. <u>Dr. Pablo Leone</u>

Dr. Leone is expected to offer a general causation opinion as to whether NDMA exposure from ranitidine causes breast cancer based upon the epidemiological evidence.[274] Defendants do not challenge Dr. Leone's qualifications.[275] To answer the general causation question, Dr. Leone reviewed the "available scientific evidence regarding, Zantac (ranitidine) and NDMA"[276] He used a method "consistent with what is followed by cancer research scientists when evaluating whether a chemical agent is a carcinogen and whether individuals are at risk of developing cancer based on exposure."[277] His methodology involved:

- a review and evaluation of extensive medical scientific literature, including epidemiological, *in vivo* animal, *in vitro* studies and reviews of all relevant topics;

- research on publicly available information related to ranitidine and NDMA, their safety and association

[273] *Id.* at *8.

[274] Pls.' Opp'n to Defs.' Mot. to Exclude Gen. Causation Experts' Op. at 200.

[275] *See id.* at 200–04 (providing summary of Dr. Leone's credentials).

[276] *Id.* at 203.

[277] *Id.*

> with cancer generally via articles and references from Dr. Leone's personal library of journals and textbooks, as well as PubMed and other relevant literature searches;
>
> - a review and analysis of publications from scientific and governmental agencies, including WHO, IARC, FDA, and the EPA. and,
>
> - a review and analysis of documents produced by Defendants in this litigation.[278]

Dr. Leone then assessed the totality of the evidence using a weight of the evidence methodology in the context of Bradford Hill and different etiology concepts, where he concluded to a reasonable degree of medical and scientific certainty that "Zantac/ranitidine can cause breast cancer in humans, [and that] the causal association is strongest for invasive ductal carcinoma."[279] Dr. Leone's methodology tracks that of many of the experts herein, including Defendants' lung expert, Anil Vachani.[280]

As noted, application of this methodology generally supports the admissibility of the opinions at issue.[281] To overcome this presumption, Defendants assert four challenges to Dr. Leone's opinion beyond the mechanics of the methodology: (1) his

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[278] *Id.* at 203–04.

[279] *Id*. at 204.

[280] *Id.* at 165.

[281] *See In re Asbestos Litig*., 911 A.2d at 1204–06; *In re Roundup,* 390 F.Supp.3d at 1150–51 (admitting expert opinion where the expert "conducted a literature review and evaluated the quality of each of the studies."). *See also Barrera,* 2019 WL 2331090, at *14, 17.

conclusions are not generally accepted;[282] (2) he cannot explain the formulation of his opinion;[283] (3) he committed "several methodological errors that are red flags under *Daubert*," such as ignoring the principle of statistical significance and applying an inappropriate substitute;[284] and (4) he perform[ed] an "unreliable Bradford Hill analysis."[285] The Court addresses these briefly, *seriatim*.

General acceptance. In considering this issue, one must bear in mind that the *Daubert* analysis, rejecting the general acceptance requirement, focuses on "the principles and methodology used in formulating an expert's testimony, not the [] resulting conclusions."[286] Defendants assert that Dr. Leone concedes no other agency or government has concluded that ranitidine can cause breast cancer and that Dr. Leone has made "an analytical leap from available data that no other scientist outside this litigation has made."[287] Not so. In the findings of the Mathes study,[288] the authors reported a "2.2-fold increased risk of ductal type breast cancer, representing a 120% increase in the risk of developing breast cancer associated with

[282] Defs.' Br. in Supp. of Brand Defs.' & Patheon's Mot. to Exclude Pls.' Gen. Causation Experts' Op. at 41.

[283] *Id.*

[284] *Id.* at 43.

[285] *Id.* at 46.

[286] Pls.' Opp'n to Defs.' Mot. to Exclude Gen. Causation Experts' Op. at 205 (quoting *Bowen*, 906 A.2d at 794).

[287] Defs.' Br. in Supp. of Brand Defs.' & Patheon's Mot. to Exclude Pls.' Gen. Causation Experts' Op. at 41 (quoting *In re Zantac*, 644 F.Supp.3d at 1187).

[288] *See* Pls.' Opp'n to Defs.' Mot. to Exclude Gen. Causation Experts' Op. at 205 n.757; Ex. 117.

current use of ranitidine."[289] Therefore, the general acceptance argument does not advance Defendants' cause.

Second, Defendants argue that Dr. Leone cannot explain how he formulated his opinion. Yet, he testified that he did not ascribe an individual weight to each element of his data set, but instead that all of the data "informed [his] opinion."[290] Dr. Leone's notes on the strengths and weaknesses of each study were taken into account in his Bradford Hill analysis.[291] He lays out in detail the various bases for his opinion.[292] To the extent Defendants dislike the explanations, they can present their protestations to a jury.

Defendants also give a short shrift to Dr. Leone's reference to the Braunstein study, asserting that it has not been "subject to the rigors of peer-review."[293] Although Braunstein was posted on a pre-print online database, the underlying epidemiological data in the study had already been peer-reviewed.[294] The effort to get the Braunstein study published does not impact the admissibility of Dr. Leone's

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[289] *Id.*

[290] Defs.' Br. in Supp. of Brand Defs.' & Patheon's Mot. to Exclude Pls.' Gen. Causation Experts' Op. at 41 (quoting Dr. Leone's Tr.).

[291] Pls.' Opp'n to Defs.' Mot. to Exclude Gen. Causation Experts' Op. at 206; Ex. 155, at 23.

[292] *See id.* at 206.

[293] Defs.' Br. in Supp. of Brand Defs.' & Patheon's Mot. to Exclude Pls.' Gen. Causation Experts' Op. at 42.

[294] Pls.' Opp'n to Defs.' Mot. to Exclude Gen. Causation Experts' Op. at 206; Ex. 113, Ex. 142, at 8–9.

opinion, especially since general acceptance is not a requirement under *Daubert*.[295] Moreover, the reasonableness of Dr. Leone's reliance on Braunstein is for the jury's consideration.

Defendants' challenges to Dr. Leone's opinion assert also that he "cherry-picks" favorable evidence, fails to consider contrary evidence,[296] and ignores the principle of statistical significance.[297] These allegations have been held repeatedly to be reserved for cross examination.[298] Moreover, Plaintiffs rebut each of these allegations.[299] At this early stage, there is more than enough evidence to overcome Defendants' challenge to Dr. Leone's formulation of his opinion.

Defendants' final challenge is that Dr. Leone has performed an unreliable Bradford Hill analysis.[300] They assert Dr. Leone's consistency conclusion is unsupported, as the studies are noteworthy for their "consistent finding of no

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[295] *See id.* at 206–07.

[296] *Id.* at 208–09.

[297] Defs.' Br. in Supp. of Brand Defs.' & Patheon's Mot. to Exclude Pls.' Gen. Causation Experts' Op. at 43.

[298] *See Karlo,* 849 F.3d at 83 ("The question of whether a study's results were properly calculated or interpreted ordinarily goes to the weight of the evidence, not to its admissibility"); *see also In re Roundup,* 390 F.Supp.3d at 1150–51 ("different interpretations of [carcinogenicity] studies are not necessarily evidence of unreliability…plaintiffs may raise their concerns via cross-examination.").

[299] *See* Pls.' Opp'n to Defs.' Mot. to Exclude Gen. Causation Experts' Op. at 208–11.

[300] Defs.' Br. in Supp. of Brand Defs.' & Patheon's Mot. to Exclude Pls.' Gen. Causation Experts' Op. at 46.

statistically significant association."[301] They declare his dose-response analysis "unscientific" in part due to his failure to use the "generally accepted definition of a "dose-response study."[302] They further reject Dr. Leone's explanations defending the applications and conclusions drawn on this issue, including his inability to identify any threshold dose of exposure.[303] Delaware law does not impose a bright line threshold dose requirement, as discussed above. Moreover, none of these challenges rises above the credibility-oriented questions that *Daubert* and progeny for years have reserved to the jury. Defendants' Motion as to Dr. Leone is **DENIED**.

8. <u>Dr. Vitaly Margulis</u>

Dr. Margulis has been asked to opine on whether it is likely that the NDMA in ranitidine can cause cancer.[304] Defendants do not challenge Dr. Margulis's qualifications.[305] Dr. Margulis reviewed publicly available literature on ranitidine, NDMA and renal cancer, including both primary studies and "publications from scientific and governmental authorities, such as WHO, TARC, FDA and others.[306]

In his report, Dr. Margulis discusses how ranitidine breaks down into NDMA

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[301] *Id.*

[302] *Id.*

[303] *Id.* at 47, 47 n.85.

[304] Pls.' Opp'n to Defs.' Mot. to Exclude Gen. Causation Experts' Op. at 212.

[305] *See id.* (providing Dr. Margulis' professional education and practice).

[306] *Id.* at 213.

and the mechanism by which NDMA can cause cancer.[307] Relying on *in vitro* and animal studies, he explains that, in the human body, NDMA metabolizes into "DNA adducts," which induce "carcinogenic point mutations."[308] Based on his review, Dr. Margulis concludes that NDMA is a "potent carcinogen in every species tested" at "single doses and after long-term exposure to smaller doses."[309] The animal studies found animals were particularly likely to develop kidney tumors.[310]

Dr. Margulis then analyzed ranitidine-specific epidemiology. Six studies reported a kidney cancer result.[311] He analyzed each, finding some strong and others seriously flawed.[312] Overall, Dr. Margulis found that every study had "non-differential misclassification of exposure" which "likely biased risk estimates toward the null;" that is, the studies "were particularly likely to report a false negative result."[313] In Dr. Margulis's expert opinion, none of the epidemiological studies could measure "important data points," which led to "limitations" impossible to overcome.

After consideration of the literature, Dr. Margulis conducted a Bradford Hill

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307 *Id.*

308 *Id.*

309 *Id.* at 213–14.

310 *Id.* at 214.

311 *Id.*

312 *Id.*

313 *Id.*

analysis, which led him to opine that "the NDMA in ranitidine can cause cancer."[314] Thereafter, Dr. Margulis authored a peer-reviewed article describing the background of NDMA and ranitidine and proffering—as a specific mechanism for carcinogenesis—his conclusions as to the harmful metabolization of NDMA.[315] The mechanism is based on human *in vitro* studies and animal studies.[316]

In both his expert report and his peer-reviewed article, Dr. Margulis "explains that animal and *in vitro* studies can be applied to humans. . . based on the similarities in NDMA metabolism seen in animal studies and *in vitro* human cellular experiments."[317] Dr. Margulis included in his article ranitidine epidemiological studies, including the same criticisms he raised in his expert report, one of which noted that "any conclusions drawn from these observational studies, whether supporting or challenging. . . should be interpreted with caution."[318]

Defendants challenge Dr. Margulis's opinion much as they have many of the others; he is inconsistent in his approach to statistical significance;[319] his conclusion

[314] *Id.* at 215.

[315] *Id.* at 215–16.

[316] *Id.* at 216.

[317] *Id.* (internal quotation marks omitted).

[318] *Id.* (emphasis omitted).

[319] Defs.' Br. in Supp. of Brand Defs.' & Patheon's Mot. to Exclude Pls.' Gen. Causation Experts' Op. at 50.

is not accepted by the scientific community;[320] he "cherry-picks" his evidence;[321] and his "principal" reliance on dietary and worker NDMA studies is not appropriate.[322]

The extended discussion of Dr. Margulis's methodology and findings make plain the detailed nature of his statistical analysis.[323] He is not a *poseur*.[324] Defendants admit he is qualified to offer his opinion, and at this stage, his methods confirm as much.

As to "principally" relying on NDMA dietary and worker studies, in his report Dr. Margulis spends one paragraph each on dietary and occupational studies, summarizing them, and emphasizes that the role those studies played in his conclusion was "not significant."[325] He further considered the contrary statistical findings in the six ranitidine studies.[326] Plaintiffs emphasize that "[t]here is nothing inconsistent about accurately reporting the actual results from these studies."[327]

Defendants pause on these mixed results as "the definition of inconsistent

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[320] *Id.* at 49.

[321] *Id.* at 50–53.

[322] *Id.* at 53–55.

[323] *See* Pls.' Opp'n to Defs.' Mot. to Exclude Gen. Causation Experts' Op. at 214, 217–19.

[324] *In re Asbestos Litig.*, 911 A.2d at 1207.

[325] Pls.' Opp'n to Defs.' Mot. to Exclude Gen. Causation Experts' Op. at 218.

[326] *Id.* at 214, 217–18.

[327] *Id.* at 217.

results,"[328] although they point out Dr. Margulis's conclusion that the six studies broke evenly, three showing an increased risk and three a decreased risk. At this level of science, any characterization of these numbers would do the data a disservice. And asking this Court to do the math is not a good idea. Numerically, the results, inconsistent or otherwise, do not tip the scale in either direction.[329]

Defendants further throw several accusations at Dr. Margulis's report. While the Court considers many herein, review of the Opposition gives a more fulsome recitation of Dr. Margulis' rebuttal in defense of his opinion.[330] Some, Plaintiffs suggest, mischaracterize his opinions.[331] Some, they claim, ignore his testimony.[332] These challenges, along with claims of cherry-picking and flawed reliance on certain NDMA studies, fall victim to the wisdom of *Daubert*: they belong to the jury.[333]

The Motion to exclude Dr. Margulis's opinion is **DENIED**.

9. <u>Dr. George Miller</u>

Plaintiffs have asked Dr. Miller to provide opinions regarding whether

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[328] *See* Defs.' Br. in Supp. of Brand Defs.' & Patheon's Mot. to Exclude Pls.' Gen. Causation Experts' Op. at 51; Pls.' Opp'n to Defs.' Mot. to Exclude Gen. Causation Experts' Op. at 217. From a non-scientist's perspective, that the six studies broke evenly on the point 3 to 3 does not seem to fit the definition of inconsistent.

[329] *Barrera*, 2019 WL 2331090, at *17 (stating that opposing experts interpreted the same studies differently "does not render [their] opinions inadmissible.").

[330] *See* Pls.' Opp'n to Defs.' Mot. to Exclude Gen. Causation Experts' Op. at 216–21.

[331] *See, e.g., id.* at 217–19.

[332] *Id.* at 219.

[333] *Karlo*, 849 F.3d at 83; *In re Roundup*, 390 F.Supp.3d at 1150–51.

NDMA exposure from ranitidine causes pancreatic cancer.[334] Defendants do not challenge Dr. Miller's qualifications to opine on that question.[335] Defendants would exploit Dr. Miller's lack of formal epidemiological training, but they have not voiced objection to the expert's qualifications to offer those opinions. Dr. Miller may testify on epidemiological issues implicated in his report.[336]

Dr. Miller is expected to opine within a reasonable degree of medical certainty that there is a causal link between ranitidine and pancreatic cancer.[337] In preparing that opinion, Dr. Miller first analyzed "whether ranitidine contains a cancer-causing agent" and—relying in part on GSK's root cause analysis—found that NDMA is a toxic degeneration byproduct of ranitidine.[338] Dr. Miller also relied upon testing outlined in the expert report by Emery Pharma.[339] He analyzed studies that showed a link between dietary sources and pancreatic cancer. Dr. Miller then compared the studies with others that did not show an association between ingestion of nitrates and pancreatic cancer, finding serious flaws with those that did not show an association.[340]

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[334] Pls.' Opp'n to Defs.' Mot. to Exclude Gen. Causation Experts' Op. at 184.

[335] *See id.* at 185–87 (providing summary of Dr. Miller's educational and professional background).

[336] *See Barrera*, 2019 WL 2331090, at *13.

[337] Pls.' Opp'n to Defs.' Mot. to Exclude Gen. Causation Experts' Op. at 187.

[338] *Id.*

[339] *Id.* at 187–88.

[340] *Id.* at 188.

Dr. Miller also analyzed studies showing a link between occupational exposure to NDMA and pancreatic cancer, and weighed the strengths and weaknesses of each study to determine if the peer-reviewed studies supported such a link. Dr. Miller then analyzed peer-reviewed studies regarding the link between NDMA exposure from ranitidine use and pancreatic cancer. After weighing the strengths and weaknesses of each study, Dr. Miller then analyzed the Bradford Hill criteria, and concluded the existence of a causal link between ranitidine and pancreatic cancer.[341] And added that "[t]here is considerable biologic plausibility to support this conclusion and lend support to the well-conducted human epidemiological studies."[342]

Defendants argue that Dr. Miller's methodology is unreliable. Pointing to a number of alleged deficiencies across the breadth of his opinion, the gist is that the augmentation of his opinions are evidence of the "results-oriented nature of his analyses."[343] These allegations do not support exclusion of his opinion.[344] Nor does what Defendants characterize as Dr. Miller's "inconsistent application of power and

[341] *Id.* at 189.

[342] *Id.*

[343] Defs.' Br. in Supp. of Brand Defs.' & Patheon's Mot. to Exclude Pls.' Gen. Causation Experts' Op. at 63.

[344] *Barrera*, 2019 WL 2331090, at *11 (changing opinion goes to the weight, not admissibility).

follow-up to the studies."[345] Their rejection of his analysis and application of follow-up time,[346] does not compel exclusion. Likewise, the arguments that Dr. Miller made a "faulty assumption" and improperly "flipped the burden" of proof,[347] or turned "*limitations* in the 'negative' studies into *strengths* in the studies he preferred,"[348] go to weight, not admissibility.[349]

In a broader attack, Defendants accuse Dr. Miller of providing no methodology for how he evaluated studies. First, this claim is rebutted by the extensive background review Dr. Miller performed as part of his preparation. Miller testified that he "conducted a systematic review of the literature and evaluated the science to arrive at his conclusions."[350] Second, Dr. Miller dedicates eleven pages of his report discussing the various studies and their strengths and limitations.[351]

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[345] Defs.' Br. in Supp. of Brand Defs.' & Patheon's Mot. to Exclude Pls.' Gen. Causation Experts' Op. at 93–94; *see* Reply Brief in Support of Brand Defendants' and Patheon's Motions to Exclude: (1) Plaintiffs' General Causation Experts' Opinions; and (2) Dr. Charles Jameson, Trans. ID 71797654 (Jan. 12, 2024) (herein "Reply Br. in Supp. of Defs.' Mot. to Exclude Pls.' Gen. Causation Experts' Op. & Dr. Jameson") at 63–64.

[346] Pls.' Opp'n to Defs.' Mot. to Exclude Gen. Causation Experts' Op. at 194–95; *see* Defs.' Br. in Supp. of Brand Defs.' & Patheon's Mot. to Exclude Pls.' Gen. Causation Experts' Op. at 94–95.

[347] Defs.' Br. in Supp. of Brand Defs.' & Patheon's Mot. to Exclude Pls.' Gen. Causation Experts' Op. at 91.

[348] *Id.* (emphasis in original).

[349] *McCullock*, 61 F.3d at 1038; *Karlo*, 849 F.3d at 83.

[350] Defs.' Br. in Supp. of Brand Defs.' & Patheon's Mot. to Exclude Pls.' Gen. Causation Experts' Op. at 91.

[351] Pls.' Opp'n to Defs.' Mot. to Exclude Gen. Causation Experts' Op. at 192.

Defendants accuse Dr. Miller of not ranking the studies by quality.[352] But Dr. Miller wrote extensively in his report regarding the strengths and weaknesses of each study.[353] They complain that Dr. Miller was not able to identify the key criteria he used to determine a study's reliability. Yet, he testified that the most critical factors for him in evaluating studies were "median age to study an appropriate population and follow-up time."[354] Defendants discredit Dr. Miller's Bradford Hill analysis, although he testified at length about same.[355]

Dr. Miller's conclusions are reliable.[356] At this stage, it cannot be said that the scope of his review and the science used to formulate his opinions do not support admissibility.[357] Defendants may have succeeded at times in making this a close call. But close calls go to the jury. The Motion to exclude his opinion is **DENIED**.

10. <u>Bruce J. Trock, MPH, PhD</u>

Dr. Trock has been disclosed to give general causation opinions regarding whether NDMA exposure from ranitidine causes prostate cancer.[358] Dr. Trock is a

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[352] *Id.* at 193.

[353] *Id.*

[354] *Id.*

[355] *See id.* at 198–99.

[356] *Barrera*, 2019 WL 2331090, at *14.

[357] *In re Asbestos Litig.*, 911 A.2d at 1205–06; *In re Roundup*, 390 F.Supp.3d at 1150–51 (expert opinion admitted where the expert "conducted a literature review and evaluated the quality of each of the studies."); *accord*, *Barrera*, 2019 WL 2331090, at *14, 17.

[358] Pls.' Opp'n to Defs.' Mot. to Exclude Gen. Causation Experts' Op. at 174.

cancer epidemiologist at Johns Hopkins University, with 37 years of experience in cancer research, 21 of which were focused on prostate cancer.[359] He has authored, or co-authored, over 320 peer-reviewed publications, 201 of which focus on prostate cancer.[360] Defendants do not challenge Dr. Trock's qualifications to testify here.[361]

In preparing his opinions, Dr. Trock reviewed and analyzed "the entirety of the relevant scientific and epidemiological literature concerning the association between ranitidine and prostate cancer."[362] In doing so, Dr. Trock "assessed the strength of the relevant evidence derived from animal and occupational studies, and Dr. Trock used his review and analysis of the medical literature, including the strengths and weaknesses of the pertinent studies, to perform a Bradford Hill analysis.[363] Based on his reviews and his Bradford Hill analysis, Dr. Trock concluded, to a reasonable degree of scientific certainty, that exposure to ranitidine can cause prostate cancer in humans.[364] His opinions are based on sound, reliable scientific methodology, and are generally admissible.[365]

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[359] *Id.*

[360] *Id.*

[361] *See id.* at 174–75 (providing a more complete summary of Dr. Trock's qualifications).

[362] *Id.* at 175; Ex. 147, at 24–38.

[363] Pls.' Opp'n to Defs.' Mot. to Exclude Gen. Causation Experts' Op. at 175.

[364] *Id.* at 176.

[365] *Id.*; *see In re Asbestos Litig.*, 911 A.2d at 1205–06; *see also In re Roundup*, 390 F.3d at 1150–51 (expert opinion admitted where the expert "conducted a literature review and evaluated the quality of each of the studies."); *accord*, *Barrera*, 2019 WL 2331090, at *14, 17.

Defendants interpose several challenges to that admissibility. Their initial challenge argues that relevant epidemiological studies "reported no statistically significant positive associations between ranitidine use and prostate cancer."[366] Plaintiffs counter that, in fact, Dr. Trock noted that of the nine relevant epidemiological studies concerning ranitidine, three actually observed "increases in the incidence of prostate cancer."[367] Dr. Trock further distinguished five of the remaining six studies as considerably flawed (i.e., they used inadequate follow up periods, had short durations of exposure to ranitidine, and failed to adjust for potential confounders).[368] Several studies "lacked data on duration or cumulative dose of ranitidine, and recorded only at baseline," and were therefore susceptible to misclassification.[369]

Defendants first reject Dr. Trock's analysis and conclusions. That is, of course, their prerogative, but does not support exclusion. Similarly, Defendants raise again the charge that his opinion is inadmissible because his conclusions are not generally accepted in the medical community.[370]

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[366] Defs.' Br. in Supp. of Brand Defs.' & Patheon's Mot. to Exclude Pls.' Gen. Causation Experts' Op. at 64.

[367] Pls.' Opp'n to Defs.' Mot. to Exclude Gen. Causation Experts' Op. at 177.

[368] *Id.*

[369] *Id.*

[370] Defs.' Br. in Supp. of Brand Defs.' & Patheon's Mot. to Exclude Pls.' Gen. Causation Experts' Op. at 64–65.

As noted, *Daubert* rejected the general acceptance requirement. Defendants nonetheless urge that general acceptance is still an indicator of unreliable methodology.[371] But, the record establishes that Dr. Trock analyzed the relevant data, and his opinions align with three of the relevant studies. This evidence is to be used flexibly when evaluating reliability. Again, *Daubert* does not charge the trial court to pick one expert's science over another's.[372]

Defendants next argue that Dr. Trock's conclusions are unreliable because he "ignores epidemiological ranitidine studies and takes the novel approach of drawing conclusions about ranitidine based on studies" of rubber workers and animals.[373] Defendants point to the MDL Order and its rejection of the Hidajat study as flawed.[374] Those may have been appropriate conclusions for that court to draw. But as presented through these experts, in Delaware, it is not the role of this Court to substitute its scientific conclusions for those of an expert scientist.

Dr. Trock analyzed the Hidajat study and compared it to a second rubber worker study, which he rejected as marred by speculation.[375] Dr. Trock did not rely

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[371] *Id.* at 65.

[372] *In re Asbestos Litig.*, 911 A.2d at 1207.

[373] Defs.' Br. in Supp. of Brand Defs.' & Patheon's Mot. to Exclude Pls.' Gen. Causation Experts' Op. at 65–67; Pls.' Opp'n to Defs.' Mot. to Exclude Gen. Causation Experts' Op. at 179.

[374] Defs.' Br. in Supp. of Brand Defs.' & Patheon's Mot. to Exclude Pls.' Gen. Causation Experts' Op. at 66.

[375] *Id.*

on animal studies alone. He considered their import along with his evaluation of the six epidemiological studies available. Defendants acknowledge that Dr. Trock analyzed the epidemiological ranitidine studies and dismissed them as "severely flawed."[376] That approach is consistent with the proper methodology applied in such circumstances.[377] Delaware law "does not require that evidence of general causation take the form of epidemiological evidence . . . Evidence such as animal studies, *in vivo* studies, *in vitro* studies, toxicology, and case studies can be used to show causation."[378] These factors are to be applied flexibly.[379]

Defendants' final charge is that Dr. Trock's Bradford Hill analysis is unreliable.[380] They argue that an expert must address epidemiological evidence that is inconsistent with his opinion.[381] As discussed above, Dr. Trock did that. Their argument about dose response, which is another of the Bradford Hill criteria that may be considered, does not suffice to compel exclusion of Dr. Trock's opinion.

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[376] *Id.* at 65–66.

[377] *See, e.g.*, *Barrera*, 2019 WL 2331090, at *14.

[378] *Id.*

[379] *See* Pls.' Opp'n to Defs.' Mot. to Exclude Gen. Causation Experts' Op. at 182 (discussing Dr. Trock's selection of studies on which he relied); *see, e.g., id.* ("Dr. Trock's analysis, placing more weight on NDMA occupational [and animal] studies, is entirely reasonable in light of the significant limitations in the nine epidemiological studies of ranitidine."); *see also id.* at 180 (discussing Dr. Trock's use of animal studies, emphasizing that "in considering the weight of the evidence, Dr. Trock considered NDMA animal studies - but not to the exclusion of the relevant epidemiological literature.").

[380] Defs.' Br. in Supp. of Brand Defs.' & Patheon's Mot. to Exclude Pls.' Gen. Causation Experts' Op. at 68–69.

[381] *Id.* at 69.

Defendants can take up these challenges before the jury. The Motion to exclude Dr. Trock is **DENIED**.

11. Emery Pharma

Plaintiffs retained Emery Pharma (hereinafter "Emery") to "conduct further testing on the levels of NDMA in ranitidine provided by Defendants and specifically the levels in Plaintiffs' own pills and opine on the nature of ranitidine's ability to degrade and transform into NDMA."[382]

Emery is a "full-service contract research laboratory, specializing in analytical, bioanalytical chemistry, microbiology and cell biology services, custom synthesis, [] general research and development and [] the standards employed in the manufacture of drugs, not in research."[383] Defendants characterize Emery as a "litigation support lab."[384] Emery counters that "only approximately twenty percent of Emery's revenues are from litigation consulting."[385] Emery describes the majority of its clients as pharmaceutical companies that reach out to Emery for "isolation characterization work;" that is, to analyze and identify "an impurity in a

[382] Pls.' Opp'n to Defs.' Mot. to Exclude Gen. Causation Experts' Op. at 223.

[383] *Id.* at 224.

[384] Brief in Support of Brand Defendants' and Patheon's Motion to Exclude Plaintiffs' Expert, Emery Pharma, Trans. ID 71408808 (Nov. 15, 2023) (hereinafter "Defs.' Br. in Supp. of Brand Defs.' & Patheon's Mot. to Exclude Emery Pharma") at 14 n.23. The Court notes Defendants' Brief to Exclude Emery Pharma is devoid of pagination, as such the Court references the corresponding PDF page numbers.

[385] Pls.' Opp'n to Defs.' Mot. to Exclude Gen. Causation Experts' Op. at 221 n.829.

drug that is being marketed."[386]

Defendants do not challenge Emery's qualifications to render the opinions requested of it.[387] Yet, the parties devote nearly 150 pages of briefing to the admissibility of the Emery opinion alone. The somewhat more aggressive and pejorative rhetoric in the briefs suggests the Emery opinion lies at the heart of the *Daubert* debate, for both sides.

Defendants offer nine challenges to the admissibility of the Emery Opinion:

> (1) Plaintiffs' use of HILIC methodology is unvalidated and unreliable;
>
> (2) Plaintiffs' opinion of manual integration, without proper protocols, is unreliable;
>
> (3) Plaintiffs failed to keep proper documentation;
>
> (4) Dr. Najafi left all operational decisions in the testing process to the discretion of his assistants, who did not follow preset protocols;
>
> (5) the Emery opinion has not been published or submitted for peer review;
>
> (6) the Emery opinion does not "fit" the parameters of the issue here;
>
> (7) Emery's simulated studies fail to meet the *Daubert* standards;

[386] *Id.*

[387] *See id.* at 224–28 (providing a more complete recitation of Emery qualifications and its representatives).

(8) Emery's simulated gastric fluid study is not reliable; and

(9) Emery's "miscellaneous tests" do not "fit" the case and are not reliable.[388]

The Court addresses briefly each of Defendants' challenges separately. The Court prefers not to get into the weeds of the science, but some digging is required.

a. Emery's Use of HILIC

Emery used Hydrophilic Interaction Chromatography ("HILIC") to test for the presence of ranitidine. Defendants argue that HILIC is unvalidated, and therefore unreliable. Defendants also charge that the increased measure of ranitidine when HILIC was used supports their charge that HILIC's use was a litigation-driven decision, made to skew the numbers in Plaintiffs' favor.

HILIC is a technique for separation of polar compounds. Plaintiffs explain that HILIC was used in the first part of Emery's separation processes "to improve sample identification and quantification."[389] Plaintiffs further indicate that Emery's method known as LC-MS/MS (the combination of liquid chromatography ("LC") and mass spectrometry ("MS")) "uses the same underlying technology the FDA used, with the difference being the type of initial column used for separation of the

[388] Defs.' Br. in Supp. of Brand Defs.' & Patheon's Mot. to Exclude Emery Pharma at 21–22.

[389] Pls.' Opp'n to Defs.' Mot. to Exclude Gen. Causation Experts' Op. at 236.

analyte."[390]

Plaintiffs further assert that HILIC is a well-established, accepted column for use in chromatography with polar compounds, which NDMA is.[391] They quote from a monograph by *Defendants'* expert, Bernard Olsen, in support:

> The popularity of [HILIC] has grown rapidly in recent years. The HILIC mode can provide retention and separation of polar compounds that are difficult to analyze by reversed-phase high-performance liquid chromatography (RPLC) or other means. HILIC has been utilized in a variety of applications including drugs and metabolites in biological fluids, biochemicals, pharmaceuticals (from drug discovery to quality control), foods and environmental.[392]

The Olsen monograph notes that HILIC "can be particularly suited in the determination of specific impurities, including polar compounds,"[393] of which NDMA is one.

Emery explains its reasons for preferring HILIC columns over reverse-phase columns.[394] Emery also showed that its protocol, including use of an HILIC column, was "fully validated."[395] Notably, the JCCP court rejected this same *Daubert*

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[390] *Id.*

[391] *Id.* at 237.

[392] *Id.*

[393] *Id.* at 237, 237 n.878.

[394] *Id.* at 236–38.

[395] *Id.* at 239.

challenge.[396] Emery's efforts notwithstanding, Defendants reject their science and stand on the MDL Order.[397] Following Delaware jurisprudence, this Court finds that HILIC has been validated and determined reliable, and its use in measuring ranitidine constitutes sound methodology to survive a *Daubert* challenge.

b. Manual Integration

Defendants' challenge of Emery's use of manual integration involves data integrity. They claim Plaintiffs did not follow a Standard Operating Procedure (SOP) to guide when "analysts perform manual integrations."[398] They further accuse Emery of performing manual integrations "unreliably, arbitrarily, and following no set standards."[399]

Emery explained that "all decisions regarding when and how to conduct manual integrations, along with the integrations themselves, were done using the same scientific principles as written in Emery's Standard Operating Procedure ("SOP") for chromatography analysis [] that was in effect at the time."[400] It appears

[396] *Id.* at 254; *see also* Pls.' Opp'n to Defs.' Mot. to Exclude Gen. Causation Experts' Op. Ex. 75, at 23.

[397] Brand Defendants' and Patheon's Reply in Support of their Motion to Exclude Plaintiffs' Expert, Emery Pharma (herein "Defs.' Reply Br. in Supp. of Mot. to Exclude Emery Pharma") at 9–11.

[398] *See* Defs.' Br. in Supp. of Brand Defs.' & Patheon's Mot. to Exclude Emery Pharma at 29.

[399] *Id.*; Ex. 15, at 1.

[400] Pls.' Opp'n to Defs.' Mot. to Exclude Gen. Causation Experts' Op. at 241.

that Defendants' expert, Dr. Olsen, also relied on the same scientific principles.[401]

"[W]hether performed automatically or manually. . . integration must be scientifically justifiable."[402] Defendants concede that an "analyst must exercise professional judgment in deciding when use of a manual integration is appropriate."[403] Emery performed manual integrations only when the default integration was scientifically unsound.[404] To the extent that Defendants rely on the Agilent monograph in support of this argument, this Court accepts the reasons set for by Plaintiffs that any data manipulation that was focused on FDA compliance is not at issue here.[405]

Defendants further argue that Emery "left manual adjustments to the unfettered discretion of its staff," and that performing manual engagements "*may*" be a sign of a "flawed method."[406] For several reasons, this argument is insufficient to warrant relief.

Emery makes the point that "Dr. Cheu," one of the primary representatives of Emery on the opinion, "did these manual integrations."[407] In their Reply, Defendants

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[401] *Id.*

[402] *Id.* at 240.

[403] Defs.' Br. in Supp. of Brand Defs.' & Patheon's Mot. to Exclude Emery Pharma at 29.

[404] Pls.' Opp'n to Defs.' Mot. to Exclude Gen. Causation Experts' Op. at 240.

[405] *Id.* at 255–56.

[406] Defs.' Br. in Supp. of Brand Defs.' & Patheon's Mot. to Exclude Emery Pharma at 30 (quoting *In re Zantac*, 644 F.Supp.3d at 1123)) (emphasis added).

[407] Pls.' Opp'n to Defs.' Mot. to Exclude Gen. Causation Experts' Op. at 240–41.

equivocate on this point while doubling down: "Emery allowed its analysts, *including Dr. Cheu*, to perform manual integrations in their sole judgment and discretion."[408] Further, Dr. Najafi testified that he supervised the work being done at Emery and double-checked the work being done by his staff scientists to make sure [he was] confident of the numbers."[409] Dr. Najafi reviewed the lab results, the lab notebooks, and synthesized that data in formulating his opinion.[410]

Manual versus electronic integration turns on the scientist's assessments of the accuracy and utility of each in a particular circumstance. As the discussion illustrates, these are complicated questions well beyond the wisdom of this trial judge, who, consistent with *Daubert* and its progeny, will not pick a winner. The answer rests with the jury.

c. Lack of Documentation of Lab Results

Defendants allege that Plaintiffs' protocols and test results fail the reliability requirement of *Daubert* due to their failure to "describe the methods they used as fully and accurately as possible."[411] Defendants emphasize that "[w]ithout

[408] Defs.' Reply Br. in Supp. of Mot. to Exclude Emery Pharma at 12.

[409] Pls.' Opp'n to Defs.' Mot. to Exclude Gen. Causation Experts' Op. at 260.

[410] *Id.*

[411] Defs.' Br. in Supp. of Brand Defs.' & Patheon's Mot. to Exclude Emery Pharma at 32 n.51; *see also id*. Defs.' Br. in Supp. of Brand Defs.' & Patheon's Mot. to Exclude Emery Pharma Ex. 35, at 48.

documentation the process is meaningless; essentially there has been no study."[412]

The initial challenge focuses on Emery's failure to adequately document its testing.[413] In response, Plaintiffs have sufficiently explained that Emery designed and created protocols for each experiment, each of which was validated and the results of that validation produced.[414] Plaintiffs add that, beyond those "standalone validations, each analytical run includes a series of calibrations and quality control injections to further validate the process in run," and each test "was documented in a lab notebook contemporaneously maintained by the analyst conducting the experiment and counter signed by "another researcher who validated the experiment."[415]

Defendants next attack Emery's lack of protocols for baseline testing, emphasizing that "none was ever created."[416] The straight-forward response is that that "Emery's task regarding baseline testing [] was simply to determine what levels of NDMA were detectible, if any, in the pills and API [active pharmaceutical ingredients] produced to Plaintiffs by Defendants. *There was no hypothesis to be tested.* There was no need for a 'study design' outside that of testing protocol and

[412] Defs.' Br. in Supp. of Brand Defs.' & Patheon's Mot. to Exclude Emery Pharma at 32 n.51.

[413] *Id.* at 35; Pls.' Opp'n to Defs.' Mot. to Exclude Gen. Causation Experts' Op. at 257.

[414] Pls.' Opp'n to Defs.' Mot. to Exclude Gen. Causation Experts' Op. at 256.

[415] *Id.* at 256–57.

[416] Defs.' Br. in Supp. of Brand Defs.' & Patheon's Mot. to Exclude Emery Pharma at 34 n.54.

method. Emery tested the pills and API and reported the results. . . ."[417]

As to the adequacy of the lab notebooks, Plaintiffs explain that "[m]ost raw and processed data for LC-MS/MS simply cannot be recorded in lab notebooks, as it is maintained electronically.[418] The lab notebooks, however, "contain a reference to exactly where on Emery's system (by folder path) that data was stored."[419] All of the written validated protocol, underlying raw and processed data from the conduct of the testing was provided to Defendants in [the relevant] format, with printed versions in the form of PDFs, and also stored electronically in the [relevant] system, where it remains to this day, and all of it was produced to the Defendants."[420]

Plaintiffs further indicate they provided Defendants with "all of [the test] results along with the corresponding test names, lot numbers, etc., in Excel format," noting that Defendants can "conduct their own data analysis to come up with whatever statistical calculations they wish," something, Plaintiffs note, Defendants have not done.[421] If Plaintiffs failed to describe their methods as fully and accurately as possible, any such failing is reserved as a topic for cross examination.[422]

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[417] Pls.' Opp'n to Defs.' Mot. to Exclude Gen. Causation Experts' Op. at 257–58 (emphasis in original).

[418] *Id.* at 257.

[419] *Id.*

[420] *Id.*; *see* Pls.' Opp'n to Defs.' Mot. to Exclude Gen. Causation Experts' Op. Ex. 202.

[421] Pls.' Opp'n to Defs.' Mot. to Exclude Gen. Causation Experts' Op. at 258.

[422] *See, e.g.*, *McCullock*, 61 F.3d at 1043–44; *Karlo*, 849 F.3d at 81–84.

d. Dr. Najafi's Reliance on the Work of His Team

Defendants take the position that Dr. Najafi, individually, should be excluded because he relied "entirely" on the work of his team. They impugn Dr. Najafi with the statement that he is "merely parroting" work done by others.[423] Not so.

Dr. Najafi testified on his role in the preparation of Emery's testing conclusions.[424] Defendants do not take that testimony on directly. Rather, they rely on the MDL Order and deposition testimony that contradicts Dr. Najafi's own testimony. With that, they argue that Emery analysts conducted testing without "guiding principles from Dr. Najafi" or without written procedures or instructions.[425] They highlight the inclusion of three signatures on the Emery Report as "tacit acknowledgement of his lack of firsthand knowledge."[426]

The fact that several scientists signed the Report may be weighed as a testament to each scientist's involvement in its preparation, and their certification of its accuracy and validity. Dr. Najafi's testimony supports that conclusion. The Defendants are free to argue that the actions of the signatories somehow implicate Dr. Najafi. But not at this juncture. Their allegations on this score present a

[423] Defs.' Br. in Supp. of Brand Defs.' & Patheon's Mot. to Exclude Emery Pharma at 40.

[424] Pls.' Opp'n to Defs.' Mot. to Exclude Gen. Causation Experts' Op. at 259–61.

[425] Defs.' Br. in Supp. of Brand Defs.' & Patheon's Mot. to Exclude Emery Pharma at 39 (citing *In re Zantac*, 644 F.Supp.3d at 1138).

[426] *Id.*

credibility issue for the jury.

e. Lack of Publication or Peer Review

Defendants cite lack of peer review or publication as a "pertinent consideration" of whether a theory or technique is valid.[427] At the outset, Defendants offer no authority in support, beyond the MDL Order in *Zantac*.[428] Moreover, the lack of peer review or publication presents an issue for the jury. Nor is Emery's science an orphan child.[429] And as previously mentioned, even Defendants' expert, Dr. Bernard Olsen, extolls the LS-MS/MS technique used by Plaintiffs.[430] As Plaintiffs' point out, when Defendants' experts were asked about publication, they refused to suggest lack of publication as evidence of unreliability.[431] If lack of peer review or publication has any utility here, it is fodder for cross-examination, not exclusion.

f. Emery's Baseline Testing "Does Not Fit"

Defendants next challenge the so-called "fit" of Emery's baseline testing to

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[427] *Id*. at 40.

[428] *Id.*

[429] *See* Pls.' Opp'n to Defs.' Mot. to Exclude Gen. Causation Experts' Op. at 261 ("[T]he use of LC-MS/MS to detect and quantify impurities in drug substances, and the methodology used to validate the specific protocol applied by Emery are both not only widely accepted and published in peer reviewed literature but have been available and in use for decades.").

[430] *Id.* at 237.

[431] *Id.* at 262.

the facts of the case.[432] The challenge rests on the premise that the amount of ranitidine in active pharmaceutical ingredients (API) is different than in a pill that a user ingests.[433] Testing API alone, Defendants argue, "skews testing results high and does not reflect what individuals actually ingest."[434] Plaintiffs argue that this is a faulty premise via this explanation:

> [N]one of the steps involved in creating the final dosage form . . . is supposed to change the included [active pharmaceutical ingredient] API. Thus, any NDMA contained in the API will be, perforce, also included in the finished pill. This is why, for example, GSK also tested and reported the NDMA in API when it conducted its root cause analysis.[435]

That is, "the NDMA contained in the API at the time the finished dose is manufactured will get transferred to the pill itself."[436] Defendants do not counter this analysis in their Reply. Emery's testing of API fits the facts of the case and will not be excluded.

g. Emery's Simulated Environmental Tests

Emery conducted three "simulated consumer experience" tests to measure

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[432] Defs.' Br. in Supp. of Brand Defs.' & Patheon's Mot. to Exclude Emery Pharma at 41; *see Daubert,* 509 U.S. at 591.

[433] Defs.' Br. in Supp. of Brand Defs.' & Patheon's Mot. to Exclude Emery Pharma at 41.

[434] *Id.*

[435] Pls.' Opp'n to Defs.' Mot. to Exclude Gen. Causation Experts' Op. at 263.

[436] *Id.*

how NDMA might form in ranitidine.[437] Plaintiffs suggest the simulations show the breakdown of ranitidine "into NDMA in various real-world scenarios, and produces high levels of NDMA, [which is] relevant to Defendants' argument that there is minimal NDMA exposure from taking ranitidine."[438] Plaintiffs suggest that such testing shows "that NDMA could reasonably form under specific instances—instances that would apply to all plaintiffs."[439] Thus, their argument follows, the simulations are relevant at the general causation stage.[440] This Court agrees.

Defendants' challenge to the simulations follows a common path. They each begin with a general acceptance attack, which they support in the main with a quotation from the MDL Order.[441] Citing to that ruling, they argue that "no other laboratory in the world has used these tests to measure drug stability; no agency requires or recognizes them [;] [and no] paper has ever been published validating their reliability."[442]

As to the car simulation, Defendants note that "Emery did not study Zantac stored in real-life cars," instead making "a series of unsupported assumptions about

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[437] Defs.' Br. in Supp. of Brand Defs.' & Patheon's Mot. to Exclude Emery Pharma at 42.

[438] Pls.' Opp'n to Defs.' Mot. to Exclude Gen. Causation Experts' Op. at 263.

[439] *Id.*

[440] *Id.*

[441] *See* Defs.' Br. in Supp. of Brand Defs.' & Patheon's Mot. to Exclude Emery Pharma at 44 (quoting *In re Zantac*, 644 F.Supp.3d at 1150).

[442] Defs.' Br. in Supp. of Brand Defs.' & Patheon's Mot. to Exclude Emery Pharma at 42.

consumer behavior and car conditions" to simulate that experience.[443] They criticize Dr. Najafi's reliance on the Vanos 1028 study, and urge that "even if modeling an experiment for a drug stability study. . . were a reliable methodology," Emery's car simulation did not comport with such a model.[444]

But the Vanos report outlines three bases for its data—Vanos, Grunstein, and the Assessment of the Common Carrier Shipping Environmental General Technical Report.[445] Defendants concede that Plaintiffs cited a few studies in support of their data.[446] And further concede they missed key data points from the Grunstein study pertaining to the average air temperature used in the Emery study.[447] As the several cases repeatedly cited above make clear, such criticism goes to weight, not admissibility.

Defendants lodge identical challenges to the bathroom simulation.[448] As with the car simulation, Defendants acknowledge the validation of the "non-peer

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[443] *Id.*

[444] *Id.* at 43 (quoting *In re Zantac*, 644 F.Supp.3d at 1147).

[445] Pls.' Opp'n to Defs.' Mot. to Exclude Gen. Causation Experts' Op. at 264.

[446] DEFAs.' Br. in Supp. of Brand Defs.' & Patheon's Mot. to Exclude Emery Pharma at 42; Ex. 10, at 230:16–17.

[447] Pls.' Opp'n to Defs.' Mot. to Exclude Gen. Causation Experts' Op. at 264.

[448] Defs.' Br. in Supp. of Brand Defs.' & Patheon's Mot. to Exclude Emery Pharma at 44 ("Emery's 'bathroom simulation' studies did not test Zantac product in a real-world bathroom, but instead attempted to recreate the conditions of a bathroom based on a series of unsupported assumptions . . . [it] has nothing to do with drug stability or the effect that a bathroom environment could have on a drug product.").

reviewed" Aizawa study, but they retrench by alleging that Plaintiffs departed from the Aizawa model by using more "extreme conditions" than contemplated.[449] Defendants also advance lack of general acceptance, and quote a near verbatim repetition from the MDL Order to that end, just as they did with the car simulation.[450] Yet, Defendants, again, missed a study relied upon by Plaintiffs that favors their position.[451]

Plaintiffs' last simulation created "climactic zones" to "simulate. . . common consumer experiences with Zantac."[452] Defendants again stress that the climatic zones on which they were based "were not designed to mimic real-world conditions," and, citing the MDL order in *Zantac*, argue that they were "designed to increase the rate of chemical degradation or physical damage of a drug substance or drug product *by using exaggerated storage conditions*[.]"[453] Defendants also attack the climactic zone testing's reliability because, they say, "it departed from the actual Zantac container closure system" and for its lack of support for the assumption that a typical plaintiff or distributor stores ranitidine at 65 % relative humidity in an outside, non-air conditioned environment.[454]

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[449] *Id.*

[450] *Id.* at 46.

[451] Pls.' Opp'n to Defs.' Mot. to Exclude Gen. Causation Experts' Op. at 264–65.

[452] Defs.' Br. in Supp. of Brand Defs.' & Patheon's Mot. to Exclude Emery Pharma at 45.

[453] *Id.* (quoting *In re Zantac*, 644 F.Supp.3d at 1152) (emphasis in original).

[454] *Id.* at 46.

That criticism appears to validate the testing, as Plaintiffs explained, "because [as noted below] a laboratory cannot actually recreate months' worth of exposure to varied temperature and humidity conditions in the time frames involved with testing."[455]

"General causation considers the possibility that a certain exposure caused a certain harm, not the likelihood that it did."[456] Plaintiffs designed the three simulations to address a corollary point; that is, "that under the conditions tested, which simulate real-world conditions, ranitidine breaks down to form NDMA, not that the exact NDMA levels reported by Emery would be the levels reported by Emery in any particular pill."[457]

Throughout their briefing on the three simulations, Defendants rely predominantly on the conclusions of the MDL Order. Plaintiffs challenge as "missing the point" Defendants' (and the MDL Order's) overarching criticism of the design of their simulations: "the *entire purpose* of stability testing is to see what happens in exaggerated conditions because a laboratory cannot actually recreate months' worth of exposure to varied temperature and humidity conditions in the time frames involved with testing."[458]

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[455] Pls.' Opp'n to Defs.' Mot. to Exclude Gen. Causation Experts' Op. at 265.

[456] *Barrera*, 2019 WL 2331090, at *4 (quoting *Tumlinson II*, 2013 WL 7084888, at *4).

[457] Pls.' Opp'n to Defs.' Mot. to Exclude Gen. Causation Experts' Op. at 266.

[458] *Id.* at 265.

These tests, like opinions—especially those evolving in response to an issue that, it appears, science has not yet caught up with—depend on the "expert's judgment in selecting and weighing her sources."[459] Defendants reject Emery's science, including the decisions made in the design and execution of the simulations, as exemplified by the container system debate: Plaintiffs say the system used in their testing was proper. Defendants argue it was not. So it goes. But Emery's opinion, and testing, are "rooted in science" and therefore "scientifically reliable."[460] That is not to say they are unassailable. But, under these circumstances, the Court cannot and will not declare one side's science as reliable and cast off the other's.[461] This dispute is appropriate grist for the jury's mill.[462]

h. Emery's Simulated Gastric Fluid Test

Defendants' attack on Emery's Gastric Fluid tests regurgitates the criticism of Emery's other tests, discussed above. They are: lack of general acceptance, lack of publication and peer review, improper and flawed assumptions, conclusions contradicted by other literature, improper premises, testing did not track hypothetical, and that the testing was results-oriented.[463] For the same reasons

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[459] *Barrera*, 2019 WL 2331090, at *4; *see Long*, 2004 WL 1543226, at *1.

[460] *Barrera*, 2019 WL 2331090, at *14, 17.

[461] *In re Asbestos Litig.*, 911 A.2d at 1207.

[462] *Id.*

[463] Defs.' Br. in Supp. of Brand Defs.' & Patheon's Mot. to Exclude Emery Pharma at 47.

previously stated, there is no need to indulge in an extended discussion of them. The challenges go to weight, not admissibility.

i. Emery's Miscellaneous Tests

On this challenge, Defendants concede at the outset that "these studies suffer the same methodological issues as the testing" above.[464] These challenges are rejected, for the same reasons.

Defendants also assert that "these tests have no purpose or connection to the facts of the case; *i.e.*, they lack the requisite fit."[465] Not so.

1. WHO NAP Test. The Nitrosation Assay Procedure ("NAP" test), developed by the World Health Organization (WHO) and the International Association for Research on Cancer (IARC), "combin[ed] an agent with sodium nitrite in simulated or real gastric fluid. . . to allow systematic comparisons between compounds is assessing their ability to nitrosate."[466] The creation of NDMA via nitrosation of ranitidine is very much a part of the analyses at issue here. The NAP test fits the case. That the test may not "represent physiological conditions" goes to weight, not admissibility.[467]

2. Simulated Gastric Fluid Testing. The Court has already addressed the

[464] *Id.* at 51.

[465] *Id.*

[466] Pls.' Opp'n to Defs.' Mot. to Exclude Gen. Causation Experts' Op. at 94.

[467] Defs.' Br. in Supp. of Brand Defs.' & Patheon's Mot. to Exclude Emery Pharma at 52.

challenges to Emery's primary Gastric Fluid Simulation. Defendants here challenge "additional SGF studies" based on the conclusions Defendants draw from "some of the experiments."[468] This challenge does not undermine the "fit" of the tests.

3. KSCN Testing. This test was performed to study the hypothesis that potassium thiocyanate, an endogenous compound present in human gastric juice, can promote nitrosation of NDMA moieties to form NDMA in the stomach.[469] This is connected to the facts of this case, as nitrosation of NDMA is one of the processes at issue in exposure.

4. Refrigeration Testing. This test was performed to confirm GSK's claim in its root cause analysis that storage at certain temperatures stops the formation of NDMA in ranitidine.[470] It is relevant to whether Emery's storage of ranitidine samples was a factor in the amount of NDMA found in baseline testing.[471] This issue "fits" as it is connected to the facts of the case.

5. Morphology Study. This challenge is more about challenges to the construct of and assumptions behind the test than "fit."[472] That said, Plaintiffs defend the test as intended to determine the accuracy of Defendant GSK's hypothesis

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[468] *Id.*

[469] Pls.' Opp'n to Defs.' Mot. to Exclude Gen. Causation Experts' Op. at 267.

[470] *Id.*

[471] *Id.*

[472] *See id.* at 266.

regarding rate of degradation of higher bulk density active pharmaceutical ingredients (API,) compared to other API. This test is relevant to degradation and to any attempt by GSK to "portray its API" as "superior or more resistant than other sourced API."[473]

6. Content Uniformity Test. Defendants again target Emery's handling of the tests, and their conclusions, more than "fit."[474] Plaintiffs defend the test as "showing that the testing of single pills from a container would be generally representative of the levels of NDMA to be found in the ranitidine container."[475] This test "fits," given the issue joined on the proper container to be used preparing opinions on degradation.

7. Manufactured Table Study. Plaintiffs point out that this study was necessary because at the time of baseline testing, Defendants had not produced any tablets from one of the manufacturing sites (Jurong).[476] Plaintiffs manufactured its own tablets from the API from both Jurong and a different manufacturer (BI), to tests for differences in degradation. It found none, countering any argument that the pill testing was not representative. Any criticisms of the test relating to Emery's

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[473] *Id.*

[474] Defs.' Br. in Supp. of Brand Defs.' & Patheon's Mot. to Exclude Emery Pharma at 53.

[475] Pls.' Opp'n to Defs.' Mot. to Exclude Gen. Causation Experts' Op. at 268.

[476] *Id.*

failure to use "proprietary protective coating or actual packaging"[477] can be advanced in cross examination.

8. Stress Testing. This challenge, like many of the foregoing, distills to the design of the test (i.e., Emery exposed ranitidine to: "high levels of heat and humidity," employing "implausible conditions.").[478] Emery explained its use of extreme conditions in defense of its simulations.[479] That aside, again these criticisms go to weight, not admissibility. They also "fit."

Defendants' final two challenges go to Reproducibility and the integrity of Emery's Delaware report.

j. Reproducibility

On reproducibility, Plaintiffs frame the formative issue this way: "The question to be answered by this Court is not whether the data reported in Emery's MDL Report is reproducible, but whether the data reported in [Emery's] Delaware Report, the only proffered opinion here, is reliable, reproducible, and admissible."[480] Plaintiffs counter that this "entire argument hinges on the claim that the results reported in the Delaware Report do not match the results reported in the MDL

[477] Defs.' Br. in Supp. of Brand Defs.' & Patheon's Mot. to Exclude Emery Pharma at 55.

[478] *Id.* at 53.

[479] *Id.*

[480] Pls.' Opp'n to Defs.' Mot. to Exclude Gen. Causation Experts' Op. at 269.

Report."[481] Plaintiffs concede that the results from the two studies do not match due to tabulation and sorting errors.[482] But they argue that those errors do not impact the reproducibility of the testing done by Emery in this case.[483]

Defendants emphasize that "[n]othing Plaintiffs did [in between the MDL Report and the Delaware Report] adequately cured the methodological shortcomings recognized by the MDL Court."[484] But as Plaintiffs emphasize, the only opinion being proffered here is the Delaware Report. As a practical matter, Defendants are inviting this Court, again, to defer to the MDL decision on reproducibility. This Court declines to do so.

The ability to reproduce a test turns on the availability and integrity of the data from the test to be reproduced. The Court has already plowed this ground. But we re-visit for ease of reference.

Plaintiffs maintain that "*all* of the underlying data has been produced to Defendants," including "the corresponding test names, lot numbers, etc., in Excel format."[485] Plaintiffs go further, adding that "all of the written validated protocol, underlying raw and processed data from the conduct of the testing was provided to

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[481] *Id.*

[482] *Id.*

[483] *Id.*

[484] Defs.' Br. in Supp. of Brand Defs.' & Patheon's Mot. to Exclude Emery Pharma at 55.

[485] Pls.' Opp'n to Defs.' Mot. to Exclude Gen. Causation Experts' Op. at 270 (emphasis in original).

Defendants in [the proper] format, with printed versions in the form of PDFs, and also stored electronically in the [proper] system."[486] Plaintiffs add that, for each experiment that was run, each of which was validated, the results of that validation were produced,[487] and that beyond the "standalone validations," they produced each analytical run including calibrations and quality control injections used to further validate the process run, as well as lab notebooks, in which each test was documented, maintained contemporaneously by the analyst conducting the experiment and counter signed by "another researcher who validated the experiment."[488]

All this production, Plaintiffs argue, allows Defendants to "conduct their own data analysis to come up with whatever statistical calculations they wish;" something, Plaintiffs note more than once, Defendants did not do.[489] Defendants "have never run any of their own tests on the pill samples tested by Emery, despite their ability to do so. . . to see if they could or could not reproduce Emery's results. They have never done any re-processing or re-integration of the raw data provided by Emery to determine whether they could or could not reproduce Emery's

[486] *Id.* at 257, 259; *see id.* at 272–73.

[487] *Id.* at 256.

[488] *Id.* at 256–57.

[489] *Id.* at 258.

results."[490] "With this information, Defendants are able to do their own analysis, their own processing and integration, report their results, and do their own calculations of means, minimum and maximum values, or any other statistical measure they wish. They did no such thing."[491] Defendants resort to *ipse dixit*: the production, characterized as they deem appropriate, makes reproduction impossible. They never say they tried to reproduce Emery's results. Instead, they cite to the MDL's Order.[492]

Defendants devote considerable space to the numerous failings and inconsistencies they find in Emery's MDL and Delaware Reports.[493] They also chastise Emery for its inability to reproduce its own results. This criticism might carry more weight if Emery were somehow prohibited from updating the report, or even more so if Emery had not explained to Defendants why the data was updated in the first instance.[494] Further, none of the changes cited by Defendants concerns the baseline testing results.[495] Also, some of the results of the changes made by Dr. Cheu following his review and re-processing are "actually lower than those reported

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[490] *Id.* at 269.

[491] *Id.* at 273.

[492] Defs.' Br. in Supp. of Brand Defs.' & Patheon's Mot. to Exclude Emery Pharma at 56–58 (citing *In re Zantac*, 644 F.Supp.3d at 1130).

[493] *See id.* at 57–63.

[494] *See* Pls.' Opp'n to Defs.' Mot. to Exclude Gen. Causation Experts' Op. at 271–74.

[495] *Id.* at 276.

in the MDL Report," belying any suggestion of bias to increase NDMA levels.[496]

None of these challenges is flattering. But many of them involve clerical errors;[497] its resolution fitted for twelve people in the jury box. For that reason, the Court will not exclude Emery's opinion. The Court has already considered the incomplete/inadequate production issue. It stands on that decision.

k. Reverse-engineering of the Emery Report

This challenge is hampered by the fact that some of the re-testing favored Defendants. Similarly, as noted above, the results from one of the changes made by Dr. Cheu, following his review and re-processing, are lower than those reported in the MDL Report.[498] That statistic also contradicts an effort to increase NDMA levels. Some of Plaintiffs' corrections skewed the testing against Plaintiffs.[499] The extended discussion of what Dr. Cheu did and why also militates against Defendants' notion of reverse-engineering.[500]

l. Transparency and Suggestion of "Lawyer-Driven" Changes

Plaintiffs detail the bases for their defense of transparency:

1. By reporting data and calculating the averages across each individual test,

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[496] *Id.* at 274–75.

[497] *Id.* at 271; *see* Defs.' Br. in Supp. of Brand Defs.' & Patheon's Mot. to Exclude Emery Pharma at 63 n.119 (stating chromatogram "mistakenly processed twice").

[498] Pls.' Opp'n to Defs.' Mot. to Exclude Gen. Causation Experts' Op. at 274–76.

[499] *Id.* at 276.

[500] *Id.* at 271–73; *see id.* at 276.

rather than reporting data as averages of multiple tests of the same lot and then calculating overall average, Emery was able to report results in a format that was fully transparent and allowed the inclusion of all the information Defendants complained about not having in the MDL.[501]

2. Plaintiffs included all baseline testing in the Delaware Report.[502]

3. Emery re-processed and re-integrated "all of the testing it had done so that the results contained in the Delaware Report matched 100% with the underlying MassHunter data, and chromatograms therefrom."[503]

These changes were made for three reasons:

First, Defendants complained that they were not able to match up the individual test data reported with individual chromatograms and underlying raw and processed data.[504] Defendants complain now that this change is evidence of an intent to bias the results.[505]

Second, Defendants accused Plaintiffs of cherry-picking data they reported because there were "many more tests in the native MassHunter data produced to

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[501] *Id.* at 277.

[502] *Id.*

[503] *Id.* at 278.

[504] *See id.* at 277.

[505] Defs.' Br. in Supp. of Brand Defs.' & Patheon's Mot. to Exclude Emery Pharma at 63 (citing Dr. Cheu's testimony) (arguing that lawyers made the decision to change methods). *Contra* Pls.' Opp'n to Defs.' Mot. to Exclude Gen. Causation Experts' Op. at 278–79.

Defendants than contained in the MDL Report."[506]

Third, Defendants complained in the MDL of problems matching test results on the printed PDF chromatograms generated by their experts from MassHunter data produced by Plaintiffs there.[507]

The re-processing and re-integration resulted in some "changes to reported values but none made a "material difference to the overall values reported."[508] "None of the above are changes in methodology[;] they are changes in the detail and manner in which the results were reported."[509] These changes, along with the production made by Plaintiffs described above, overcome any suggestion that Plaintiffs' methodology was not transparent.

Defendants' final challenge to the Emery study sounds in the unfortunate allegation that changes in Emery's method of presentation of chromatograms and underlying data, raw and processed, were "lawyer driven."[510] In support of that accusation, Defendants cite one question and its response:

> Q: Okay. Well, then why did your methodology of averaging change?
>
> A: This was a decision that was made I believe with the -

[506] *See* Pls.' Opp'n to Defs.' Mot. to Exclude Gen. Causation Experts' Op. at 277.

[507] *Id.* at 277–78.

[508] *Id.* at 276–78.

[509] *Id.* at 278.

[510] Defs.' Br. in Supp. of Brand Defs.' & Patheon's Mot. to Exclude Emery Pharma at 65.

what is - the MDL lawyers.[511]

Defendants celebrate this answer as "definitive proof that Emery lacked a pre-set protocol."[512] But contrary testimony followed only pages away.[513] Dr. Cheu's testimony makes clear that "the method of presentation of the averaging and selected results *in the MDL Report* was a decision made 'with. . . the MDL lawyers.'"[514] But the immediately following testimony "makes clear that the method of presentation of the results *in the Delaware Report was made by Emery*."[515]

The Court finds insufficient evidence that a lawyer-driven methodology manipulated the Emery study and rejects that assertion. Those allegations comprise only questions to be resolved by those in the jury box.

The Motion to exclude the Emery Pharma opinions is **DENIED**.

V. CONCLUSION

Although *Daubert* may have been intended to streamline expert practice under Rule 702, this case, like many around the country, suggests that goal has proven elusive. Differences in jurisprudence, interpretation of the law, and analyses may confound simpler approaches to such motions.

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[511] *Id.* at 68.

[512] *Id.*

[513] Pls.' Opp'n to Defs.' Mot. to Exclude Gen. Causation Experts' Op. at 279; Pls.' Opp'n to Defs.' Mot. to Exclude Gen. Causation Experts' Op. Ex. 173, at 160:7–161:11.

[514] Pls.' Opp'n to Defs.' Mot. to Exclude Gen. Causation Experts' Op. at 278–79.

[515] Pls.' Opp'n to Defs.' Mot. to Exclude Gen. Causation Experts' Op. at 279 (emphasis added).

In Delaware, our jurisprudence counsels that, subject to earnest deliberation, trial courts entrust questions of science to the scientists. Here, opposing teams of highly educated, skilled expert medical witnesses offer competing opinions. Through well-trained counsel, their efforts only clarify the distinct opposition that defines their respective positions. It would be improper to simply dismiss these experts as "poseurs or witnesses for hire. They are serious scientists."[516] As gatekeeper, the Court has found that each side has carried its required burden of demonstrating the reliability of its proffered Rule 702 evidence. Any remaining challenges will be made at trial via cross-examination and introduction of counter evidence. Having considered the full record herein, the parties' *Daubert* challenges fail and their Motions to Exclude are **DENIED**.

IT IS SO ORDERED.

/s/ Vivian L. Medinilla
Vivian L. Medinilla
Judge

cc: All Counsel of Record

[516] *In re Asbestos Litig.*, 911 A.2d at 1207.