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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

APPELLANTS' REPLY BRIEF

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INTRODUCTION

The Superior Court did not apply Rule 702's most basic requirements. As a result, the Superior Court failed to carry out its essential gatekeeping function and deferred all questions about the reliability of Plaintiffs' experts' general-causation testimony to the jury. The Superior Court's errors took three main forms, and Plaintiffs' arguments to the contrary are unavailing.

First, decisions in multiple federal and state courts and two prior Delaware Superior Court decisions require a general-causation expert to identify the threshold dose of a substance capable of causing the asserted injury. Plaintiffs largely ignore the federal decisions and mischaracterize the Delaware ones. They ask this Court to uncritically accept that exposure to even a single molecule of NDMA could cause ten types of cancer. Not even Plaintiffs' experts agree with that radical position, which would lead to absurd results, given NDMA's ubiquitous presence in substances humans commonly eat, drink, and breathe. Plaintiffs acknowledge that, ***every day***, humans ingest NDMA from water and food. A-014302; Ans.Br.10. Without a threshold-dose requirement, a general-causation expert could opine that one sip of water or one bite of bacon can cause ten types of cancer. But as FDA has observed, such "low levels" of NDMA "would not be expected to lead to an increased risk of cancer." A-011886; *contra* Ans.Br.1 (incorrectly asserting FDA warned about ranitidine increasing cancer risk).

Second, the Superior Court erroneously focused its general-causation analysis on NDMA rather than ranitidine. Thus, it overlooked two fatal flaws in Plaintiffs' experts' opinions. Plaintiffs' general-causation experts assumed that the NDMA exposures in dietary and rubber worker studies correlate to NDMA exposure from real-world ranitidine use, and they offered no reliable basis to reject the body of ranitidine-specific epidemiology studies involving one million ranitidine users that overwhelmingly found no increased risk of cancer.

Finally, the Superior Court abused its discretion by finding that serious methodological errors go only to the weight rather than the admissibility of the opinions. This approach deviated from Rule 702, *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 509 U.S. 579 (1993), *Kumho Tire Co. v. Carmichael*, 526 U.S. 137 (1999), and Delaware precedent, including *Tumlinson v. Advanced Micro Devices, Inc.*, 81 A.3d 1264 (Del. 2013). The Superior Court instead sided with decisions from non-*Daubert* state courts like California. Op.16. And it flat-out rejected the only then-existing *Daubert* decision evaluating a claim that ranitidine can cause cancer: the MDL Order, which persuasively explained the lack of reliable general-causation evidence. Op.16-17. A Florida state court applying *Daubert* subsequently reached the same conclusion as the MDL court, leaving the Superior Court as the only court to deem opinions like these reliable under *Daubert*. Op.Br.13-14. Plaintiffs' response is to demand deference to their experts, claiming

judges are unqualified to make reliability determinations about scientific evidence. That misinterprets Rule 702, which requires courts to act as gatekeepers for all expert opinions.

Allowing this decision to stand would perpetuate a gross misapplication of Rule 702, with substantial negative consequences for Delaware law and its courts. Plaintiffs claim the Superior Court's Rule 702 ruling had no impact in Delaware, yet more than 10,000 Zantac lawsuits have been filed since the ruling. Companies value the predictability of Delaware's jurisprudence, including its adoption of Rule 702. This Court should apply those well-established standards here, reverse the Superior Court's decision, and remand with instructions to grant Defendants' motion to exclude Plaintiffs' general-causation experts.

ARGUMENT

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

Plaintiffs assert that their experts need not identify the threshold doses (or even dose ranges) of ranitidine or NDMA because they claim NDMA can cause cancer at any dose. If Plaintiffs' legal position were correct, experts could opine that any amount of cheese, or even water, each of which contain NDMA, can cause all ten types of cancer at issue here. That absurd result cannot be the product of reliable science, and, unsurprisingly, Plaintiffs identify no sound legal or scientific support for their position.

A. Plaintiffs' Position Contravenes Clear Rule 702 Precedent Imposing a Threshold-Dose Requirement in These Circumstances.

More than thirty federal and state courts, including most federal appellate courts, have excluded general-causation opinions that fail to identify reliable evidence of a threshold dose. *Krik v. Exxon Mobil Corp.*, 870 F.3d 669, 677 (7th Cir. 2017); Op.Br.18-19,21 (citing cases from the Second, Fourth, Fifth, Seventh, Eighth, Tenth, and Eleventh Circuits). Plaintiffs do not address these cases, instead pretending that Defendants' only support for the threshold dose requirement is the MDL court's well-reasoned decision applying *McClain v. Metabolife Int'l, Inc.*, 401 F.3d 1233, 1239 (11th Cir. 2005). Ans.Br.30-31. Worse yet, Plaintiffs claim that *McClain* held threshold dose is just "one of the factors to be considered" and that it

is relevant only to specific causation. Ans.Br.31. In *In re Deepwater Horizon BELO Cases*, 119 F.4th 937 (11th Cir. 2024), a case Plaintiffs fail to cite, the Eleventh Circuit emphatically rejected that interpretation of *McClain*, concluding that it "turns *McClain* on its head." *Id.* at 946. The court affirmed the exclusion of general-causation experts for failing to identify a threshold dose, explaining that an expert must establish "whether a harmful level of the toxin exists in the first place." *Id.* Without this requirement, plaintiffs could proceed on the unsupported theory that "any exposure" to a potential carcinogen can cause cancer, contrary to the consensus of courts and experts. *Krik*, 870 F.3d at 677.

Plaintiffs incorrectly assert that no Delaware court has required plaintiffs to establish threshold dose or treated threshold dose as more than a non-dispositive consideration. Ans.Br.28-29. As explained in *Tumlinson v. Advanced Micro Devices, Inc.*, 2013 WL 7084888, at *7 (Del. Super. Ct. Oct. 15, 2013), *aff'd*, 81 A.3d 1264 (Del. 2013), a general-causation expert "must address" whether "exposure to X chemical(s) in Y dose for Z time" is likely to cause the injury in question. The court located that requirement in Rule 702's testability prong. *Id.* Although this Court noted that the testability prong by itself is not dispositive, this Court did not question the underlying holding that an expert must identify the threshold dose required to increase the risk of the at-issue disease. 81 A.3d at 1270.

Additionally, in *Wilant v. BNSF Railway Co.*, the court excluded an expert's opinion, characterizing the failure to identify a threshold dose as an "acute" problem. 2020 WL 2467076, at *5 (Del. Super. Ct. May 13, 2020). Plaintiffs are simply wrong that these cases treated threshold dose as one non-dispositive issue among many. *See* Ans.Br.27-29.

Plaintiffs cannot avoid the overwhelming weight of caselaw with the sweeping assertion that courts do not apply threshold-dose requirements in cancer cases. Ans.Br.23-24. No cancer carve-out exists. Courts have widely applied the same threshold-dose standard for cancer as for other injuries. *See, e.g.*, *Mitchell v. Gencorp Inc.*, 165 F.3d 778, 781 (10th Cir. 1999) (leukemia); *Allen v. Pa. Eng'g Corp.*, 102 F.3d 194, 199 (5th Cir. 1996) (brain cancer); *Krik*, 870 F.3d at 677 (lung cancer); *McLaughlin v. BNSF Railway*, 439 F. Supp. 3d 1173, 1182-83 (D. Neb. 2020) (same); *Wilant*, 2020 WL 2467076, at *5 (bladder cancer).

Tumlinson observed that "imprecision" in identifying a threshold dose "has been excused" only in cases involving an established causal relationship or known signature harm. 2013 WL 7084888, at *3, *8. Plaintiffs wrongly malign *Tumlinson*'s rule as "circular." Ans.Br.27. The rule reflects the commonsense understanding that for certain substances and diseases, like asbestos and mesothelioma, the causal relationship is so well-established and undisputed that courts need not re-assess general causation. *See, e.g.*, *McClain, Inc.*, 401 F.3d at

1239.[1] This Court, like others, has applied that exception narrowly; the Court did not even excuse the general-causation inquiry for refined asbestos when its carcinogenicity was uncertain. *Gen. Motors Corp. v. Grenier*, 981 A.2d 524, 528-30 (Del. 2009) ("*Grenier I*"). Plaintiffs do not—and cannot—claim that ranitidine involves an established causal relationship with cancer or causes a signature disease.

Plaintiffs tellingly cite only one case for their special cancer rule: *In re TMI Litigation*, 193 F.3d 613 (3d Cir. 1999), *amended*, 199 F.3d 158 (3d Cir. 2000). But *TMI*, which involved the nuclear accident at Three Mile Island, does not support Plaintiffs. That court was willing to forgo the threshold-dose analysis not because the injuries were cancer, but because undisputed scientific evidence had long confirmed the strong causal association between cancers and full-body nuclear radiation exposure. *Id.* at 638-39, 642; *In re Hanford Nuclear Reservation Litig.*, 292 F.3d 1124, 1136-37 (9th Cir. 2002) (distinguishing radiation cases from cases involving allegedly toxic substances like medications with "no definitive evidence" of general causation). The known, undisputed risks of full-body exposure to nuclear radiation are not comparable to ranitidine or NDMA. *TMI* does not excuse Plaintiffs' obligation to present reliable expert testimony demonstrating the

[1] *Long v. Weider Nutrition Grp.*, 2004 WL 1543226 (Del. Super. Ct. June 25, 2004), which Plaintiffs invoke, did not address threshold dose. Ans.Br.32.

threshold dose at which ranitidine could purportedly cause each of the ten cancers at issue.

B. No Scientific Support Exists for Plaintiffs' Attempt to Avoid Threshold Dose for Cancer Cases.

Plaintiffs' contention that threshold dose "is not applicable to cancer" is also unsupported by the scientific and regulatory record. Ans.Br.23. As Plaintiffs' prostate-cancer expert, Dr. Trock, testified, "most carcinogens take prolonged exposure to produce a cancer." A-011176-77 ("[T]hree years of NDMA exposure probably is not sufficient to induce prostate cancer."). Plaintiffs expressly conceded below that they are not claiming "short term use" of ranitidine causes any of the ten cancers. A-014337.

The so-called "dose response" charts Plaintiffs include in their brief, Ans.Br.19-21, are entirely inconsistent with their attempt to avoid evidence of threshold dose. For one thing, Plaintiffs misleadingly present these charts, which *did not appear* in any expert report; instead, the charts were created by *Plaintiffs' counsel* in briefing the Rule 702 issues below. The charts as presented also lack basic context, such as descriptive titles or axes labels, that could give any meaning to the data. Plaintiffs nonetheless argue these charts somehow suggest a "dose response" relationship they claim establishes causation. But that suggestion is lawyer argument, not the analysis of Plaintiffs' experts. *DeAngelis v. Harrison*, 628 A.2d 77, 81 (Del. 1993) ("[A]rguments of counsel are not evidence."). In fact, *none*

of Plaintiffs' general-causation experts relied on these charts or the data on which they are based.

Even taking the data at face value, they are not reliable evidence of general causation and do not eliminate the requirement to establish threshold dose. The lawyers' charts were purportedly based on the report of Dr. Sawyer, Plaintiffs' toxicology expert, who attempted to convert doses of *inhaled* NDMA reported in the Hidajat rubber worker study into doses of orally ingested NDMA. Putting aside whether Dr. Sawyer's conversion effort was reliable science (it was not), his analysis assumes that doses of NDMA below 461,000 nanograms (the left-hand point on the x-axis) pose *no increased risk* of developing cancer (because at that level, the risk ratio on the y-axis is 1). A-014354-56; A-010802-04.

As this discussion highlights, Plaintiffs are further incorrect that "dose response" alone, without threshold dose, can show general causation. Ans.Br.21-22. Plaintiffs accuse Defendants of "conflat[ing]" the two concepts, but it is Plaintiffs' argument that mischaracterizes their dispositive differences. The threshold-dose inquiry asks, "how much of the alleged toxin must be used for how long to increase the risk," *Deepwater Horizon*, 119 F.4th at 945—that is, a threshold dose is the lowest exposure level at which an association can be established between a substance and a medical outcome. If an association is established, then dose-response—whether the risk of the outcome increases as the dose increases above the threshold

dose—is one Bradford Hill criterion for assessing whether the observed association is causal. *See In re Lipitor (Atorvastatin Calcium) Mktg. Sales Pracs. & Prods. Liab. Litig.*, 892 F.3d 624, 638 (4th Cir. 2018).

The regulatory and other sources that Plaintiffs cite do not justify their experts' failure to identify a threshold dose. Ans.Br.8-9. None of those authorities has accepted Plaintiffs' theory that a single molecule of NDMA can cause ten types of cancer in humans. Instead, these agencies have reiterated the importance of threshold dose. For example, FDA's method for determining the acceptable daily intake of NDMA in medications is a conservative "estimate of safe exposures for any mutagenic compound." A-011810. And FDA determined only that "*sustained higher* levels of [NDMA] exposure may increase the risk of cancer in humans." A-011886 (emphasis added).[2] The International Agency for Research on Cancer similarly has explained that "[t]he cancer risk associated with substances or agents assigned the same classification may be very different, depending on factors such as the type and extent of exposure and the degree of the effect of the agent at a given

[2] Plaintiffs claim ranitidine is clearly a carcinogen containing high levels of NDMA. Ans.Br.10-11. But Plaintiffs cherry-picked the highest NDMA levels from ranitidine tested worldwide and by Plaintiffs' experts. *See In re Zantac*, 644 F. Supp. 3d 1075, 1158-59 (S.D. Fla. 2022) (excluding expert opinion that "cherry-pick[ed]" results with high NDMA levels). FDA found that some, but not all, of the ranitidine it tested contained NDMA above the agency's guideline—and the NDMA levels it found were similar to those in common foods like grilled meat. A-011867-69; A-022741-42. Moreover, Plaintiffs' assertion that all Defendants "knew ranitidine formed NDMA" is untrue and unsupported by the record. Ans.Br.1; A-022741 n.10.

level of exposure." *IARC Monographs on the Identification of Carcinogenic Hazards to Humans* (Dec. 10, 2019).[3] Although Plaintiffs quote the World Health Organization's statement that NDMA may be carcinogenic "potentially at relatively low levels of exposure," Ans.Br.8-9, that qualified statement (which says nothing about ranitidine) just underscores why a threshold dose is needed in the courtroom: it is unclear what dose, duration, or manner of NDMA exposure constitutes a "low level of exposure."

Meanwhile, international regulatory agencies have investigated and found *no evidence of a causal link* between ranitidine and cancer—contrary to Plaintiffs' claim that no such evaluation was undertaken. Ans.Br.12-13. The European Medicines Agency surveyed available data and found "no evidence of a causal association between ranitidine therapy and the development of cancer in patients." A-011764. FDA concluded that "the levels of NDMA in ranitidine and nizatidine are similar to the levels you would expect to be exposed to if you ate common foods like grilled or smoked meats." A-011867-69. Plaintiffs argue that these findings predate newer ranitidine epidemiology studies, Ans.Br.13, but this critique fails because the newer studies provide further support for Defendants' position, Op.Br.9-10. And the non-ranitidine studies on which Plaintiffs' experts relied did exist when

[3] Available at https://monographs.iarc.who.int/wp-content/uploads/2018/07/IARC Monographs-QA.pdf.

FDA and EMA reached their conclusions. The regulators' analyses confirm that bypassing a threshold-dose requirement renders a general-causation opinion unreliable.

Plaintiffs attempt to pluck support from a law journal article, claiming it says proof of a threshold dose is unnecessary in cancer cases. Ans.Br.30-31. But Plaintiffs omit the sentence immediately following the one quoted in their brief, which explains that "many scientific and practical reasons indicate that, at very low doses, the significance of such [carcinogenic] risks, if real, become trivial and are lost in the background of other daily risks." David Eaton, *Scientific Judgment and Toxic Torts—A Primer in Toxicology for Judges and Lawyers*, 12 J.L. & Pol'y 5, 16 (2003).[4]

Plaintiffs selectively cite the *Federal Reference Manual on Scientific Evidence*, claiming its brief discussion of a hypothesis that cancer might arise from a single mutation supports their no-threshold dose argument. Ans.Br.23-24. But Plaintiffs' own experts reject that hypothesis. *E.g.*, A-007911-12 (Dr. Miller

[4] Contrary to Plaintiffs' claims, Ans.Br.25, this journal article states there is a level of cigarette smoking that "is not likely to be distinguishable from 'background risk' of cancer from all other causes." *Scientific Judgment and Toxic Torts*, 12 J.L. & Pol'y at 17. Plaintiffs cite the testimony of GSK's corporate representative and a defense expert for the notion that no threshold dose exists for cigarette smoking and cancer. Ans.Br.25. But GSK's representative testified that though he was not an expert in this area, he was aware of data showing "30 pack-years being an inflexion point where the risk is significantly increased." A-17039. Plaintiffs mischaracterize the expert's testimony for the reasons explained in the opening brief. Op.Br.24.

testifying that an accumulation of mutations causes prostate cancer). In any case, the *Manual* itself explains that, even under the proposed one-molecule hypothesis, the theoretical cancer risk from a single-molecule exposure is no more than a "not zero" risk. A-016862-63. A hypothesis about possible risk is not sufficient legal proof of causation, which is why the *Manual* acknowledges that various courts have rejected it as a basis to prove general causation. A-016862-63 n.28; *supra*, Section I.A.[5]

* * *

The Superior Court refused to address Plaintiffs' experts' failure to identify a threshold dose of ranitidine or NDMA they contend is required to cause each type of cancer—ruling it a jury issue. Op. 32. That alone warrants a remand. But the failure to opine reliably on threshold dose warrants outright exclusion. That conclusion is supported by this State's decisions, the overwhelming weight of persuasive Rule 702 precedent, FDA's and EMA's conclusions, and Plaintiffs' own experts' admissions. The Court should thus reverse the Superior Court's decision and remand with instructions to exclude Plaintiffs' experts based on this fundamental flaw in their opinions.

[5] Even FDA, known for its extensive preventative measures, has not adopted the no-threshold model for NDMA. *See supra*, Section I.

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

Unable to refute Defendants' argument, Plaintiffs resort to attacking a strawman, insisting that Defendants criticized *any* consideration of non-ranitidine data. Ans.Br.34 (citing nothing). That is mistaken. Defendants argued the Superior Court should not accept as reliable Plaintiffs' experts' unsupported extrapolation that: (1) NDMA through different routes of exposure may cause cancer at some undetermined level; (2) *trace* levels of NDMA have been found in some ranitidine pills; (3) therefore, ranitidine use can cause ten types of cancer. A-024281-82; A-023643-44.

This methodology is unreliable. Measurable quantities of NDMA are ubiquitous in the environment. The human body even naturally forms NDMA. A-004272. Framing general causation around NDMA rather than ranitidine is thus at odds with the very aim of the analysis—establishing that a defendant's product, under real-world exposure conditions, *increases* the risk of the disease in the general population. *See*, *e.g.*, *Amorgianos v. Nat'l R.R. Passenger Corp.*, 303 F.3d 256, 269-70 (2d Cir. 2002) (affirming exclusion of general-causation opinion that failed to establish that the same level and duration of exposure to xylene in paint experienced

by plaintiff could cause the disease).[6] Yet the Superior Court accepted this non-scientific framework when assessing the reliability of Plaintiffs' experts' general-causation opinions, holding that "[t]he discrete issue before the Court at this stage is whether NDMA can cause cancer." Op.18.

Plaintiffs deny reality when they claim it "is not true" that the Superior Court "focused its *Daubert* analysis on NDMA and not ranitidine." Ans.Br.34. The Superior Court was unequivocal: "General Causation Focuses on NDMA." Op.18. Its entire Rule 702 analysis was shaped by a singular focus on NDMA in the abstract. Op.22 ("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 NDMA-focus produced two key errors.

First, the Superior Court allowed Plaintiffs' experts to opine that ranitidine can cause ten types of cancer based on food, rubber, and animal studies[7]—only some of which studied NDMA specifically—even though ***none*** of Plaintiffs' general-

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[6] In this way, the failure to require a threshold dose is a related error to the Superior Court's improper focus on NDMA as opposed to ranitidine. Even assuming NDMA can cause cancer at some level, only trace amounts of it are found in ranitidine. This explains why ranitidine-specific data overwhelmingly shows no link between ranitidine and increased cancer risk. Although the Superior Court's two errors are related, each is an independent basis for reversal.

[7] The animal data most analogous to humans—primates—show no association between NDMA and any cancer. A-007504-05; *see* Ans.Br.1 (falsely claiming NDMA causes cancer in every species tested).

causation experts correlated the dose, duration, route, or frequency of exposure necessary for a comparable exposure to ranitidine. This was error. *See Amorgianos*, 303 F.3d at 269-70. Dr. Hatzaras did not "assess how inhalation of any NDMA in rubber worker studies compares to the levels of oral exposure to NDMA from ranitidine." A-003783. Nor did Drs. Neugut, Rustgi, and Miller. A-008281; A-010089; Op.Br.35.

Plaintiffs do not contest three key undisputed facts: (1) their toxicologist, Dr. Sawyer, was the only expert to attempt to correlate any of the study results (using NDMA inhalation from rubber fumes) with an equivalent oral dose; (2) Dr. Sawyer did *not* offer general-causation opinions, Op. 39; and (3) *none* of Plaintiffs' general-causation experts relied on Dr. Sawyer's calculations.[8] *See* A-010892; A-011221 (Trock); A-010207 (Rustgi); A-009570 (Raz); A-008200 (Neugut); A-007744 (Miller); A-002488 (Hatzaras); A-006277 (Leone); A-007337-38 (Margulis). Instead, Plaintiffs' general-causation experts assumed that because prolonged exposures to NDMA (and other substances that are, unlike NDMA, classified as known carcinogens) in rubber dust and fumes may increase the risk of certain cancers, causation can be established for exposure to trace levels of NDMA in ranitidine. A-003783; A-008281; A-010089; Op.Br.35-36.

[8] Dr. Sawyer's calculations were limited: he did not correlate the dose for breast, colorectal, or kidney cancers. A-018219; A-024283.

Plaintiffs wrongly claim that *General Motors Corp. v. Grenier*, 981 A.2d 531 (Del. 2009) ("*Grenier II*"), provides a "rule" that allows experts to assume the level and duration of exposure to NDMA in other contexts are similar to exposure to NDMA in ranitidine. Ans.Br.40. *Grenier II* makes clear that experts cannot assume exposures in different contexts are equivalent. Neither Judge Slights nor this Court permitted the experts to rely on raw asbestos data to conclude that exposure to refined asbestos in friction products could cause disease. After careful analysis, the Court found the experts' testimony admissible only because they proffered reliable scientific evidence linking raw asbestos exposure to refined asbestos exposure as the cause of the signature disease, mesothelioma. *Grenier II*, 981 A.2d at 536-37 (explaining one expert relied on his own published research that exposures were similar); *id.* at 537-38 (describing the other expert's exhaustive research, including case studies on refined asbestos in friction products). On remand, Judge Slights observed that the expert's proffered testimony would have been inadmissible if he only relied on raw asbestos data and on the "assumption" that the exposure was similar to refined asbestos. *In re Asbestos Litig.*, 2009 WL 1034487, at *8 (Del. Super. Ct. Apr. 8, 2009) ("*Asbestos II*"). Although Defendants here argued this point, A-024280-83, the Superior Court did not discuss Plaintiffs' experts' failure to correlate NDMA exposures in other settings to exposures in ranitidine. Such a

methodological gap is precisely the kind of threshold reliability issue that courts are charged with resolving.

Second, because of its mistaken focus on NDMA, the Superior Court failed to recognize the methodological flaws of Plaintiffs' experts who inexplicably discounted the large body of ranitidine-specific epidemiology studies involving one million ranitidine users, which overwhelmingly showed *no association* between real-world exposure to ranitidine and any of the cancers alleged. Op.38-39 (Jameson); Op.46-47 (Neugut); Op.50 (Hatzaras); Op.59-60 (Leone); Op.65 (Margulis); Op.68-69 (Miller). Had the Superior Court properly focused its general-causation evaluation on the effects of real-world ranitidine use, with whatever trace levels of NDMA that ranitidine contained, it would not have allowed Plaintiffs' experts to prioritize studies involving rubber fumes and food at the expense of a massive epidemiologic dataset of the product at issue.[9]

Plaintiffs respond by claiming that independent scientists extrapolate from rubber studies involving NDMA to real-world ranitidine use. Ans.Br.36-37. But

[9] For example, Dr. Trock rejected six ranitidine studies that reported no overall association with prostate cancer and instead relied on studies of rubber workers, most of which did not mention NDMA, to reach his conclusion that ranitidine causes prostate cancer. A-000181; A-010901-02; A-023583; A-011908; A-011915. Dr. Trock also relied on animal studies where no rats given NDMA developed prostate cancer, and where the lowest daily dose of NDMA that caused any cancer in rats was 2,767 times higher than the highest dose reported by FDA in any ranitidine batch. A-023511; A-023584.

they cite no such independent scientists. And they cannot, because only Plaintiffs' retained experts have attempted such speculative leaps—without peer review and only in litigation. A-008310-11. While dietary and occupational studies involving NDMA might prompt a researcher to *examine* whether ranitidine use could cause cancer, they offer no basis to *conclude* that ranitidine use causes cancer. *See Daubert*, 509 U.S. at 593; *Tumlinson*, 81 A.3d at 1269. That is why independent scientists conducted the ranitidine epidemiologic studies in the first place, and the great weight of ranitidine-specific data shows that ranitidine use does not increase the risk of any of the ten cancers.

None of the scientists involved in the studies cited in Plaintiffs' brief make this leap from non-ranitidine studies to ranitidine. Ans.Br.36-37. Take the Joung ranitidine-specific study, which found "no association" between ranitidine use and cancer risk. A-011502. Joung explained that dietary and occupational studies did not affect this conclusion, because a "direct comparison" between ranitidine and non-ranitidine data "would not be suitable." A-011499. The same is true for every study cited in Plaintiffs' brief. Ans.Br.36-37. Though some of those authors referenced dietary and occupational studies of NDMA to explain why it was worth examining whether any association between ranitidine and cancer risk exists, each of these study authors then drew their conclusions through analysis of ranitidine-specific epidemiology data. A-011709 (You); A-011531-32 (Kim S.); A-011683

(Wang); A-016759 (McGwin, an adverse-event reporting analysis). As one of Plaintiffs' experts acknowledged, ranitidine-specific studies "represent real-world use of ranitidine" that "account[s] for how ranitidine is used by patients." A-007617-18.

Plaintiffs' contaminated groundwater hypothetical reinforces *Defendants'* point. Ans.Br.35. Plaintiffs suggest that if groundwater were contaminated with NDMA, general-causation experts would not need to show that exposure to water causes cancer, and could instead rely on NDMA-specific studies. But Plaintiffs' hypothetical misses the critical link: a general-causation opinion must address whether the level, duration, and manner of NDMA exposure in the groundwater can cause cancer. *See* Op.Br.31-32 (citing cases assessing the effects of zinc in Fixodent and benzene in gasoline); *Amorgianos*, 303 F.3d at 269-70 (level of xylene in paint); *Grenier II*, 981 A.2d at 538 (refined asbestos in friction products). It would be equally improper in that hypothetical to focus only on the risks of NDMA, without considering dose and duration of NDMA in the substance in question (the groundwater). That is the error the Superior Court committed here.

* * *

The Superior Court erred by focusing its general-causation analysis on NDMA rather than ranitidine. Moreover, Plaintiffs' arguments cannot change the fact that their general-causation experts' opinions depend on unreliable and

speculative extrapolation from non-ranitidine data and the unsubstantiated rejection of voluminous ranitidine data that directly addresses the relevant product in question. Plaintiffs' brief thus confirms that, under a correct analysis, their experts cannot make the requisite showing and must therefore be excluded.

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

Plaintiffs champion the Superior Court's finding that all challenges to experts' application of their methodology go to the weight, rather than the admissibility, of their opinions. Ans.Br.42-43. But Delaware law requires that an expert use a reliable methodology and reliably apply it to the facts of the case, and that the trial court make that determination in exercising its gatekeeping responsibility. *Grenier I*, 981 A.2d at 529 & n.14 (citing D.R.E. 702 and *McClain*, 401 F.3d at 1245); *see also Tumlinson*, 81 A.3d at 1269 n.24.

Despite Defendants' tailored challenges to each expert's methodological flaws, the Superior Court found that problems like "improper and flawed assumptions," "outcome driven reasoning," "results-oriented" analyses, "cherry-picking evidence," "reliance on bad science," "lack of peer review," and "lack of general acceptance," all go to weight rather than admissibility. Op.38,46,50,67,84,88,90-91,99. Based on the Superior Court's reasoning, it is difficult to conceive of *any* situation that would warrant exclusion under Rule 702.

Tellingly, in its 102-page opinion, the Superior Court found *no* methodological challenges that it could adjudicate. *See* Op.37,55 (declining to "second guess researchers" and holding that "[a]ny quarrel with the application of [the] methodology is for the fact finder"). The Superior Court would not even

exclude Plaintiffs' kidney cancer expert whose *own peer-reviewed publication* contradicted his litigation opinion by acknowledging the available data *did not establish general causation*. A-011428.

Similar inconsistencies were present in all of Plaintiffs' experts' application of their methodologies. For example, Drs. Margulis and Neugut testified that, in their professional work, they would only find an association between a toxin and a disease based on statistically significant results. As paid litigation experts, however, they ignored statistical significance, which is critical to the Bradford-Hill and weight-of-the-evidence analyses as *Tumlinson* emphasized, 2013 WL 7084888, at *10. A-009046-48; A-007376; A-007379-80; A-007391-92. The Superior Court left these methodological differences between the scientists' professional and paid-expert work for the jury to resolve. Op.45-46,63-64. But an expert must employ "in the courtroom the same level of intellectual rigor that characterizes the practice of an expert in the relevant field." *Kumho Tire*, 526 U.S. at 152.

Plaintiffs' primary response is to claim that judges are unqualified to distinguish sound science from unsupported speculation. Ans.Br.32,48. But that contradicts this Court's precedents, which recognize, regardless of "the complexity and sheer volume of the testimony," a judge must "act as arbiter" and "fulfill[] the gatekeeping duties *Daubert* and D.R.E. 702 mandate." *Grenier I*, 981 A.2d at 528 n.7; *see also Asbestos II*, 2009 WL 1034487, at *3 n.12. Underscoring the weakness

of the evidence, in the five Zantac cases that have reached a jury verdict in non-*Daubert* states, *none* found in plaintiffs' favor. Rule 702 is designed so that courts weed out these scientifically weak opinions that are unreliable due to methodological lapses, rather than ask juries to evaluate all such questions.[10]

Plaintiffs attempt to defend the Superior Court's let-it-all-in approach with a string of federal cases and two Delaware decisions. They misread these cases. In *Minner v. American Mortgage & Guaranty Co.*, the Superior Court explained that "[c]ourts are *not* just to let the opinion of the credentialed expert into evidence for what it is worth and leave its evaluation to the jury." 791 A.2d 826, 841 (Del. Super. Ct. 2000) (emphasis added). The Superior Court here cited *Minner* for its conclusion that *Daubert* "emphasiz[ed] the limitations on the court's role in deference to the role of the jury." Op.9. But *Minner* says no such thing. Both *Minner* and the second Delaware case Plaintiffs cite make clear that "it is the trial judge who must perform that [reliability] exercise before the evidence is put before the jury." *Bowen v. E.I. Du Pont De Nemours & Co.*, 2005 WL 1952859, at *8 (Del. Super. Ct. June 23, 2005), *aff'd*, 906 A.2d 787 (Del. 2006); Ans.Br.45.

[10] Plaintiffs' brief references settlement agreements involving both GSK and Pfizer, but those agreements encompassed cases pending in multiple other jurisdictions and do not extend to every Delaware case filed against those Defendants. As with any settlement, the agreements involved a variety of considerations and say nothing about the merits of Plaintiffs' cases or the issues on appeal.

Plaintiffs' federal cases likewise show the error in the Superior Court's approach. Ans.Br.44. These cases stress that *Daubert*'s statement about the "liberal thrust" of the Federal Rules of Evidence helped explain the U.S. Supreme Court's departure from the *Frye* standard. *See, e.g.*, *Cavallo v. Star Enter.*, 100 F.3d 1150, 1158 (4th Cir. 1996). Neither this Court nor the U.S. Supreme Court has accepted Plaintiffs' effort to water down Rule 702 by suggesting courts should apply Rule 702 with a "liberal thrust" and punt essential reliability determination to the jury.

On the contrary, two of the cases Plaintiffs cite affirmed the *exclusion* of unreliable experts. In *Cavallo*, the Fourth Circuit affirmed exclusion of a plaintiff's toxicologists because their opinions were speculative and not based on published and adequately tested science. *Id.* at 1159. In *Amorgianos*, the court affirmed exclusion and praised the district court's "rigorous examination" of the expert's citation to facts, methodology, and application of his methodology. 303 F.3d at 269.

None of Plaintiffs' cited cases affirmed a trial court's holding that criticisms of an expert's methodology go only to weight, not admissibility. And Plaintiffs offer no rebuttal of the authority cited by Defendants, Op.Br.41-45, and no defense of the Superior Court's reliance on *McCullock v. H.B. Fuller Co.*, 61 F.3d 1038 (2d Cir. 1998). Under the text of Rule 702 and its settled construction in Delaware and federal courts, the Superior Court's failure to scrutinize how Plaintiffs' experts applied their methodologies to the relevant facts is reversible error.

CONCLUSION

The decision below should be reversed and remanded with instructions to grant Defendants' motion.

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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

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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.

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DATED: January 14, 2025

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CERTIFICATE OF SERVICE

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