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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

APPELLEES' ANSWERING BRIEF

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NATURE OF PROCEEDINGS

N-Nitrosodimethylamine ("NDMA") is a carcinogen. Since 1978, every scientific and regulatory body has agreed that NDMA exposure is carcinogenic to humans. It causes cancer in *every* species ever tested. This is why, in 2020, after the U.S. Food and Drug Administration ("FDA") learned that ranitidine inherently degrades into NDMA, accelerated by heat and humidity, it ordered the immediate recall of all ranitidine products from the market and instructed consumers to dispose of the drug. The FDA specifically warned that sustained higher levels of exposure to NDMA *from ranitidine* could increase the risk of cancer.

Litigation unearthed a dark truth. Before ranitidine was approved in 1983, Appellants *knew* ranitidine formed NDMA. They knew this because they *tested* and found NDMA formation. Appellants concealed their NDMA data and misled the FDA. Thus, the truth about NDMA and ranitidine did not emerge until late 2019. But, before the truth emerged, ranitidine-containing drugs, sold as Zantac, became one of the most successful drugs in history, catapulting Appellants into the stratosphere of the pharmaceutical industry. Appellants made billions while exposing tens of millions of Americans to a carcinogen for over four decades.

It is against this backdrop that thousands of cases were brought against Appellants, alleging that their cancer was caused by exposure to NDMA from Appellants' ranitidine products. Even with a large docket, the Parties have worked

cooperatively. No party has filed a single discovery motion despite dozens of lengthy and contested depositions and millions of documents being produced. Indeed, all eight case management orders entered below ("CMOs") were *stipulated*, laying out an organized process for managing the docket through a phased bellwether trial process. As part of the negotiated CMOs, the Parties agreed to first address "general causation," i.e., whether NDMA from ranitidine is capable of causing cancer. That process involved dozens of experts on both sides, with hundreds of hours of deposition, over 1,000 pages of briefing, over 20,000 pages of exhibits, and three full hearing days of carefully negotiated and time-restricted argument. The result—a thoughtful and detailed 102-page order, carefully applying Delaware's *Daubert* jurisprudence to determine whether Appellees' experts could provide admissible general causation opinions. After considering Appellants' arguments, the Honorable Vivian L. Medinilla joined multiple courts in California and Illinois, which reviewed opinions of the *same* experts, disagreed with a non-binding order from a federal multidistrict litigation ("MDL") court in Florida involving *different* experts, and denied Appellants' *Daubert* motions.

Undergirding this appeal—discussed in the opening brief and by the *amici*—is an implicit threat. Appellants and their *amici* warn that if the Superior Court's *Daubert* decision is allowed to remain, Delaware courts will become a magnet for

mass tort litigation, which might cause businesses to stop incorporating here—none of which has actually happened. In other words, Appellants and their amici groups are demanding that the rule of law, enshrined in over 200 years of Delaware jurisprudence, take a backseat to political exigency. They ask this Court to fashion rules of law, not based on the law or what is right or fair, but in a way that makes it easier for corporate actors to evade tort liability because, if not, they might take their business elsewhere. Such an argument is meritless. This Court has earned a reputation of independence and fairness. Threatening political ramifications, whether implicit or explicit, to persuade a court of law is as inappropriate as it is unpersuasive. This Court should reject it, *explicitly*.

Reality also rejects this argument. Since the Superior Court's *Daubert* decision, there has been no flood of mass tort litigation into Delaware. Rather, the largest Appellant, Defendant GlaxoSmithKline, LLC ("GSK")—the company that invented ranitidine—negotiated $2.2 billion in settlements with cancer victims.[1] The Delaware forum—far from being a "problem" for GSK, now serves as *the forum* for resolving cases and allowing deft reconciliation of GSK's liabilities. Another Appellant, Pfizer, Inc., has also resolved the lion share of its liability

[1] *See* Press Release, GlaxoSmithKline, LCC, *Statement: Zantac (ranitidine) litigation – settlement agreements reached* (Oct. 9, 2024), https://www.gsk.com/en-gb/media/press-releases/statement-zantac-ranitidine-litigation-settlement-agreements-reached/.

following the initiation of the Delaware litigation.[2] In other words, Delaware courts, through fair application of law, are creating an environment that allows for *justice*, for *all sides* and expedient resolution without taking extensive court resources. And, as far as a mass exodus, there is none; Appellants remain incorporated in Delaware.

In truth, the Superior Court's *Daubert* order reflects the diligence and hard work that Superior Court judges do every day. Delaware law gives broad discretion to the trial court to assess the admissibility of expert opinion. *Daubert* is supposed to be a flexible standard, applied to the specific facts and circumstances of a case. Unless a Superior Court engages in that gatekeeping role in an arbitrary or capricious manner, this Court cannot find an abuse of discretion, nor should it. The Superior Court's decision, here, was detailed and thoughtful. The Court correctly drew the lines between gatekeeping and fact finding, as required by *Daubert*. The decision should be affirmed.

[2] *See* Utkarsh Shetti, *Pfizer offers up to $250 mln to settle Zantac cancer lawsuits, FT reports*, REUTERS (May 15, 2024), *available at* https://www.reuters.com/business/healthcare-pharmaceuticals/pfizer-offers-up-250-mln-settle-thousands-zantac-cancer-lawsuits-ft-reports-2024-05-16/.

SUMMARY OF ARGUMENT

1. Denied. Appellees' experts considered and evaluated whether there was a dose response between NDMA exposure—from ranitidine and other sources—and cancer. However, identifying a specific "threshold dose" at which NDMA is harmless defies logic because threshold doses do not exist for substances that cause cancer through stochastic mutations. *See In re TMI Litig.*, 193 F.3d 613, 642 (3d Cir. 1999). The Superior Court held that determination of a "threshold dose" was not a prerequisite for admissibility, but was *one* factor, among others, to consider under *Daubert*. *In re Zantac (Ranitidine) Litig. ("Zantac")*, 2024 WL 2812168, at *12-14 (Del. Super. May 31, 2024). In reaching that conclusion, the Superior Court did not act in an arbitrary or capricious manner. While threshold doses can be established for many toxic effects, it cannot be done with stochastic or probabilistic risks like cancer. Cancer is caused by a single mutation. If a substance can cause a mutation, then there is no level of exposure where the risk drops to zero. This point is accepted among scientists, regulators, and even Appellants' experts. Thus, the Superior Court's decision not to impose a "threshold dose" as a prerequisite for admissibility was entirely appropriate and in line with scientific experts outside the courtroom. Moreover, while consideration of dose is important, Delaware law has never imposed an arbitrary "threshold dose" requirement on admissibility. Instead, Delaware law has long emphasized

that *Daubert* must be flexible and adapted to the facts of a case. Here, the Superior Court correctly refused to incorporate a scientifically dubious concept into a rule of law—leaving the door open for "threshold dose" to play a non-dispositive role, where applicable, under *Daubert*.

2. Denied. Below, Appellants argued that experts should not be allowed to even consider NDMA data in assessing whether NDMA exposure from ranitidine causes cancer. The Superior Court rejected that argument, holding that Appellees' experts are permitted to consider *both* NDMA and ranitidine data in rendering their general causation opinions. *Zantac*, 2024 WL 2812168, at *9-10. This decision was neither arbitrary nor capricious. The cancer-causing agent at issue in this case *is NDMA*. Thus, relying on NDMA data is reasonable. Delaware law agrees. In the *Asbestos Litigation*, experts were permitted to rely on chrysotile (a type of asbestos) data because the chrysotile found in the product (brake pads) was shown to be the same. *In re Asbestos Litig*., 911 A.2d 1176, 1202 (Del. Super. 2006). Here, there is no dispute that the NDMA molecules found in ranitidine are the same NDMA molecules in food, water, and air. Thus, the Superior Court did not abuse its discretion in holding that Appellees' experts could rely on *both* NDMA and ranitidine data.

3. Denied. The Superior Court applied the correct Delaware *Daubert* standard. The purpose of *Daubert* is to ensure that a jury is not misled by clearly

false “scientific” opinion testimony. When the issue is a close one, the presumption is that the opinion should be allowed, leaving the veracity of otherwise “shaky” opinions subject to vigorous cross examination. This is the “liberal thrust” of admissibility that was described in the *Daubert* decision. It is also the standard Delaware courts consistently apply. The Superior Court, in conducting its rigorous and detailed *Daubert* analysis, applied the correct *Daubert* standard and did not act in an arbitrary or capricious manner. There was no abuse of discretion.

STATEMENT OF FACTS

I. NDMA Is a Potent Carcinogen, Causing Cancer in Every Species Ever Tested, Including Humans

Banned in 1976 because of carcinogenicity, NDMA is only currently used as a positive control in animal studies to induce tumors. A-014953–014954. Fifty years ago, the International Agency for Research on Cancer ("IARC") deemed it a Class 2A "probable human carcinogen" and warned that NDMA "*should be regarded* for practical purposes as if it were *carcinogenic to humans*." A-014689; A-014627 (emphasis added). Both the FDA and the Environmental Protection Agency ("EPA") consider NDMA to be a "probable human carcinogen." A-015124; A-015133. The Department of Health and Human Service's ("HHS") Report on Carcinogens states that NDMA is "reasonably anticipated to be a human carcinogen[.]" A-015137.

In 1989, the HHS's Agency for Toxic Substances and Disease Registry ("ATSDR"), in conjunction with the EPA, concluded: "oral exposures of acute and intermediate duration are sufficient to *induce cancer*." A-014762 (emphasis added). They stated that "it is reasonable to expect that exposure to NDMA by eating, drinking, or breathing could cause cancer *in humans.*" A-014718 (emphasis added). In 2023, ATSDR noted that "NDMA's carcinogenicity is widely recognized." A-014852.

In 2002, the World Health Organization ("WHO") issued a chemical

assessment for NDMA, and stated:

> Based upon laboratory studies in which [tumors] have been induced in *all species* examined at relatively low doses, *NDMA is clearly carcinogenic. There is overwhelming evidence that NDMA is mutagenic and clastogenic. ….* as a result, *it is considered highly likely that NDMA is carcinogenic to humans, potentially at relatively low levels of exposure.*

A-015077 (emphasis added).

In 2020, when the FDA ordered the immediate recall of all ranitidine because of NDMA, FDA stated that "NDMA is a probable human carcinogen (a substance that *could cause cancer*)." A-015133 (emphasis added). The FDA explained, specifically in the context of NDMA-contaminated ranitidine, that "sustained higher levels of exposure may increase the risk of cancer *in humans*."[3] A-015133 (emphasis added).

II. Ranitidine Naturally Degrades into NDMA

In 2020, following the FDA's recall, GSK published a study concluding that NDMA "is formed in ranitidine drug substances because of an intermolecular degradation reaction of ranitidine molecules" and that the degradation starts "from the point of manufacture; both elevated temperature and [relative humidity] contribute to an increase in the rate of degradation." A-015724. This is why FDA

[3] Appellant GSK's internal analysis of NDMA confirms carcinogenicity. A-015225–A-015226; *see Zantac*, 2024 WL 2812168, at *9 (discussing GSK's study).

pulled ranitidine off the market: "FDA testing … confirmed that NDMA levels increase in ranitidine *even under normal storage conditions*, and NDMA has been found to increase significantly in samples stored at higher temperatures, including temperatures the product may be exposed to during distribution and handling by consumers." A-015134.

Thus, it is undisputed that ranitidine degrades into NDMA from the moment it is manufactured until the moment it is ingested, orally exposing anyone that takes ranitidine to NDMA.

According to the WHO, the average male adult should consume less than 200 nanograms ("ngs") of NDMA per day to reduce cancer risk. A-015787–A-015788. It is estimated that the average adult consumes 100 to 110 ng of NDMA daily in water and food. *Id.* Thus, the FDA's acceptable daily intake ("ADI") limit for NDMA in ranitidine is 96 ngs per day. A-015751. This ADI translates into a concentration of 0.32 parts per million ("ppm") in a 300 mg dose.

Routinely, the levels of NDMA found in ranitidine exceeded the ADI. The FDA observed NDMA at 2.85 ppm—nine times over the ADI. A-015870. The Korean Ministry of Food and Drug Safety found NDMA levels up to 53.5 ppm—333 times over the ADI. A-015888. In Australia, the Therapeutics Goods Administration found NDMA levels up to 14 ppm—forty-four times over the ADI. A-015875; A-015875.

Similarly, GSK's own internal testing found NDMA levels up to 7.6 ppm—twenty-four times over the ADI. *See* A-015901; A-015719. GSK also tested ranitidine drug substance and found NDMA levels up to 41.4 ppm—130 times over the ADI. A-015719. Appellant Sanofi found NDMA as high as 5.98 ppm—eighteen times over the ADI. A-015907.

The most comprehensive testing on ranitidine was completed by Appellees' expert, Emery Pharma. A-015949–A-016104 (Emery Report). Appellants produced samples of every ranitidine product in their possession and Emery's laboratory tested samples from every lot. A-016024–A-016030. Emery found average NDMA levels of 10.5 ppm in unexpired ranitidine and 15.8 ppm in expired products. A-015955. Levels far above the FDA's ADI of 0.32 ppm.

III. Although There Is Consensus Regarding the Carcinogenicity of Oral NDMA Exposure, No Regulatory or Scientific Body Has Specifically Assessed Oral NDMA Exposure *from Ranitidine*

There *is* regulatory and scientific consensus that NDMA, more likely than not, causes cancer in humans. The ability of NDMA to cause cancer has been established through multiple routes of exposure, with the primary routes being oral (ingestion), intravenous, and inhalation. *See* A-014851– A-014852 (discussing data linking NDMA to cancer). Ingestion of NDMA from a ranitidine pill is a form of oral NDMA exposure. Regardless of the route or source (food, water, occupational fumes), NDMA induces mutagenicity and causes tumors. *E.g.*, A-

014851 (citing numerous associations of NDMA with cancer).

To date, although numerous regulatory bodies have considered whether oral exposure to NDMA causes cancer, no regulatory body has specifically looked at the narrower question of whether oral NDMA exposure *from ingesting ranitidine* causes cancer. Appellants seize on this point to argue that because no regulator concludes that oral NDMA exposure from ranitidine causes cancer, as opposed to oral ingestion of NDMA generally, it means ranitidine does not cause cancer. *See* Opening.Br.1. This is misleading.

Regulators make assessments about the cancer-causing agent, not the delivery vehicle of that agent. For example, while it is understood that asbestos causes cancer, regulators do not consider whether individual asbestos-containing products, i.e., fiberboards, insulation, or brake pads, cause cancer. Instead, the focus is on asbestos, regardless of the source.

The same applies to NDMA. Oral ingestion of NDMA exposes one to a carcinogen—and numerous regulatory bodies, including the FDA, hold as much. Whether that exposure comes from food, or from taking a pill every day, does not matter. Thus, while the FDA has concluded that orally ingested NDMA is a probable human carcinogen, *id.*, the FDA has not systematically reviewed the literature concerning NDMA in ranitidine. The FDA has never decided, one way or another, whether NDMA exposure from ranitidine causes cancer. Nor has any

regulatory body. To use this fact as evidence against carcinogenicity is, thus, a fallacy. The absence of evidence is not evidence of absence.

Appellants misstate that "[t]he 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." Opening.Br.10. But the source of that assertion belies the claim. The citation to the "FDA" comes from a 2021 publication looking at urinary concentrations of NDMA after taking ranitidine, it did not assess causation, *see* A-011393, and was published *before* the vast majority of NDMA-ranitidine epidemiological studies were even available. The statement attributed to the European Medicines Agency comes from 2020—even *earlier*—before *any* NDMA-ranitidine epidemiological study was published. Thus, neither agency has actually "reviewed the epidemiological literature" or rendered an opinion about causation.

Instead, independent researchers have grappled with the emerging data, and several have reached *causation* conclusions. For example, a 2020 study concluded, "[i]n conjunction with a large body of epidemiologic and human and animal basic science research, the study results support the hypothesis that NDMA-contaminated ranitidine increases the risk of cancer and supports the withdrawal of these medications from the market." A-016758–A-016765. A 2021 study focused on bladder cancer, and after seeing an association with ranitidine,

stated: "increased risk in bladder cancer among ranitidine users is consistent with concerns that ranitidine use can lead to exposure to NDMA[.]" A-016793. In another study from 2022, the authors concluded, "the clear data from our real-world observational study strongly support the *pathogenic role* of NDMA contamination, given that long-term ranitidine use is associated with a higher likelihood of cancer development[.]" A-016740. In a 2024 study, researchers concluded, "[r]anitidine may *induce* various tumor-related adverse reactions, especially in long-term users and elderly patients."[4] In other words, even though regulators are silent about whether oral NDMA exposure from ranitidine causes cancer—as opposed to oral NDMA exposure generally—Appellees' experts' conclusions about causation *are* supported by conclusions reached by independent peer-reviewed scientists.

IV. The Superior Court Conducted a Robust *Daubert* Analysis of Appellees' Experts' General Causation Opinions

By stipulation, the Parties agreed to address general causation first. Issues related to specific causation, i.e., whether a person's exposure to NDMA from ranitidine caused their specific cancer, would be addressed as bellwether cases proceeded to trial.[5]

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[4] Liu, M, et al., *Adverse tumor events induced by ranitidine: an analysis based on the FAERS Database*, 21 EXPERT OPIN DRUG SAF. 1-13 (2024).

[5] The first bellwether trial is set for May 2025. The parties are continuing discovery and the bellwether trial process during this interlocutory appeal process.

IARC provides that different types of data are relevant to whether a substance causes cancer: experimental animal data, mechanism data, and human cancer data. *See Barrera v. Monsanto Co.*, 2019 WL 2331090, at *9 (Del. Super. May 31, 2019); *Tumlinson v. Advanced Micro Devices, Inc.*, 2013 WL 7084888, at *9 (Del. Super. Oct. 15, 2013), *aff'd*, 81 A.3d 1264 (Del. 2013)); *In re Asbestos Litig.*, 911 A.2d 1176, 1194 (Del. Super. 2006) (IARC "provides methodologies to determine if a substance can be classified as a carcinogen."); A-016740 (IARC methodology). Experts review and consider the strengths and weaknesses of the data and then, after considering all the evidence, apply the Bradford Hill[6] considerations to determine whether an observed association is causal. *See Barrera*, 2019 WL 2331090, at *4 (citing *Tumlinson*, 2013 WL 7084888, at *7).

Appellees presented nine experts on general causation. *See* A-016908–A-016945 (Dr. Neugut - bladder cancer); A-022220–A-022285 (Dr. Hatzaras - colorectal, gastric, and esophageal cancer); A-017206–A-017245 (Dr. Rustgi - liver cancer); A-019599–A-019708 (Dr. Trock - prostate cancer); A-019958–A-020022 (Dr. Miller - pancreatic cancer); A-019437–A-019512 (Dr. Raz - lung cancer); A-020120–A-020176 (Dr. Leone - breast cancer); A-000857–A-000947

[6] Sir Bradford Hill's 1965 address, where he outlined epistemological precepts in establishing causation—considerations born from his work proving that tobacco smoke caused cancer—is regarded by regulators and scientific bodies as a reliable methodology in determining whether an association is causal. *See* A-017385–A-017390.

(Dr. Margulis - kidney cancer); A-015763–A-015844 (Dr. Jameson re- overall carcinogenicity of NDMA). Appellees also proffered experts on ranitidine testing. A-015949–A-016104 (Emery Pharma).

Their credentials are unassailable. Indeed, Appellants did not challenge them. Importantly, *none of the general causation experts were proffered in the MDL*. Appellees' experts reviewed *all* of the evidence—peer-reviewed studies, internal studies, direct experimental evidence, and other published and unpublished data—discussed the strengths and weaknesses of that data and systematically applied the Bradford Hill considerations to render a general causation opinion.

Appellants moved to exclude each expert under *Daubert.* The briefing spanned over 1,000 pages and included over 20,000 pages of exhibits. The Superior Court conducted a three-day *Daubert* hearing. Ultimately, the Superior Court issued a 102-page order denying the motions. After Appellants obtained leave to file an interlocutory appeal, this appeal followed.

ARGUMENT

I. A "Threshold" Dose Is Not Required to Reach an Opinion on General Causation

A. Question Presented

Whether experts must identify a "threshold dose," i.e., the level of exposure where the risk is zero, before rendering an admissible opinion that a substance can cause cancer?

B. Scope of Review

A Superior Court's decision to admit or exclude expert evidence is reviewed on appeal for an abuse of discretion. *Tumlinson v. Advanced Micro Devices, Inc.*, 81 A.3d 1264, 1268 (Del. 2013). "To find an abuse of discretion, there must be a showing that the trial court acted in an arbitrary and capricious manner." *Id.* (quoting *Spencer v. Wal–Mart Stores E., LP*, 930 A.2d 881, 887 (Del. 2007). Importantly, "[t]hat standard applies as much to the trial court's decisions about how to determine reliability as to its ultimate conclusion." *Gen. Motors Corp. v. Grenier*, 981 A.2d 531, 536 (Del. 2009). Trial courts are given "broad latitude to determine whether *Daubert*'s specific factors are, or are not, reasonable measures of reliability in a particular case." *M.G. Bancorporation, Inc. v. Le Beau*, 737 A.2d 513, 522 (Del. 1999).

Thus, on this question, which deals with *how* the Superior Court considered the admissibility of Appellees' experts, the scope of this Court's review is limited

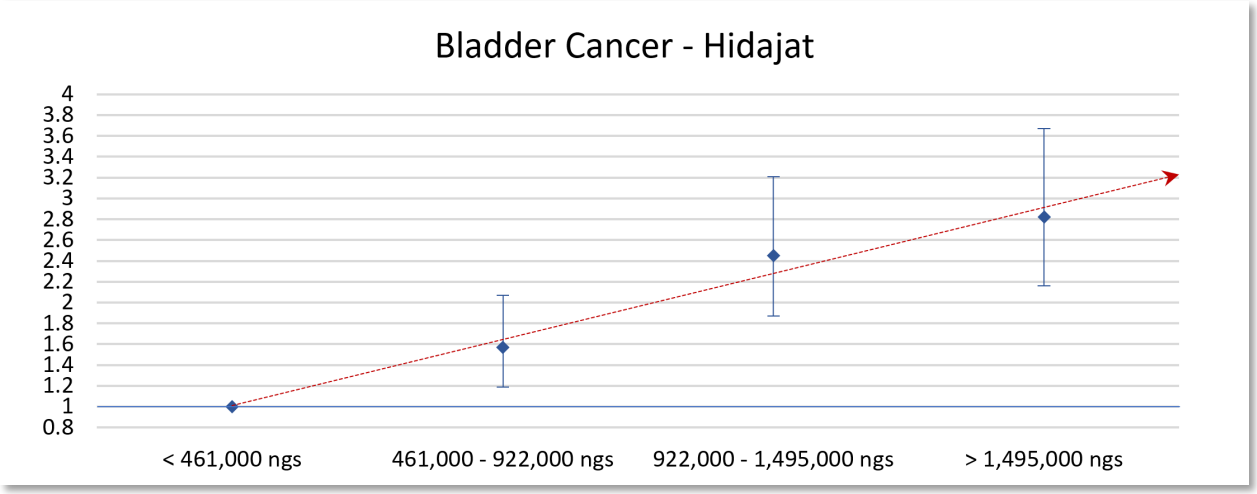
to whether the Superior Court's ruling constituted an abuse of discretion, i.e., whether the Superior Court acted in an arbitrary and capricious manner. *See Tumlinson*, 81 A.3d at 1270 ("This Court will not usurp the gatekeeping function of the trial court unless it is shown that the trial court abused its discretion … As gatekeeper, the trial court had the benefit of a four-day *Daubert* hearing ... We will not disturb the trial court's result unless its analysis is found to be arbitrary and capricious.").

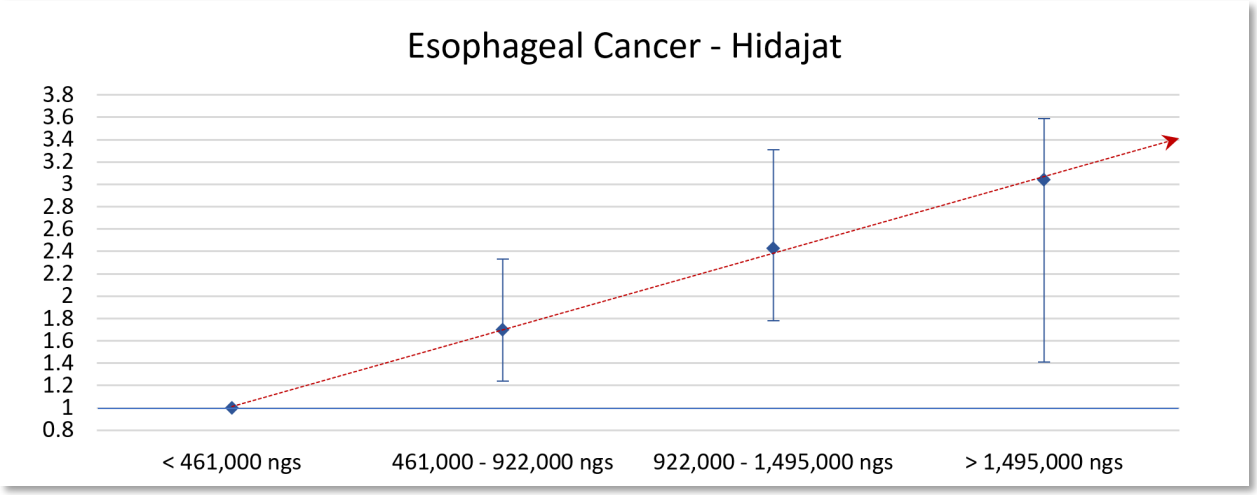
C. Merits of Argument

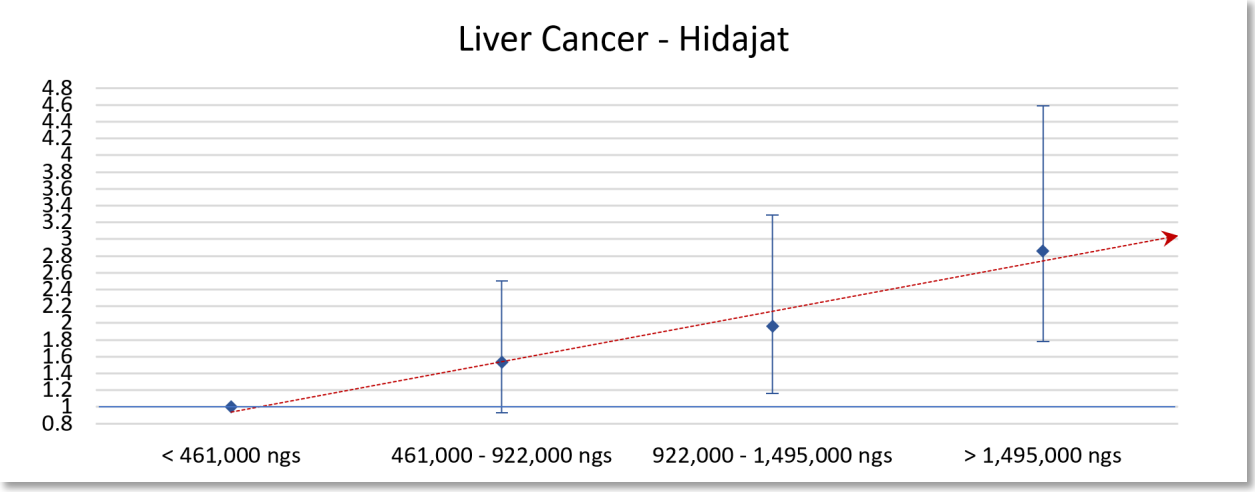
At trial, a plaintiff will need to prove that, more likely than not, exposure to NDMA from taking ranitidine caused their cancer. The plaintiff will present expert testimony about whether their exposure to NDMA from ranitidine, after considering the specifics of their risk profile—such as genetic susceptibilities, synergistic exposures, immunodeficiencies, etc.—caused their cancer. However, whether a specific plaintiff's exposure to NDMA from ranitidine was sufficient to cause their cancer is *not* at issue *yet*. A plaintiff's specific dose and whether that dose caused cancer—after considering the specific facts and susceptibilities of that plaintiff—is, as the Superior Court held, the domain of *specific* causation, not *general* causation.

As to general causation, at issue now, each of Appellees' experts specifically considered, consistent with Bradford Hill, whether there was a *dose response* (or

biological gradient) between increasing NDMA exposure and cancer risk. For each cancer type, a dose-response *was* observed—the greater the exposure to NDMA, the greater the cancer risk. The following charts depict data from the most robust human epidemiological study on NDMA, with the Y-axis showing increasing NDMA exposure, and the X-Axis showing increased risk of cancer. The data shows a dose-response.






Liver Cancer - Hidajat
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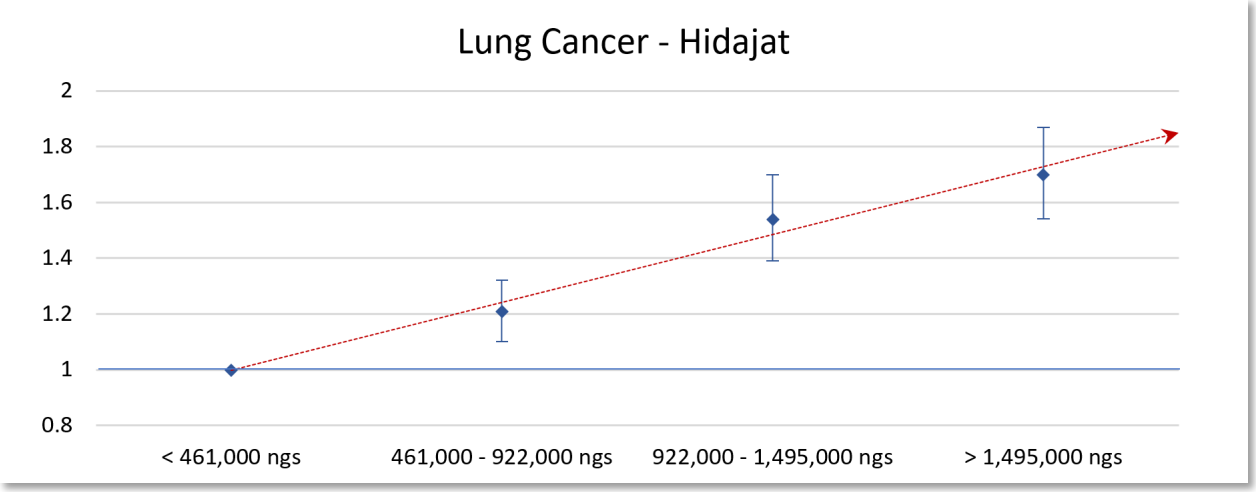
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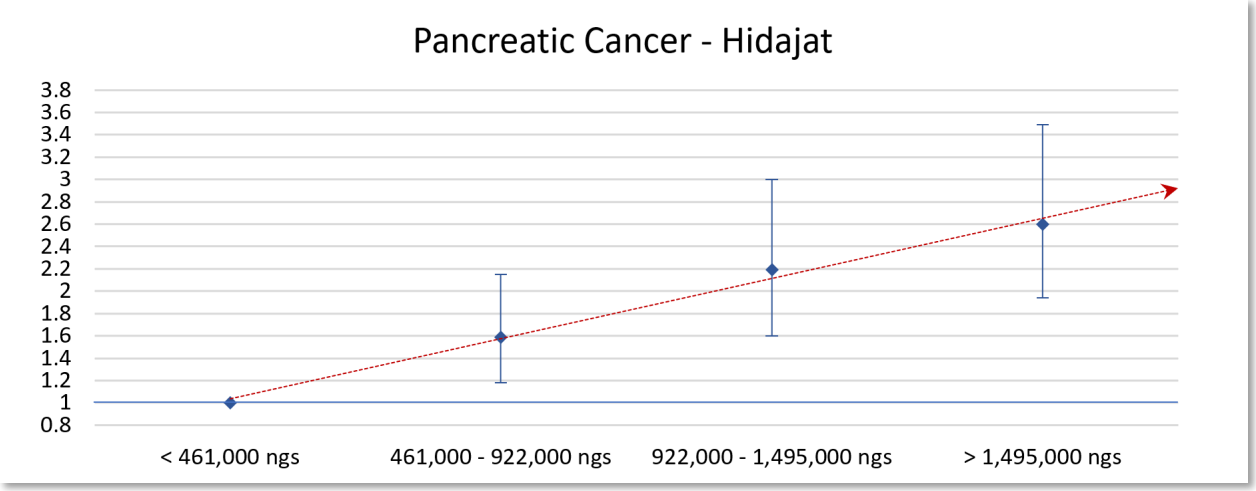
Pancreatic Cancer - Hidajat
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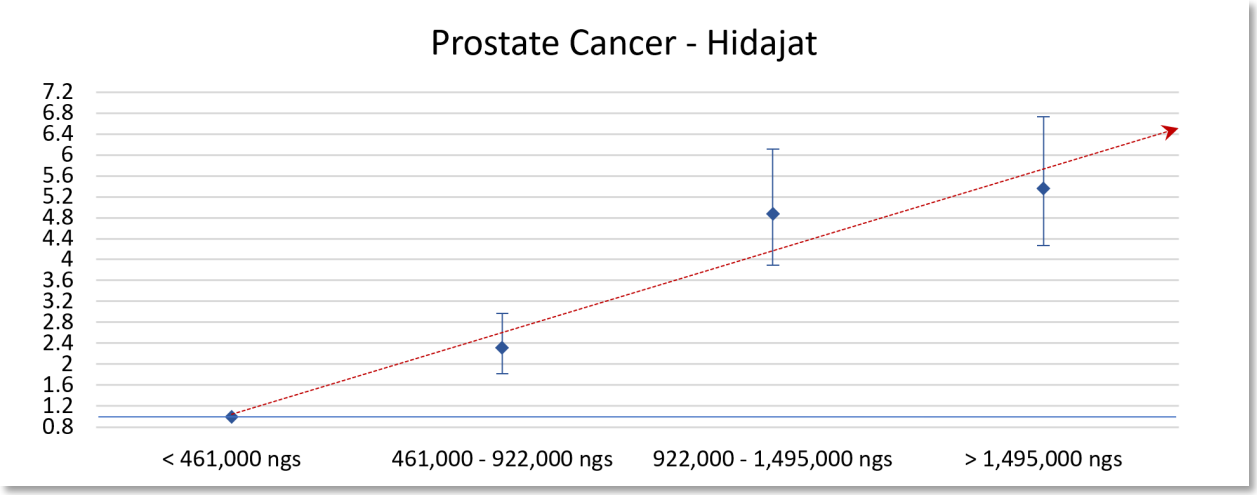

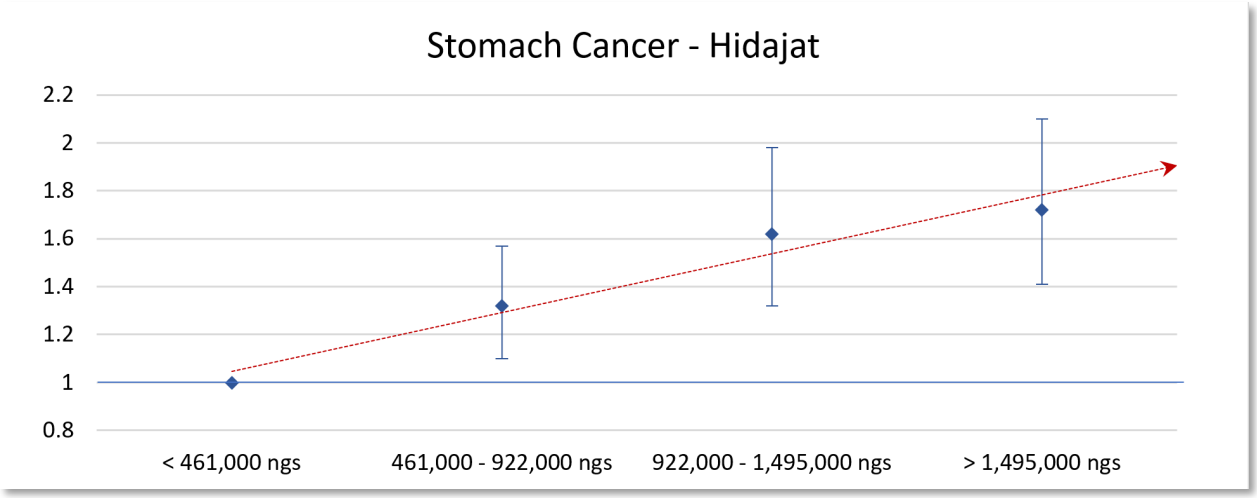

A-014354–A-014356.

Appellants, however, conflate "dose response" with "threshold dose." Whereas a dose response examines whether increasing risk of cancer is associated with increasing exposure to NDMA, a "threshold dose" is a limit of exposure where there is no risk. *See* Opening.Br.19. They are *different*. One can have a dose response with no threshold dose, and *vice versa*. Indeed, while dose-response is a Bradford Hill consideration for assessing causality, *see* A-017388 (biological

gradient), "threshold dose" is *not*. As discussed below, the concept of threshold dose as applied to cancer is scientifically incoherent.

Here, Appellants ask this Court to create a new rule of law: *before* an expert can render a *general causation* opinion about whether a substance can generally cause cancer, they *must* define a "threshold dose" of exposure "below which the substance would not cause the disease or effect" or else their opinions are *categorically* excluded under *Daubert*.

While the Superior Court did not fully endorse the view that "threshold dose" was scientifically incoherent, it agreed that a brightline rule on admissibility was legally unsupported. The Superior Court held that threshold dose, to the extent applicable, was "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." *Zantac*, 2024 WL 2812168, at *13. Then, using this rule, the Superior Court considered each expert's testimony and views about threshold dose, among other considerations, in assessing admissibility under *Daubert*.

The Superior Court's analysis should be affirmed for two reasons. First, a threshold dose for cancer is scientifically unsound, and it would be a mistake to incorporate a scientifically incoherent standard into a rule of law. Second, imposing a *legal* requirement based on a controversial scientific proposition is not

appropriate under Delaware law or *Daubert*. Such a rule would fundamentally violate the flexible gatekeeping role entrusted to trial courts under *Daubert*.

1. A Threshold Dose Requirement for Cancer Risk Is Scientifically Unsound

It is undisputed that experts should consider the Bradford Hill factors in assessing causality. Dr. Hill was clear that no single factor "can bring indisputable evidence for or against the cause-and-effect hypothesis and none can be required as the *sine qua non*." A-017389. This is why, even if the experts found *no* dose response whatsoever—one of the Bradford Hill considerations, *see* A-017388 (discussing biological gradient)—they could still draw a causal inference under the reliable, time-tested Braford Hill methodology. The same is true for a threshold dose. Surely, if a dose response, which *is* one of the Bradford Hill considerations, is not required to find causation, then a "threshold dose," which is not a Bradford Hill factor, is also not *required*.

This is particularly true when it comes to cancer. "Threshold dose," while relevant in some toxic torts, is *not applicable* to cancer. The chapter on Toxicology in the Federal Reference Manual on Scientific Evidence ("Reference Manual") specifically states that the concept of threshold dose "***is <u>not</u> applied to substances that exert toxicity by causing mutations leading to cancer***" because "***any exposure at all*** to mutagens may increase the risk of cancer[.]" A-016890 (emphasis added); A-016889. Indeed, the Reference Manual has a section

specifically titled, "No-threshold model and determination of cancer risk" explaining how a threshold dose does not apply to cancer. A-016862–016865. The reason is obvious—the biology of cancer does not allow for zero risk. "In virtually all cancers, the overgrowth of cells can be traced to a single mutation[.]" A-016874. Thus, "[i]n theory, the cancer-causing mutation to the genetic material of the cell can be produced by any one molecule of certain chemicals." A-016862. "[E]ach molecule of a cancer-causing chemical has some finite possibility of producing the mutation that leads to cancer." A-016862. Although the likelihood that a single molecule will cause cancer is "very small … the risk is not zero." A-016862.

In *In re TMI Litig.*, the Third Circuit discusses the problem with imposing a "threshold dose" on the stochastic event of cellular mutation. 193 F.3d at 642. Because a carcinogenic agent can theoretically induce mutations that lead to cancer at *any* dose, "there is a finite possibility for the occurrence of a stochastic event even at very small doses" and, thus, "it is currently believed that there is no threshold dose below which the probability of cancer induction is zero." *Id.* Indeed, "[i]t is presumed that any transformed cell can become cancerous and become a malignant tumor." *Id.* The Third Circuit specifically reversed the trial court for imposing a threshold dose requirement at summary judgment. *Id.* at 726.

Recognizing that zero risk is impossible, regulators instead define an

"acceptable" level of risk. Here, FDA set its "acceptable" risk at 1 in 100,000; meaning if an exposure increases cancer for 1 in 100,000 people, then it is, from a *regulatory perspective*, "acceptable," even though it is not zero. A-018379; *see* 21 C.F.R. § 556.3. The ADI for NDMA from ranitidine is 96 ng/day. A-018383. Testing shows that NDMA levels in ranitidine greatly exceed the ADI—frequently by magnitudes of over a hundred-fold. *Supra* at 10-11. While none of Appellees' experts believe a "threshold dose" is scientifically appropriate, each expert cites to and relies on the FDA's ADI and the testing evidence.

The problem of applying a threshold dose to a carcinogen is illustrated by the most studied carcinogen in history—tobacco smoke. Everyone agrees that smoking causes lung cancer. That said, there is no minimum number of cigarettes that is considered safe. Appellants' own corporate representative agreed. A-017039. So did Appellants' experts, with one expert disclaiming threshold dose as "meaningless" in assessing causation. A-017120-A-017121. Tobacco smoke is perhaps the most well-known carcinogen in human history, but there has *never* been an established threshold dose. This makes sense. While there is a clear *dose-response* relationship, i.e., the more one smokes the greater the risk (just like there is for NDMA and cancer), science has never identified a dose where smoking cigarettes is safe. No expert would ever adopt such a position. Likewise, ingesting NDMA is not safe, which is why it is banned.

Appellants, their experts, and Appellees' experts *all agree*—a substance can be a carcinogen without a defined threshold dose. Indeed, Appellants have not identified a *single* example of a threshold dose that exists for a human carcinogen. If such a determination is not required to establish general causation among scientists, how could it possibly be a *legal* requirement? It cannot because that is not the law, nor is it science. The question at *Daubert* is whether the expert is employing "the same level of intellectual rigor that characterizes the practice of an expert in the relevant field." *Kumho Tire Co. v. Carmichael*, 526 U.S. 137, 152-53 (1999). Because experts "in the relevant field" do not consider threshold doses for cancer, then as a matter of law, an expert not opining on threshold dose *cannot* provide a basis for exclusion.

Imposition of a threshold dose also blurs the line between general and specific causation. If a general causation expert is required to define a dose wherein a substance goes from being non-carcinogenic to carcinogenic (assuming such a thing were possible), it begs the question—a dose for whom? Necessarily, the dose needed to increase the risk of cancer depends on the individual. The same dose will have different effects on different people. The risk of cancer for a 25-year-old female athlete is different than an elderly man with genetic predispositions. To define a threshold dose, for all people, is not possible or scientifically coherent.

Faced with this truth, Appellants propose a nuanced, albeit similarly doomed, rule: threshold doses should only be required for substances that are not already known to be carcinogens. *See* Opening.Br.27. This argument fails before getting started. Scientists and regulators *agree* that NDMA, more likely than not, causes cancer. So, even under Appellants' nuanced rule, imposition of a threshold dose would not be required.

That said, the proposed rule is circular and untenable. If established carcinogens do not need a threshold dose, then how were they "established" in the first place? The answer—because threshold dose is neither required nor scientifically possible when it comes to carcinogens. *See In re TMI Litig.*, 193 F.3d at 642. Imposing such a requirement on experts opining about newly discovered carcinogens would effectively prevent any new carcinogens from ever being established. Incorporating a spurious scientific proposition as a *per s*e bar to admissibility would be misplaced, and fundamentally usurp the flexible and case-specific inquiry that animated *Daubert* in the first place. *See State v. McMullen*, 900 A.2d 103, 113 (Del. Super. 2006).

2. There Is No Legal Basis to Disturb the Superior Court's Holding that "Threshold Dose" Is One *Non-Dispositive* Consideration Under *Daubert*

Appellants do not argue that the Superior Court failed to consider threshold dose. The Superior Court specifically held that consideration of threshold dose

was one consideration, among others, to be reviewed. Instead, Appellants argue that determination of a threshold dose should be *dispositive* of admissibility. Putting aside the scientific problems with such a rule, as detailed above, *legally* this proposition finds no support in Delaware law. No Delaware court has *ever* held that determination of a threshold dose is dispositive of admissibility.

Appellants cite two Delaware Superior Court cases. In *Wilant v. BNSF Ry. Co.*, an expert opined that diesel exhaust exposure caused the plaintiff to develop bladder cancer while working at a railroad facility. 2020 WL 2467076, at *5 (Del. Super. May 13, 2020), *order vacated in part on denial of reconsideration*, 2020 WL 3887881 (Del. Super. July 9, 2020). The court identified a "dosage problem" with the expert's opinion. *Id.* The court noted that "we do not know how much diesel exhaust the Plaintiff inhaled while employed at BNSF"—an issue of specific causation—and that "even if we did, we do not know how much diesel exhaust one would need to inhale to increase the risk of bladder cancer." *Id.* The court criticized the expert for relying on exposure data related to lung cancer, as opposed to bladder cancer. *Id.* The court ultimately excluded the expert's bladder cancer opinion under *Daubert*. However, the court did *not* hold that a threshold dose was a *prerequisite* for general causation. In fact, the court's concern about dose was one issue, among others, that "amplify[ied] the Court's concerns"—it was *not dispositive*. *Id.*

In *Tumlinson*, plaintiffs alleged that exposure to unidentified chemicals at the defendant's semiconductor facility caused different birth defects in their respective children. 2013 WL 7084888, at *1. The case was not about cancer. The court excluded the plaintiffs' causation expert on multiple grounds, one of which related to the "testability" of the expert's hypothesis. *Id.* at *7-8. The expert had identified ten chemicals the plaintiffs *may* have been exposed to while working at the semiconductor facility, but "never opine[d]… which toxins specifically, alone or in combination, caused Plaintiffs' very different birth defects." *Id.* This failure to identify the injury-causing substance or provide a dose estimate of exposure to that substance, rendered the opinion little more than an "untested hypothesis." *Id.* The court never held that an expert must establish a threshold dose before rendering a causation opinion.

On appeal, this Court concluded that the Superior Court did not abuse its broad discretion under *Daubert*. *Tumlinson*, 81 A.3d at 1272. This Court explained that the expert "was unable to identify which specific chemicals, either individually or in combination, caused the Plaintiffs' 'very different' birth defects" or "distinguish between the Plaintiffs' differing work environments and how those environments may have impacted exposure levels[.]" *Id.* at 1270. This expert opinion, thus, lacked sufficient "specificity required to pass muster under *Daubert's* 'testability' factor" even if that "factor alone" was "not dispositive of a

Daubert reliability analysis." *Id.* at 1271. Again, at no point did this Court hold that an expert was required to define a threshold dose; if anything, this Court held the opposite.

Lacking *any* Delaware authority, Appellants rely on the MDL *Daubert* ruling. There, the MDL Court stated that, under Eleventh Circuit law, "[a] reliable general causation opinion must provide a threshold dose at which the substance becomes harmful." *In re Zantac (Ranitidine) Prod. Liab. Litig.*, 644 F. Supp. 3d 1075, 1266 (S.D. Fla. 2022) (citing *McClain v. Metabolife Int'l, Inc.*, 401 F.3d 1233, 1242 (11th Cir. 2005)). But a careful review of the underlying authority undermines this rule. The MDL Court relies on an article—David L. Eaton, *Scientific Judgement and Toxic Torts—A Primer in Toxicology for Judges and Lawyers*, 12 J. L. & Pol'y 1, 16 (2003)[7] ("Eaton Article")—to support the application of a threshold dose. 644 F. Supp. 3d at 1266. This citation comes from the *McClain* case. *See McClain*, 401 F.3d at 1242 (discussing Eaton Article). But, the Eaton Article, like the Reference Manual, confirms that the concept of threshold dose does *not apply to carcinogens*:

> For most types of dose-response relationships following chronic (repeated) exposure, thresholds exist, such that there is some dose below which even repeated, long term exposure would not cause an effect in any individual. … However, ***in the case of chemical carcinogens***, particularly those that increase risk of cancer by causing

[7] *Available at* https://brooklynworks.brooklaw.edu/jlp/vol12/iss1/2/ (accessed Dec. 7, 2024).

> direct damage to DNA in cells, many regulatory agencies assume that there are no "thresholds," and that ***risk is proportionate to dose at all levels of exposure***[.]

Eaton Article at 16 (emphasis added). Thus, the MDL's "scientific basis" for imposing a threshold dose requirement is *refuted* by the very source of that scientific information. Threshold dose is not a scientific or legal requirement in cancer cases.

Moreover, the underlying *McClain* case never held that a threshold dose was a *prerequisite* for general causation. Rather, in the context of discussing dose response—an issue Appellees' experts considered and expressly addressed—the *McClain* court held that the expert failed to demonstrate a relationship between dose and effect, rendering the opinions unreliable under *Daubert*. 401 F.3d at 1242. In fact, *McClain* was clear that whether a dose was sufficient in causing a harm, was an "issue of *individual causation*." *Id.* (emphasis added).

This stands in stark contrast to Appellees' experts here, who each carefully relied on peer-reviewed literature directly linking increasing NDMA doses (and, for some cancers, ranitidine doses) to the development of specific cancers. But, even so, *McClain* did not hold that threshold dose (or even dose response) is a *prerequisite* for admissibility, but one of the factors to be considered. For example, other courts in the Eleventh Circuit, applying *McClain* eschew the "threshold dose" concept as a *requirement*, instead holding, like the Superior Court here, that

it is *one* consideration in the analysis. *See, e.g.*, *In re Abilify (Aripiprazole) Prod. Liab. Litig.*, 299 F. Supp. 3d 1291, 1331 (N.D. Fla. 2018).

Regardless, Delaware and *McClain* stand apart. When faced with the *same* substances (ephedrine and caffeine), *same* injuries (cardiac events), and *same* body of literature as in *McClain*, Delaware did *not* order exclusion. *Long v. Weider Nutrition Grp., Inc.*, 2004 WL 1543226, at *4-6 (Del. Super. June 25, 2004). In *Long*, in evaluating the same general causation question as *McClain*, the court did not believe it was appropriate for it to dictate what peer-reviewed publications should be considered reliable or what conclusions should be drawn. *Id.* at *6. With each side presenting reasonable opinions based on the peer-reviewed literature, the court noted that this "case presents a classic battle of the experts." *Id.* In Delaware, the Superior Court takes its gatekeeping role seriously—a fact demonstrated by the well-developed record and comprehensive order entered by the Superior Court here—but that obligation stops short of putting on a lab coat. *See In re Asbestos Litig.*, 911 A.2d at 1210 ("An undergraduate political science degree coupled with a law degree, however, hardly qualifies the Court to undertake this exercise."); *Barrera*, 2019 WL 2331090, at *10.

* * *

Appellees respectfully request the Court not adopt the scientifically spurious new rule proposed by Appellants. The Superior Court did not abuse its discretion

in holding that the determination of a threshold dose is one non-dispositive consideration under *Daubert*. The Superior Court's ruling was neither arbitrary nor capricious. The ruling should be affirmed.

II. The Superior Court Correctly Considered Each Expert's Reliance on NDMA *and* Ranitidine Data in Assessing Admissibility

A. Question Presented

Whether the Superior Court abused its discretion in allowing Appellees' experts to consider both NDMA and ranitidine data in arriving at their causation opinions?

B. Scope of Review

The Superior Court's *Daubert* decision is reviewed for an abuse of discretion. *See supra* at 17.

C. Merits of Argument

Appellants state the Superior Court focused its *Daubert* analysis on NDMA and not ranitidine. Opening.Br.28. That is not true. The Superior Court expressly held that consideration of *both* NDMA *and* ranitidine data was important. *Zantac*, 2024 WL 2812168, at *10. Below, Appellants vigorously argued that all non-ranitidine NDMA data, i.e., animal, in vitro, and human dietary and occupational studies, should be disregarded. However, the Superior Court held that the wholesale disregard of an entire body of peer-reviewed literature on NDMA was inappropriate—especially when the cancer-causing agent in the case is NDMA. It was within this context that the Superior Court held that "[t]his 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." *Zantac*, 2024 WL 2812168, at *10. At no point did the Superior Court put special importance on NDMA data. Instead, the Superior Court focused its analysis on whether the Appellees' experts' consideration of that literature was methodologically reliable.

1. Consideration of the Cancer-Causing Agent, NDMA, Is Important in Assessing the Carcinogenicity of NDMA Exposure from Ranitidine

That NDMA *and* ranitidine data are considered in assessing whether NDMA exposure from ranitidine causes cancer is commonsense. NDMA is the cancer-causing agent at issue, and the route of exposure to that carcinogen is from ingesting ranitidine. This concept is illustrated by a simple example. Assume a community was exposed to NDMA from groundwater contaminated by a rubber factory. In assessing whether that NDMA exposure caused a person's cancer, it would be absurd to argue that the expert could only consider whether water causes cancer. Nobody claims uncontaminated water causes cancer; just as nobody claims uncontaminated ranitidine causes cancer. Rather, the expert would be well within her scientific purview to consider NDMA data generally, including data wherein people were exposed to NDMA from water and *other sources*.

Here, the analysis is the same. NDMA exposure, whether through occupational inhalation, food or water ingestion, intentional poisoning, or ingestion through contaminated medications, are all pieces of information that an expert can

and should consider before arriving at an opinion of whether NDMA exposure from ranitidine causes cancer. This is supported by independent scientists.

The peer-reviewed research that emerged following the revelation of NDMA in ranitidine specifically cites to and relies on NDMA data. In the Joung study about ranitidine, the researchers concluded that the follow-up time in their study "was not long enough to confirm the relationship between NDMA and cancer incidence" by relying on data from dietary NDMA studies. A-016751, A-016754. In the McGwin article, it discusses the mechanistic and epidemiological data for NDMA before reaching a conclusion that "NDMA contaminated ranitidine is associated with the occurrence of gastrointestinal cancer" in part because that conclusion "was bolstered by an abundance of evidence demonstrating that NDMA exposure is associated with an increased risk of cancer in humans as well as animals." A-016765. In the Wang study—another ranitidine epidemiological study—the authors state that their causation conclusions regarding the carcinogenicity of ranitidine are supported by dietary NDMA studies. A-016729. In the Kim S. ranitidine study on gastric cancer, the authors cite NDMA dietary studies and state "that the findings of various studies support the hypothesis that the consumption of … high levels of nitrosamines might be associated with an increased risk of upper gastrointestinal tract cancer." A-015887. In the You ranitidine study, the authors conclude that ranitidine findings are inconsistent, and

specifically note that "[d]ietary NDMA intake has been reported to be associated with an increased risk of gastrointestinal cancer, especially rectal cancer." A-011718. In nearly every ranitidine study after 2019, researchers specifically cite and rely on NDMA data.

Indeed, when the FDA pulled ranitidine off the market, it was in *response* to the presence of NDMA in ranitidine. The FDA specifically warned the public about NDMA in ranitidine. A-015133. The FDA did not address whether ranitidine, by itself, caused cancer. The FDA discussed the carcinogenicity of NDMA in ranitidine because the cancer-causing agent at issue *is NDMA*.

There are countless examples in the peer-reviewed literature of scientists discussing NDMA data in the context of considering ranitidine cancer risk—confirmation of the commonsense fact that consideration of NDMA *and* ranitidine data is appropriate in assessing whether NDMA exposure from ranitidine can cause cancer. The fact that independent scientists do what Appellees' experts did means, as a matter of law, the experts are not outside "the range where experts might reasonably differ[.]" *Kumho Tire*, 526 U.S. at 152-153.

2. Experts Can Rely on Data About the Underlying Cancer-Causing Agent in Contamination Cases

Remarkably, Appellants cite the *Asbestos Litigation* to *support* reversal, even though those opinions *clearly support* the Superior Court's ruling.

In the *Asbestos Litigation*, before the Honorable Joseph R. Slights, plaintiffs

alleged that exposure to chrysotile (a type of asbestos) from Chrysler's friction brake products caused various asbestos-related diseases. 911 A.2d at 1180. Plaintiffs argued that its experts could rely on raw chrysotile data, arguing that it was undisputed that the brake pads contained chrysotile, which is known to cause asbestos-related diseases. *Id.* Chrysler claimed that raw chrysotile data was not appropriate because it refined the chrysotile in a way that did not have biological activity once inhaled. *Id.* at 1182. The court agreed that if, in fact, the chrysotile found in Chrysler's brake pads was different than raw chrysotile, the data on raw chrysotile would not be helpful. *Id.* The court commented, however, that if the plaintiff could establish "that the chrysotile in friction products maintains its carcinogenic properties after the manufacturing process," then "the evidence of general causation with respect to chrysotile *becomes relevant to the question of general causation[.]*" *Id.* (emphasis added). After plaintiffs presented expert testimony that Chrysler's products released the same raw chrysotile, Judge Slights held that "plaintiffs' experts may rely upon this body of evidence to support their conclusions that exposure to friction products increases the risk of developing these diseases." *Id.* at 1204, 1202-1206.

The first case went to trial and the jury returned a plaintiff's verdict. *Grenier*, 981 A.2d at 526. On appeal, this Court held that Judge Slights incorrectly considered the record regarding the similarity of refined chrysotile in brake pads to

raw chrysotile and remanded the case to clarify the *Daubert* ruling. *Id.*

On remand, Judge Slights again denied the *Daubert* motions. *In re Asbestos Litig.*, 2009 WL 1034487, at *1 (Del. Super. Apr. 8, 2009), *aff'd sub nom. Grenier*, 981 A.2d at 531. The court observed that the epidemiology data dealing with refined chrysotile exposure was equivocal. *Id.* at *9. However, the epidemiology related to raw chrysotile was strong. *Id.* The court held that equivocal occupational epidemiology did not, as a matter of law, require exclusion under *Daubert* because the plaintiff could establish that use of friction products exposed people to raw chrysotile and that the refining process did not materially alter that chrysotile. *Id.* In face of competing experts, the Court reasoned, "it would not decide who was right and who was wrong in the dispute but would instead allow the parties to present their scientifically sound methodologies and conclusions to the jury for resolution." *Id.*

This Court *affirmed*, holding that it was appropriate for the experts to rely on raw chrysotile epidemiology to render general causation opinions about the chrysotile found in the friction brakes. *Grenier II*, 981 A.2d at 538. This Court also rejected Chrysler's argument that the plaintiff needed to prove causation with an epidemiological study linking friction brakes directly to cancer. *Id.* The Court explained, "there is no *a priori* requirement that an expert opinion be based on epidemiology in order to be admissible." *Id.* at 538-539.

The *Asbestos Litigation*, thus, provides a rule: in assessing whether a substance in a product causes cancer, an expert can rely on data about that cancer-causing agent if, in fact, the product exposes the user to that agent. And here, it is *undisputed* that the NDMA found in ranitidine is the *same* NDMA found in food, occupational settings (rubber factories), and other contaminated pharmaceutical products. It is also undisputed that all ranitidine degrades into NDMA. *See* A-015724 (GSK's root cause analysis confirming NDMA formation). Indeed, the FDA's recall of ranitidine was based on NDMA contamination. A-015133. Nobody has ever argued, much less suggested, that the NDMA found in ranitidine is somehow different than the NDMA found elsewhere—an NDMA molecule is an NDMA molecule. Unlike in the *Asbestos Litigation*, where there was a dispute about the type of asbestos in the product, there is no dispute here. Indeed, in Appellants' post-*Daubert* hearing brief, they *concede* that "the experts can ***consider*** NDMA epidemiology" and that "the 'agent' at issue is NDMA from ranitidine." A-024281–024282 (emphasis in original). Any suggestion that the NDMA in ranitidine is somehow different than the NDMA found in food, water, or air is unfounded. Thus, the Superior Court's holding that Appellees' experts could consider both NDMA and ranitidine science was neither arbitrary nor capricious.

* * *

The Superior Court held that it would allow Appellees' experts to consider

both NDMA and ranitidine data in rendering their general causation opinions. Appellants' assertion that the Superior Court somehow prioritized NDMA data over ranitidine data is not correct. The Superior Court's conclusion that both NDMA and ranitidine data could be considered did not constitute an abuse of discretion. It was neither arbitrary nor capricious because it was based on the undisputed fact that NDMA is found in ranitidine and that NDMA is the cancer-causing agent. The Superior Court's *Daubert* ruling should be affirmed.

III. The Superior Court Applied the Correct *Daubert* Standard

A. Question Presented

Whether the Superior Court applied the correct legal standard in reviewing the admissibility of Appellees' Experts' general causation opinions under *Daubert*?

B. Scope of Review

The Superior Court's *Daubert* decision is reviewed for an abuse of discretion. *See supra* at 17.

C. Merits of Argument

1. The Superior Court Correctly Applied the *Daubert* Standard in Reviewing the Admissibility of Appellees' General Causation Experts

The Superior Court carefully outlined its gatekeeping role under *Daubert*. *Zantac*, 2024 WL 2812168, at *4–10. The Superior Court correctly held that a *Daubert* analysis "may require trial courts to dive deeper into certain preliminary facts than had historically been the case" but cautioned that *Daubert* "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." *Zantac*, 2024 WL 2812168, at *4 (citing *In re Asbestos Litig.*, 911 A.2d at 1199). The Superior Court drew upon well-established Delaware jurisprudence that "[w]here 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 ensure that the jury is not misled or confused." *Id.*, at *5 (quoting *Bowen v. E.I. Du Pont De Nemours & Co.*, 2005 WL 1952859, at *8 (Del. Super. June 23, 2005), *aff'd sub nom. Bowen v. E.I. DuPont de Nemours & Co.*, 906 A.2d 787 (Del. 2006)). This fundamental deference to juries—subject, of course, to *Daubert* gatekeeping—is born of the *Daubert* decision itself: "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 evidence." *Daubert v. Merrell Dow Pharms., Inc.*, 509 U.S. 579, 596 (1993). The United States Supreme Court specifically recognized the liberal thrust favoring admissibility because the adversarial process was often best positioned to address admissible but shaky scientific opinions. *Id.* "*Daubert* emphasized that the filtering effect of the adversarial trial system should not be discounted." *In re Asbestos Litig.*, 911 A.2d at 1199. It is this fundamental tension between admission and gatekeeping—and the fundamental need for flexibility in applying this standard based on the facts of a specific case—*see McMullen*, 900 A.2d at 113—that gives rise to the considerable deference given to trial courts to exercise that discretion. *See Tumlinson*, 81 A.3d at 1270.

Appellants argue that the Superior Court's citation to a Ninth Circuit case describing *Daubert* as announcing a "liberal thrust favoring admissibility" was

wrong because that view of *Daubert* is an "outlier" perspective. Opening.Br.39–40. A search of the case law debunks that argument. The "liberal thrust" language is *from* the *Daubert* decision. *Daubert*, 509 U.S. at 588. And, it has been repeatedly recognized by courts throughout the country. *See, e.g.*, *Lauzon v. Senco Prod., Inc.*, 270 F.3d 681, 686 (8th Cir. 2001) (noting the liberal thrust of admissibility under *Daubert*); *Jahn v. Equine Servs., PSC*, 233 F.3d 382, 388 (6th Cir. 2000) ("Rule 702 displays a 'liberal thrust' with the 'general approach of relaxing the traditional barriers to 'opinion' testimony.'"); *United States v. Davis*, 40 F.3d 1069, 1073 (10th Cir. 1994) ("[T]he new standard adopts the 'liberal thrust' of the Federal Rules and their 'general approach of relaxing the traditional barriers to 'opinion' testimony[.]'"); *Pineda v. Ford Motor Co.*, 520 F.3d 237, 244 (3d Cir. 2008) ("This liberal policy of admissibility extends to the substantive as well as the formal qualifications of experts."); *Cavallo v. Star Enter.*, 100 F.3d 1150, 1158 (4th Cir. 1996) (noting the "liberalization" of expert testimony under *Daubert*); *Amorgianos v. Nat'l R.R. Passenger Corp.*, 303 F.3d 256, 267 (2d Cir. 2002) ("[A] bright-line requirement would be at odds with the liberal admissibility standards of the federal rules and the express teachings of *Daubert*."); *United States v. Brown*, 415 F.3d 1257, 1268 (11th Cir. 2005) (refusing to overturn trial court's Daubert ruling, citing the liberal admissibility of evidence under Daubert); *Ambrosini v. Labarraque*, 101 F.3d 129, 134 (D.C. Cir. 1996) ("[T]he threshold for

admissibility has been lowered … because of the liberal theory of admissibility adopted by the Federal Rules of Evidence[.]").

The Ninth Circuit also disclaims that it applies any different standard, which the Supreme Court did not disturb when it denied *certiorari*. *Hardeman v. Monsanto Co.*, 997 F.3d 941, 961 (9th Cir. 2021) *cert. denied*, 142 S. Ct. 2834 (2022). More importantly, this view is recognized by *Delaware* courts. *See, e.g.*, *Minner v. Am. Mortg. & Guar. Co.*, 791 A.2d 826, 841 (Del. Super. 2000) (noting liberal thrust of admissibility under *Daubert*); *Bowen*, 2005 WL 1952859, at *8 (close questions under *Daubert* fall toward admissibility). The Superior Court applied the correct legal standard under *Daubert* and did so in a cautious and thoughtful way.

2. After Finding Each Expert's Opinion Methodologically Reliable and Reasonable under *Daubert*, the Superior Court Was Right to Leave Challenges to the "Correctness" of Those Opinions to the Jury

"It is a given that there will be disagreement among reasonable scientists about which evidence to emphasize in cases where the evidence does not point unequivocally toward a particular conclusion." *In re Roundup Prods. Liab. Litig.*, 390 F. Supp. 3d 1102, 1130 (N.D. Cal. 2018). This is because "the methods used by an [expert] to form an opinion as to causation substantially rely on the expert's judgment in selecting and weighing her sources." *Tumlinson*, 2013 WL 7084888, at *6. *Daubert* does not prescribe a specific weight that evidence should be given.

Indeed, it is not the court's role to weigh evidence, second guess independent researchers, or pass judgment on substantive scientific issues. *Barrera.*, 2019 WL 2331090, at *10. Complex scientific matters are appropriately left to experts: "the courtroom is not intended to be a scientific laboratory and the 'judge is not a scientist.'" *Id.* (quoting *In re Asbestos Litig.*, 900 A.2d at 145). "Judges, both trial and appellate, have no special competence to resolve the complex and refractory causal issues raised by the attempt to link low level exposure to toxic chemicals with human disease." *In re Asbestos Litig.*, 900 A.2d at 1152 (quoting *Ferebee v. Chevron Chem. Co.*, 736 F.2d 1529, 1534 (D.C. Cir. 1984)).

Within these constraints, the Superior Court systematically reviewed the opinions offered by each of Appellees' experts, the materials considered, the methodology used, and whether their approach was reasonable and reliable under *Daubert*. *Zantac*, 2024 WL 2812168, at *14–17 (Dr. Jameson), *18–20 (Dr. Neugut), *20–21 (Dr. Rustgi), *21–22 (Dr Hatzaras), *22–23 (Dr. Raz), *23–25 (Dr. Leone), *26–28 (Dr. Margulis), *28–29 (Dr. Miller), and *29–30 (Dr. Trock). For *each* expert, the Superior Court held that the expert's methodology had a reliable scientific basis, relegating Appellants' "weight" challenges, credibility challenges based on "cherry-picking" or "results-driven" opinions, to the fact finder. *Id.* In other words, the Superior Court diligently and carefully performed its gatekeeping responsibility under *Daubert*.

Appellants take issue with the Superior Court's analysis, claiming that it "did not consider most of the flaws Defendants identified in the experts' methodologies[.]" Opening.Br.40. This is not true. Most of the purported "flaws" identified by Appellants are simply their view of "better" science. Take, for example, the accusation of "cherry-picking" or being "results-driven." Appellees' experts considered and reviewed all the literature and available data. *See* A-016908–A-016945 (Dr. Neugut); A-022220–A-022285 (Dr. Hatzaras); A-017206–A-017245 (Dr. Rustgi); A-019599–A-019708 (Dr. Trock); A-019958–A-020022 (Dr. Miller); A-019437–A-019512 (Dr. Raz); A-020120–A-020176 (Dr. Leone); A-000857–A-000947 (Dr. Margulis). They considered the strengths and weaknesses of each study. Then, applying the Bradford Hill factors, each expert worked through whether the association between NDMA exposure in ranitidine and a specific cancer was causal. Using scientific judgment, they explained their thinking on each of the Bradford Hill considerations, the data supporting their opinions, and after balancing all the information, rendered an ultimate "more likely than not" causation opinion.

Appellants believe that certain studies and certain results were superior and more "reliable." And, they claim that because Appellees' experts did not similarly weigh Appellants' preferred studies and results, that means Appellees' experts were surely "results-driven" and "cherry picked" the data. In other words, Appellants

take an earnest scientific disagreement about how to interpret data and elevate it to a "methodological flaw" simply because Appellants have a different view of the science. Judges, who are not scientists, are not equipped to resolve which view of science is correct. Provided that the differing views are based on *reliable methodologies* and data, the truth should be discerned through the crucible of the adversarial process. It is, as the Superior Court noted repeatedly, a "classic battle of the experts." *Zantac*, 2024 WL 2812168, at *17, 21, 22.

Can cherry-picking cross the line from legitimate scientific dispute to unreliable methodology? Of course it can. But figuring out where that line is, and whether a criticism of "cherry picking" is really a credibility attack versus a methodological challenge, is the job of the trial court in the first instance. Here, the Superior Court exercised that discretion appropriately. For example, Appellants accuse Dr. Neugut of being "results-oriented," using "cherry picked" data, engaging in "outcome driven reasoning," and being "contradict[ed] by his prior [deposition] testimony." *Zantac*, 2024 WL 2812168, at *20. But, in considering these attacks, the Superior Court "spent considerable effort in considering Dr. Neugut's opinion and Delaware's jurisprudence" and concluded that "[t]hese criticisms attack the expert's credibility, the bases and calculations underlying his opinion, or seek to elevate Defendants' science over that of Dr. Neugut." *Id.* None of these, according to the Superior Court, constituted valid

Daubert challenges. The Superior Court considered and rejected the Appellants' attacks, and held Dr. Neugut's methodology and opinions were sufficiently reliable to pass muster under *Daubert*. *Id.* Appellants' claims of "cherry picking" were not *methodological* challenges; they were partisan attacks on credibility, which was the proper domain of the factfinder. In reaching that decision, the Superior Court was neither arbitrary nor capricious. Thus, there was no abuse of discretion.

* * *

The Superior Court applied the correct legal standard, drawing upon a deep well of Delaware jurisprudence. After considering over 1,000 pages of briefing, over 20,000 pages of exhibits, and three days of argument, the Superior Court carefully detailed its *Daubert* analysis in a 102-page order. In so doing, the Superior Court considered the numerous challenges posed by Appellants and exercised its discretion in determining which "criticisms" concerned methodological challenges under *Daubert* and which "criticisms" constituted scientific disagreements. In drawing those lines, the Superior Court did not act in an arbitrary or capricious manner and, thus, did not abuse its discretion.

CONCLUSION

The decision below should be affirmed.

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Respectfully submitted,

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IN THE SUPREME COURT OF THE STATE OF DELAWARE

No. 255, 2024

IN RE ZANTAC (RANITIDINE) LITIGATION

CASE BELOW:

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

CERTIFICATE OF COMPLIANCE

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