UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

IN RE: VALSARTAN, LOSARTAN, AND IRBESARTAN PRODUCTS LIABILITY LITIGATION **This Document Relates to All Actions**	MDL No. 2875 Honorable Robert B. Kugler, District Court Judge Oral Argument Requested

NOTICE OF MOTION FOR RECONSIDERATION OR, IN THE ALTERNATIVE, TO CERTIFY THIS MATTER FOR INTERLOCUTORY APPEAL

PLEASE TAKE NOTICE that on January 16, 2023, or as soon thereafter as counsel may be heard, the undersigned Defendants' counsel, on behalf of all Defendants named below, shall move for an entry of Order reconsidering the Court's denial of Defendants' motions to exclude Plaintiffs' experts' general causation opinions, or, in the alternative, to certify this issue for interlocutory appeal.

PLEASE TAKE FURTHER NOTICE that in support of their motion, the undersigned Defendants shall rely upon the Memorandum of Law in Support submitted herewith, and any reply submissions made hereafter; and

PLEASE TAKE FURTHER NOTICE that a proposed Order is submitted herewith; and

PLEASE TAKE FURTHER NOTICE that oral argument is requested.

Dated: December 20, 2022

Respectfully submitted,

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CERTIFICATE OF SERVICE

I HEREBY CERTIFY that on December 20, 2022, I electronically filed the foregoing with the Clerk of the Court by using the CM/ECF system, which will send a notice of electronic filing to all CM/ECF participants in this matter.

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UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY
CAMDEN VICINAGE

IN RE: VALSARTAN, LOSARTAN, AND IRBESARTAN PRODUCTS LIABILITY LITIGATION **This Document Relates to All Actions**	MDL No. 2875 Honorable Robert B. Kugler, District Court Judge **ORAL ARGUMENT REQUESTED**

DEFENDANTS' MEMORANDUM OF LAW IN SUPPORT OF MOTION FOR RECONSIDERATION OR, IN THE ALTERNATIVE, TO CERTIFY THIS MATTER FOR INTERLOCUTORY APPEAL

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Plaintiffs' claims in this litigation all rest on a central premise that no scientist outside of litigation embraces: that trace amounts of N-nitrosodimethylamine ("NDMA") and/or N-nitrosodiethylamine ("NDEA") in medication can cause human cancer. Because Plaintiffs' general causation theory lacks scientific support, Defendants moved to exclude the experts who espoused it. The motions were largely denied. (*See Daubert* Hr'g Order 1 Regarding Parties' Mots. to Preclude Test. By Expert Witnesses at 1, Mar. 4, 2022, ECF No. 1958 ("*Daubert* Order").)

Two weeks ago, another court reached the opposite conclusion on the same issue, effectively ending another multidistrict litigation ("MDL"). In the *Zantac* MDL proceeding, the court excluded as unreliable general causation opinions that are indistinguishable from those presented here, based on the same sources and methods—and in one instance, even the same expert. *See In re Zantac (Ranitidine) Prods. Liab. Litig.*, MDL No. 2924, 2022 U.S. Dist. LEXIS 220327 (S.D. Fla. Dec. 6, 2022).

Defendants now move the Court to reconsider its prior rulings.[1] The *Zantac* ruling, which spans 341 pages, highlights the fundamental flaws in the theory that medications containing trace amounts of NDMA are linked to human cancer. The

[1] In the alternative to reconsideration, Defendants renew their *Daubert* motions and ask the Court to consider the intervening *Zantac* opinion and recent relevant literature.

ruling is detailed and compelling, and it amply supports reconsideration and exclusion of Plaintiffs' general causation experts. Moreover, following this Court's ruling, the science has continued to evolve. Some of the key literature addressing medication containing NDMA or NDEA was published after expert reports in this case were written and exchanged—and in one instance after the *Daubert* Order; thus, the Court has not yet had had the opportunity to fully consider it.

Alternatively, Defendants respectfully submit that the *Zantac* ruling supports certification of the Court's *Daubert* rulings for interlocutory review under 28 U.S.C. § 1292(b). The 1292(b) standard is easily met because: (1) a comparison of the *Zantac* ruling and this Court's contrary ruling plainly illustrates that there are substantial grounds for a difference of opinion on whether Plaintiffs' experts' general causation opinions are reliable despite the absence of supportive epidemiologic evidence; and (2) reliability is a controlling, central question of law in every case in the litigation, and immediate appeal could "materially advance" the "ultimate termination" of the 1,000+ cases in this MDL proceeding.

BACKGROUND

General causation—i.e., whether NDMA or NDEA at the levels allegedly contained in valsartan-containing drugs ("VCDs") can cause certain human cancers—is a controlling question in this litigation. Because the general causation

question is central to every case in the MDL proceeding, whether sounding in personal injury, medical monitoring or economic loss, the Court set a schedule that prioritized resolution of that issue. (*See* Rev. Case Mgmt. Order No. 22, Jan. 11, 2021, ECF No. 726.)

1. Plaintiffs' Experts And The Court's *Daubert* Ruling. Plaintiffs disclosed five general causation experts: Drs. Stephen Hecht, Ph.D., David Madigan, Ph.D., Dipak Panigrahy, M.D., Mahyar Etminan, MSc, and Stephen Lagana, M.D. Due to the lack of epidemiological evidence supporting their theories, Plaintiffs' experts relied upon studies involving dietary and occupational exposure to nitrosamines contained in food and air. (*See, e.g.*, Report of Stephen S. Hecht, Ph.D. at 14 (July 6, 2021), ECF No. 1714-3 ("Hecht Rep."); Report of David Madigan, Ph.D. at 3-10, ECF No. 1715-4 ("Madigan Rep."); Rule 26 Expert Report of Dipak Panigrahy, M.D. at 96-97, 111, 120, 129-30, 133-34, 137 (July, 6, 2021), ECF No. 1716-3 ("Panigrahy Rep."); Report of Mahyar Etminan, MSc at 14-24 (July 6, 2021), ECF No. 1717-3 ("Etminan Rep."); Report of Stephen Lagana, M.D. at 12-16 (July 26, 2021), ECF No. 1718-4 ("Lagana Rep.").) Plaintiffs' experts also relied heavily on secondary sources of evidence such as animal research (*see, e.g.*, Hecht Rep. at 7-10; Panigrahy Rep. at 35-37), cherry-picked data from studies that rejected their conclusions (*see, e.g.*, Hecht Rep. at 16) and regulatory standards, such as those set by the Food and Drug Administration

("FDA") (Hecht Rep. at 16-18, 23; Panigrahy Rep. at 11-12, 148-49; Lagana Rep. at 4, 27-28). Finally, because they could not identify a threshold dose, some of Plaintiffs' experts have adopted an unscientific any-exposure theory—i.e., a theory that a single exposure to NDMA or NDEA can cause cancer. (*See, e.g.*, Panigrahy Rep. at 83-85; Dep. of Stephen Hecht, Ph.D. 369:9-9-23 (Aug. 17, 2021), ECF No. 1714-16.)

Defendants moved to exclude these experts, arguing that their methods (ignoring the applicable body of literature, relying on animal studies, cherry-picking, resorting to an unsupported any-exposure theory, and treatment of regulatory standards as though they were indicative of a causal threshold) were unreliable. Defendants explained that the totality of the epidemiological evidence tends to disprove an association[2] between medications containing nitrosamine impurities—i.e., valsartan and Zantac—and cancer, and there is no support in the scientific literature for a causal connection. The Court denied the motions in primary part, concluding that "[t]he jury is going to have to determine which of

[2] The only epidemiological studies that have specifically assessed whether there is an association between users of affected VCDs and cancer both found no association. *See, e.g.*, Willy Gomm, et al., *N-Nitrosodimethylamine-Contaminated Valsartan And The Risk of Cancer*, 118 Deutcsches Arzteblatt 357 (2021); Anton Pottegård, et al., *Use of N-nitrosodimethylamine (NDMA) Contaminated Valsartan Products and Risk Of Cancer: Danish Nationwide Cohort Study*, 362 BJM k3851 (2018).

these studies they think are important and which are not." (Mar. 2, 2022 Hr'g Tr. 151:4-6; *see also Daubert* Order at 2.)

2. The *Daubert* Ruling In *Zantac*. On December 6, a court in the Southern District of Florida overseeing a large MDL proceeding encompassing thousands of cases looked at largely the same evidence and reached the opposite conclusion. The *Zantac* litigation involves allegations that the active pharmaceutical ingredient in that medication—ranitidine—has the potential to degrade into NDMA. The question at general causation—like the question here—was whether the scientific evidence reliably demonstrates that NDMA from ranitidine is capable of causing cancer at the highest level of exposure a plaintiff might have experienced. To address this question, Plaintiffs put forward a series of experts—including Dr. Panigrahy, who is familiar to this Court—to testify that the NDMA in ranitidine could cause five of the same cancers at issue here: bladder, esophageal, gastric, liver and pancreatic. In a 341-page order, the court excluded all of the experts' opinions and "carefully explain[ed] each reason why Plaintiffs' experts ha[d] utilized unreliable methodologies." *Zantac*, 2022 U.S. Dist. LEXIS 220327, at *162.

ARGUMENT

I. THE COURT SHOULD RECONSIDER ITS PREVIOUS ORDER IN LIGHT OF THE *ZANTAC* RULING.

Defendants respectfully submit that the Court should reconsider its general causation *Daubert* rulings in light of the *Zantac* court's thorough ruling that reached the opposite conclusion. The *Zantac* court's compelling analysis of several fatal flaws in the same methods employed by the experts here raises critical questions not addressed in this Court's *Daubert* order. Reconsideration of that order is necessary to promote uniformity in the law and prevent the manifest injustice that would result from treating similarly situated parties differently and subjecting Defendants to continued litigation that the *Zantac* ruling makes clear should come to an end.

An interlocutory order "may be revised at any time before the entry of a [final] judgment." Fed. R. Civ. P. 54(b).[3] A court may reconsider a prior order

[3] Defendants acknowledge that in many cases, Local Rule 7.1(i) limits the time to file for reconsideration. However, this motion seeks reconsideration of an interlocutory order and thus arises under Rule 54(b) rather than Rule 59 or 60. Because "Rule 54(b) expressly permits a motion to be filed at any time," the time limits of Local Rule 7.1(i) do not apply. *See Harding v. Jacoby & Meyers, LLP*, No. 14-5419, 15-6559, 2021 WL 2472323, at *1 (D.N.J. June 16, 2021). And courts in this district have reconsidered orders under Rule 54(b) as much as two years later. *See, e.g.*, *Ownbey v. Aker Kvaerner Pharms. Inc*., No. 2:07-cv-2190 (KSH) (CLW), 2017 WL 3872377, at *4 (D.N.J. Sept. 1, 2017) (reconsidering order from September 2015). This makes sense because any other reading of Local Rule 7.1(i) would effectively abrogate Rule 54(b) and make it impossible to *(cont'd)*

where "(1) new evidence is available; (2) a supervening new law has been announced; or (3) the earlier decision was clearly erroneous and would create manifest injustice." *Ownbey*, 2017 WL 3872377, at *4 (finding a previous order "clearly erroneous and would create manifest injustice" (citation omitted)). This list is not exhaustive; "[r]econsideration of interlocutory orders . . . 'may be had even if the movant cannot show an intervening change in controlling law, the availability of new evidence that was not available when the court issued the underlying order, or the "need to correct a clear error of law or fact or to prevent manifest injustice."'" *Nyamekye v. Mitsubishi Elec. Power Prods., Inc.*, No. 17-852, 2018 WL 3933504, at *3 (W.D. Pa. Aug. 16, 2018) (citation omitted). "[T]he court may permit reconsideration whenever consonant with justice to do so." *Id.* (alteration in original) (citation omitted).[4]

Reconsideration is appropriate here because the *Zantac* order highlights five fundamental flaws in Plaintiffs' experts' causation opinions that render them inadmissible under Rule 702 and *Daubert*: (1) their reliance on regulatory

seek reconsideration based on new law or new evidence, which almost never arise within two weeks of an interlocutory order.

[4] While the *Zantac* ruling is not controlling authority, courts can consider persuasive decisions (including unpublished ones) from other circuits. *See, e.g.*, *City of Newark v. U.S. Dep't of Labor*, 2 F.3d 31, 33 n.3 (3d Cir. 1993) (noting that "[a]lthough we recognize that this unpublished opinion [from another circuit] lacks precedential authority, we nonetheless consider persuasive its evaluation of a factual scenario virtually identical to the one before us in this case").

standards; (2) their focus on NDMA (and to a lesser degree NDEA) rather than VCDs as a whole; (3) their reliance on occupational and dietary studies; (4) their any-exposure assumption; and (5) their reliance on animal studies.

A. Plaintiffs' Experts' Reliance On Regulatory Standards Merits Reconsideration.

Plaintiffs' experts make much of the fact that the FDA and its analogue in the European Union, the European Medicines Agency ("EMA"), establish limits for the permissible levels of NDMA in medication, and some batches of VCDs exceeded that level. (*See* Hecht Rep. at 16-18; Panigrahy Rep. at 148-49; Etminan Rep. at 7; Lagana Rep. at 4.) The Court appeared persuaded by this argument, noting that "numerous government agencies found that these substances are probably carcinogenic." (Mar. 2, 2022 Hr'g Tr. 156:16-17; *see id.* 142:7-10 (association established "through all the action by the government agencies").)

But such regulatory pronouncements cannot support a general causation theory in a tort case. *Zantac*, too, involved a medication that had been recalled by the FDA, and the *Zantac* court acknowledged that "at first blush it may appear surprising" to exclude the plaintiffs' general causation experts in that case "notwithstanding the FDA's . . . recall." 2022 U.S. Dist. LEXIS 220327, at *161. But the *Zantac* court went on to explain that a regulator like the FDA or EMA has a fundamentally different job from a judge or jury in a product liability action. Regulators "choose to err on the side of caution" and therefore "will remove drugs

from the marketplace upon a lesser showing of harm to the public than the preponderance-of-the-evidence . . . standard used to assess tort liability." *Id.* at *668-69 (quoting *McClain v. Metabolife Int'l, Inc.*, 401 F.3d 1233, 1250 (11th Cir. 2005)). Put another way: regulatory agencies "build in considerable cushion . . . to . . . prophylactically protect the public'" and make "a number of protective, often 'worst-case' assumptions." *Id.* at *667-68 (first quoting *Williams v. Mosaic Fertilizer, LLC*, 889 F.3d 1239, 1246-47 (11th Cir. 2018); and then quoting *In re Denture Cream Prods. Liab. Litig.*, No. 09-2015-MD-ALTONAGA, 2015 WL 392021, at *29 (S.D. Fla. Jan. 28, 2015)). Regulatory standards are thus "simply incompatible" with the standard of proof that Plaintiffs bear in establishing causation in this case. *Id.* at *669.

Many courts around the country have recognized this distinction. *See, e.g.*, *Glastetter v. Novartis Pharms. Corp.*, 252 F.3d 986, 991 (8th Cir. 2001) (stating same distinction between regulatory and tort standards because regulators use a "preventive perspective . . . in order to reduce public exposure to [potentially] harmful substances" (quoting *Hollander v. Sandoz Pharms. Corp.*, 95 F. Supp. 2d 1230, 1234 n.9 (W.D. Okla. 2000))); *In re Zicam Cold Remedy Mktg., Sales Pracs. & Prods. Liab. Litig.*, No. 09-md-2096-PHX-FJM, 2011 WL 798898, at *10-11 (D. Ariz. Feb. 24, 2011) (excluding expert to the extent he relied on FDA reports as evidence of causation).

The facts of this case strikingly illustrate the distinction between tort law and the precautionary principle that underlies regulatory decisions. The *Zantac* court found that exposure to NDMA at or slightly above the FDA maximum has only been tied "to an infinitesimal, unprovable risk of cancer." 2022 U.S. Dist. LEXIS 220327, at *161; *see id.* at *207 (if NDMA at the FDA limit "were taken every day for 70 years" it would "result in an infinitesimal, unobservable risk of cancer of .001%"—i.e., one in one-hundred thousand). The FDA itself has acknowledged as much and "cautioned against" using its daily limits "as a 'realistic indication of actual risk.'" *Id.* at *668 (citing FDA Ctr. for Biologics Evaluation & Rsch., *M7(R1) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk* 5-6 (2018)). Moreover, the FDA has recognized the conservative nature of its standards by repeatedly allowing the distribution of medication with nitrosamine impurities exceeding the regulatory threshold to prevent drug shortages (including in circumstances after this Court issued its *Daubert* ruling). *See* FDA Works To Avoid Shortage Of Sitagliptin Following Detection Of Nitrosamine Impurity, https://www.fda.gov/drugs/drug-safety-and-availability/fda-works-avoid-shortage-sitagliptin-following-detection-nitrosamine-impurity (Aug. 9, 2022) (temporarily allowing distribution of a medication with nitrosamine levels "above the acceptable intake limit" and

"determin[ing] that it presents minimal additional cancer risk").[5] This alone is reason to reconsider the Court's prior order.

B. Plaintiffs' Experts' Focus On NDMA And NDEA, Rather Than Medication As A Whole Merits Reconsideration.

As in *Zantac*, Plaintiffs' experts in this litigation also failed to apply a reliable methodology because they focused on whether NDMA and NDEA can cause cancer ***in the abstract*** rather than whether ***VCDs*** with NDMA/NDEA impurities can cause cancer.

As the *Zantac* court emphasized, "the general causation question" must be "framed" around "the product the Plaintiffs consumed"—in that case, a medication called ranitidine sold under the brand name Zantac—rather than "the mechanistic theory by which Plaintiffs seek to prove their case." 2022 U.S. Dist. LEXIS 220327, at *199. "[R]anitidine is not simply *interchangeable* with NDMA," and

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[5] *See also* FDA Statement On The Agency's List Of Known Nitrosamine-Free Valsartan & ARB Class Medicines, As Part Of Agency's Ongoing Efforts To Resolve Ongoing Safety Issue, https://www.fda.gov/news-events/press-announcements/fda-statement-agencys-list-known-nitrosamine-free-valsartan-and-arb-class-medicines-part-agencys (Apr. 4, 2019) (allowing distribution of "losartan that contain[s] impurities above the interim acceptable intake limit" as it will "not have a meaningful increased risk for cancer"); FDA Updates & Press Announcements On Nitrosamine In Varenicline (Chantix), https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-and-press-announcements-nitrosamine-varenicline-chantix (July 16, 2021) (allowing distribution of medication with nitrosamine levels "above FDA's acceptable intake limit" as "it presents minimal additional cancer risk"). In addition, as Defendants have noted in earlier briefing, the FDA instructed users to continue taking the VCDs at issue in this case given the minimal cancer risk.

"there is no widespread acceptance that **ranitidine** causes cancer." *Id.* at *429; *see also id.* at *491 ("unpersuasive" to rely heavily on studies that "focused on NDMA" rather than "focus[ed] on ranitidine"). This distinction matters because "while an apple may simply be compared to another apple, for an apple to be compared to an orange the comparison must be accompanied with an explanation." *Id.* at *429.

The same is true here. Plaintiffs must prove that ***VCDs*** with NDMA and NDEA impurities can cause cancer, not that NDMA and NDEA are carcinogenic as a ***general*** matter. Yet, their experts spend essentially no time on that topic. For instance, Dr, Etminan titled her report "Risk of Cancer with Exposure to NDMA" (*see* Etminan Rep.), while Dr. Lagana opines that "NDMA causes cancer by various mechanisms" (Lagana Rep. at 5). This fundamental flaw leads to many of the additional errors discussed in greater detail below—in particular, reliance on studies involving other forms of exposure or on animals dosed with enormous amounts of pure NDMA.

C. Plaintiffs' Experts' Reliance On Occupational And Dietary Studies Merits Reconsideration.

The *Zantac* court also provided a detailed analysis of why the plaintiffs' experts' reliance on studies involving occupational NDMA exposure in a rubber factory and through food (predominately meat) did not satisfy *Daubert*. Notably,

the dietary and occupational studies upon which Plaintiffs' experts rely are nearly identical in both litigations.

The experts in both *Zantac* and in this case (including Dr. Panigrahy whose opinions were excluded by the *Zantac* court) rely heavily on work by Mira Hidajat and colleagues on rubber factory workers. (*See, e.g.*, Hecht Rep. at 11; Panigrahy Rep.; Etminan Rep. at 14-15 (all citing Mira Hidajat, et al., *Lifetime Exposure To Rubber Dusts, Fumes & N-Nitrosamines & Cancer Mortality In A Cohort Of British Rubber Workers With 49 Years Of Follow-Up*, 76 J. Occupational & Env'tl Med. 250 (2019)).) That study was not designed "to answer the question at issue in this MDL" and does not provide a reliable basis for general causation opinions here for a host of reasons. *Zantac*, 2022 U.S. Dist. LEXIS 220327, at *488. In fact, "the number of assumptions and estimations necessary to render this study helpful to a jury are staggering." *Id.* at *487.

As an initial matter, "[r]ubber creation leads to the formation of many different types of carcinogens" in the workplace, and working with rubber is a "Group 1"—i.e., known—carcinogen, according to the International Agency for Research on Cancer. *See id.*at *482; *see also id.* at *161 ("rubber factory fumes . . . contain many carcinogens in addition to NDMA"). Thus, it impossible to isolate the effect, if any, of NDMA specifically in that occupational environment. In addition, routes of exposure matter and "often affect health

outcomes." *Id.* at *499 (citing Fed. Jud. Ctr., *Reference Manual on Scientific Evidence* at 518 (3d ed. 2011)). Rubber workers were exposed through fumes and skin exposure, not through taking medication orally. Thus, for the study to have relevance to the litigation, the testifying expert would have to "testify . . . that the inhaled and absorbed fumes from a 1967 rubber factory may be reliably converted into an ingested dose of" medication. *Id.* at *490. But, as the *Zantac* court explained, the study author herself has declined to say "whether inhalation or skin absorption of NDMA" at a rubber factory "is analogous to NDMA exposure via oral medication." *Id.* at *489. And an expert must not "exceed the limitations the authors themselves place on the study." *Id.* (quoting *In re Accutane Prods. Liab.*, 511 F. Supp. 2d 1288, 1291 (M.D. Fla. 2007)).

Finally, the study was flawed even on its own terms because "[d]ata on the workers' NDMA exposure" did not exist, and data on the workers' employment history were sparse. *See id.*at *483. As a result, the researchers had to make a host of speculative assumptions about both issues, assuming that "each worker stayed in the same department until they reached 70 years of age" and then "estimat[ing] each worker's level of NDMA exposure based upon the location and duties of the workers' department." *Id.* In addition, "[w]hether any worker had, after 1967, been exposed to a non-NDMA carcinogen or otherwise had some predilection for cancer was unknown to the researchers." *Id.* at *484. Thus, any expert that relies

on the study would need some way to "weigh[it] in conjunction with assumptions about how long a worker worked, where they worked, and what they were exposed to," which Plaintiffs' experts do not offer. *Id.* at *490. In sum, "with assumption piled upon assumption, estimation piled upon estimation, and with route-of-exposure conversions being necessary . . . the analytical leap from the Hidajat data to the operative inquiry in this MDL is simply too great." *Id.* at *490-91.

Plaintiffs' experts' reliance on dietary studies (*see, e.g.*, Panigrahy Rep. at 96, 106, 116, 120-21, 137; Etminan Rep. at 15-24; Lagana Rep. at 4, 12-16) is similarly unreliable. As the *Zantac* court explained, because meat is an NDMA-rich food, this literature "is really, for all intents and purposes, epidemiology on high levels of meat consumption." *Zantac*, 2022 U.S. Dist. LEXIS 220327, at *485-86. The studies tended to show an association between dietary NDMA and cancer, although the results were frequently statistically insignificant. Importantly, as with rubber, meat (especially processed meat) includes a host of potentially toxic or carcinogenic chemicals beyond NDMA, not to mention high levels of fat and (if processed) salt, and is itself a known carcinogen. *Id*. In addition, many of the dietary studies only asked respondents what they had eaten in a particular week, which says nothing about their diets over the course of a lifetime. And those studies that did ask about lifetime consumption were retrospective, and thus suffer serious risks of recall bias because "people struggle to accurately remember what

they have eaten the prior day, let alone what they have eaten throughout the entire course of their lifetime." *Id.* at *161; *see id.* at *474-75 ("Cancer victims can struggle to remember what their diets were over the course of their lifetime and thus accurately estimate the volume of the unhealthy foods that they ate.").

Given these realities, the *Zantac* court identified ***seven*** analytical leaps that an expert had to take to render diet studies relevant: (1) assuming the accuracy of a subject's memory about what they have eaten; (2) assuming never-changing eating habits (since many of the studies only asked about current dietary habits rather than past or future ones); (3) assuming average NDMA values in food; (4) accounting for other carcinogens in food; (5) accounting for confounders like smoking; (6) accounting for random chance (given statistically insignificant results); and (7) comparing diet to medication. *Id.* at *486. Taken together, this is a "leap too far." *Id.*

Reliance on these studies is particularly unreliable when the carcinogenic risks of VCDs containing NDMA and NDEA have been studied directly. *See* Willy Gomm, et al., *N-Nitrosodimethylamine-Contaminated Valsartan And The Risk of Cancer*, 118 Deutcsches Arzteblatt 357 7 (2021); Anton Pottegård, et al., *Use of N-nitrosodimethylamine (NDMA) Contaminated Valsartan Products and Risk Of Cancer: Danish Nationwide Cohort Study*, 362 BJM k3851 (2018). In addition, 11 other studies have investigated ranitidine containing NDMA, which is

a closer analogue to the VCDs in this litigation than food or factory work. *See Zantac*, 2022 U.S. Dist. LEXIS 220327, at *414-428 (summarizing studies). Notably, much of the literature on medication containing nitrosamines was published after expert reports in this case were written and exchanged—and in one case after the *Daubert* Order; thus, the Court has not yet had the opportunity to fully consider it. In light of that fact, and given the serious flaws that the *Zantac* court highlighted, Defendants request that this Court reconsider whether Plaintiffs have established the reliability of the indistinguishable expert opinions offered here.

Finally, insofar as the vast body of scientific literature studying the possible association between NDMA and human cancer is insufficient to prove a valid causal link, the scant evidence of causation between NDEA and cancer that Plaintiffs have presented must be rejected. As the Court is aware, Plaintiffs rely almost exclusively on a single dietary study, the Zheng paper, to establish causation with respect to NDEA and pancreatic cancer—the only type of cancer left at issue with regard to NDEA (*see Daubert* Order at 1). A single study, however, is never sufficient to prove general causation. *See In re Zoloft (Sertraline Hydrocloride) Prods. Liab. Litig.*, No. 12-md-2342, 2015 WL 7776911, at *3 (E.D. Pa. Dec. 2, 2015) ("Even where the confidence interval is narrow and the increased risk is statistically significant, scientists will not draw firm conclusions

from a single study, as apparent associations may reflect random error, bias, confounding, or some weakness in the study design, or they may be incongruous with existing scientific knowledge about biological mechanisms."), *aff'd*, 858 F.3d 787 (3d Cir. 2017). Moreover, the Zheng study is not entitled to significant weight due to the many limitations on dietary studies identified by the *Zantac* court. Indeed, the authors of the Zheng study cautioned that their paper should not be interpreted as establishing a causal link between NDEA and pancreatic cancer, stating: "Although some of our findings probably reflect reverse causation bias due to lower meat intake in cases with latent disease, biologically plausible findings for pancreatic carcinogens, NDEA and NDMA, warrant further prospective investigation." As the *Zantac* court recognized, courts should be skeptical of any expert who purports to offer conclusions the authors themselves could not reach, as this demonstrates that the expert's conclusions are not generally accepted. *See Zantac*, 2022 U.S. Dist. LEXIS 220327, at *489; *see also In re Accutane Prods. Liab.*, 511 F. Supp. 2d at 1291 (instructing that an expert "must not exceed the limitations the authors themselves place on the study"); *In re Denture Cream Prods. Liab. Litig.*, 795 F. Supp. 2d 1345, 1362 (S.D. Fla. 2011) ("Because the [study authors] themselves do not conclude [that] there is a causal relationship . . . it is inappropriate for Plaintiffs' experts to draw that conclusion for them."). For these reasons, Plaintiffs' experts' sole reliance on the Zheng study to conclude that

there is a causal relationship between trace levels of NDEA in valsartan and pancreatic cancer demonstrates that their methodology is fatally flawed and cannot be helpful to the jury under Rule 702.

D. Plaintiffs' Experts' Reliance On Animal Models Merits Reconsideration.

Like the *Zantac* experts, Plaintiffs' experts in this case also rely heavily on animal research. (*See, e.g.*, Hecht Rep. at 7-10; Panigrahy Rep. at 21-24, 48-52, 55-57, 63-67, 80-86; Lagana Rep. at 32.) Once again, the *Zantac* court rejected those studies as a reliable basis for an opinion on general causation. As the *Zantac* court explained, animal studies (much like in vitro studies) constitute "secondary evidence" that "cannot alone prove general causation," 2022 U.S. Dist. LEXIS 220327, at *398, but they can serve "as [a] confirmatory piece[] of the totality of the evidence," *id.* (quoting *In re Seroquel Prods. Liab. Litig.*, No. 6:06-MD-1769-ORL-22D, 2009 WL 3806435 (M.D. Fla. June 23, 2009)).[6] And even in that limited role, an expert must account for, among other things, "interspecies variability in the bioavailability of NDMA" and "how [to] reliably extrapolate from the dosage of NDMA administered in animals to the dosage consumed by Plaintiffs via" medication. *Id.* at *642-60. The court rejected as woefully

[6] Given the lack of reliable epidemiological evidence for the plaintiffs' theory, the *Zantac* court found that defendants would have been entitled to summary judgment even if the animal studies were credited. However, the *Zantac* court addressed them in the interest of completeness.

insufficient boilerplate claims that "humans and animals metabolize NDMA similarly," *id.* at *656, and that the one referenced rat study (also relied on by Plaintiffs' experts here) "proves that NDMA can cause cancer at any dose," *id.* at *660. Ultimately, the *Zantac* court held that "the analytical gap between the animal data and the causation question is too great; furthermore, the Plaintiffs' experts' extrapolation from the animal data is grossly lacking (if not non-existent by the Plaintiffs' own admission), for their reliance on the animal data to be reliable." *Id.*at *665.

The *Zantac* court's decision is consistent with the general principle that "it is scientifically invalid to extrapolate observations in animal experiments directly to human beings." *Wade-Greaux v. Whitehall Lab'ys, Inc.*, 874 F. Supp. 1441, 1453 (D.V.I. 1994). Instead, an expert must reliably "explain[] how and why [he or she] could have extrapolated their opinions from these seemingly far-removed animal studies." *Gen. Elec. Co. v. Joiner*, 522 U.S. 136, 144-45 (1997).

The experts failed to do so in *Zantac*, and they failed to do so in this litigation as well. Dr. Panigrahy claims that "[a]nimal data on the carcinogenicity of a variety of chemicals have preceded as well as predicted later epidemiological observations in humans." (Panigrahy Rep. at 22 (emphasis omitted).) But the fact that some other (unidentified) chemicals ultimately proved to be harmful in both lab animals and humans says nothing about whether an expert can extrapolate from

animals to humans in the case of NDMA. At most, it suggests that animal studies can be a starting point for hypotheses, not that they provide causal proof. And the other experts make even less effort to bridge the gap from mega-doses of pure NDMA in animals to trace NDMA and NDEA impurities in VCDs in human beings. Dr. Lagana, for instance, offers one block quote and claims that "experimental animal data . . . is so well-accepted" that he should not have to explain it. (Lagana Rep. at 32.) As the *Zantac* court made clear, this cavalier and conclusory approach is not reliable science.

E. Plaintiffs' Experts' Any-Exposure Theory Merits Reconsideration.

Finally, and relatedly, Plaintiffs' experts have failed to reliably establish a threshold dose, and some advanced the unproven theory that "even one molecule . . . may cause cancer." (Panigrahy Rep. at 83; Mar. 2, 2022 Hr'g Tr. 66:15-16 ("there's no threshold with the dose"); *see also* Pls.' Br. in Opp'n to Defs.' Mot. to Exclude the General Causation Op. of Pls.' Expert Stephen S. Hecht, Ph.D. at 20-21, Dec. 1, 2021, ECF No. 1793 (arguing in favor of Dr. Hecht's no-threshold model).)[7] The *Zantac* court rejected that theory too, explaining that "Plaintiffs are required to provide a threshold dose at which

[7] The Court suggested at the hearing that "the FDA and other regulatory agencies have already done threshold level calculations." (Mar. 2, 2022 Hr'g Tr. 154:2-3.) As discussed above, such cautionary calculations are inapposite to the tort law standard of proof.

ranitidine becomes toxic to humans to meet their general causation burden." 2022 U.S. Dist. LEXIS 220327, at *638. The court further explained that "[c]ourts universally reject general causation theories based upon the idea that *any* amount of a carcinogen, no matter how small, is actionable[,] because an infinitesimal risk can neither be proven nor disproven." *Id.* at *202. This Court should adopt the same reasoning because "[t]he use of the no safe level or linear 'no threshold' model for showing unreasonable risk 'flies in the face of the toxicological law of dose-response, that is, that "the dose makes the poison."'" *In re W.R. Grace & Co.*, 355 B.R. 462, 476 (D. Del. Bankr. 2006) (citing Fed. Jud. Ctr., *Reference Manual on Scientific Evidence* (2d ed. 2000)). Reconsideration is warranted for this reason as well.

II. ALTERNATIVELY, THE COURT SHOULD CERTIFY ITS *DAUBERT* RULING FOR INTERLOCUTORY APPEAL.

If the Court chooses not to reconsider its previous order, Defendants request that it permit an interlocutory appeal so that the Third Circuit can untangle these difficult legal issues without the time and expense of years of additional litigation.

A district judge can allow appeal of any interlocutory order that "involves a controlling question of law as to which there is a substantial ground for difference of opinion and [where] an immediate appeal from the order may materially advance the ultimate termination of the litigation." 28 U.S.C. § 1292(b). The rule is intended to avoid "the possibility of considerable . . . wasted trial time and

litigation expense." *Katz v. Carte Blanche Corp.*, 496 F.2d 747, 756 (3d Cir. 1974); *see, e.g.*, *Knipe v. SmithKline Beecham*, 583 F. Supp. 2d 553, 599 (E.D. Pa. 2008) (certifying interlocutory appeal where reversal could "spare[]" "both the [c]ourt and the parties . . . the cost and time of both litigating . . . multiple . . . motions and engaging in a lengthy jury trial"). Because motions to exclude experts can be case-dispositive, and "a district court's discretion in these types of pretrial evidentiary matters is not unfettered," they can be particularly appropriate candidates for interlocutory appeal. *Larson v. Tyson Fresh Meats, Inc.*, No. 800CV529 et al., 2005 WL 1048099, at *2 (D. Neb. May 4, 2005) (citing, *inter alia*, *Katz*, *supra*).[8]

Each prong of Section 1292(b) is satisfied here.

[8] "[N]either section 1292(b) nor interpretive caselaw set any time constraints on when a party must file a motion for permission to seek prompt review of a non-final order [but] the entire procedure for departing from the normal course of appealing only final orders suggests a need for timeliness." *Koger Inc. v. Klco*, Civil Action No. 08-4175, 2010 WL 4553522 (SRC), at *2 (D.N.J. Nov. 3, 2010). Thus, a party's petition seeking certification of an order for interlocutory appeal must be filed with the district court within a reasonable time. *Stanley v. St. Croix Basic Servs., Inc.*, Civil No. 2003/0055, 2008 WL 4861448, at *1 (D.V.I. Nov. 3, 2008) (citation omitted). Defendants' alternative request for certification under § 1292(b) is brought within a reasonable time—14 days after issuance of the *Zantac* ruling, which demonstrates why there is a substantial ground for difference of opinion on the central causation issue in this litigation. Nor does the timing of the request pose any undue prejudice to any other party. At this stage, all parties and the Court stand to benefit from expedited, final appellate resolution of the causation issue before more time, effort and resources are expended in pursuit of further litigation.

A. The *Daubert* Issue Presents A Substantial Ground For Difference Of Opinion.

A substantial ground for difference of opinion exists "when the matter involves 'one or more difficult and pivotal questions not settled by controlling authority.'" *Knipe*, 583 F. Supp. 2d at 599 (*McGillicuddy v. Clements*, 746 F.2d 76, 76 n.1 (1st Cir. 1984)). The standard can be met even when the district court "is confident that [its] [o]rder is correct." *Mest v. Cabot Corp.*, No. CIV.A 01-4943, 2004 WL 1058155 (E.D. Pa. May. 10, 2004); *see, e.g.*, *Pub. Interest Rsch. Grp. of N.J. v. Hercules, Inc.*, 830 F. Supp. 1549, 1557 (D.N.J. 1993) (substantial grounds for difference of opinion existed although court "believe[d] . . . its decision [was] mandated by the clear language and purpose" of statute). As is particularly relevant here, a "party may establish that substantial grounds for difference of opinion exist by demonstrating that different courts have issued conflicting and contradictory opinions." *Miron v. BDO Sideman, L.L.P.*, No. CIV.A. 04-968, 2006 WL 3742772, at *3 (E.D. Pa. Dec. 13, 2006); *see, e.g.*, *Knipe*, 583 F. Supp. 2d at 600 ("Conflicting and contradictory opinions can provide substantial grounds for a difference of opinion."); *Aluminum Bahrain B.S.C. v. Dahdaleh*, No. 8-299, 2012 WL 5305169, at *2 (W.D. Pa. Oct. 25, 2012) (substantial ground for difference of opinion existed because "various circuit courts and district courts disagree on . . . application" of settled theory).

As discussed at length above, the *Zantac* order highlights the many ways that Plaintiffs' experts' opinions are insufficiently reliable and based on lines of evidence—like dietary and factory studies, animal models, and regulatory standards—that are far afield from the question of whether the VCDs in this litigation can cause cancer. If this Court believes they still pass muster under *Daubert* and Rule 702, however, it also demonstrates that reasonable judges not just can, but do, disagree about whether opinions based on essentially the exact same scientific evidence meet the standard for admissibility. Accordingly, this requirement for interlocutory review is concretely established.

B. The *Daubert* Issue Presents A Controlling Question Of Law And Resolving It Would Materially Advance The Litigation.

The requirement that "there be a 'controlling' question of law" often "blend[s] with the . . . requirement that an appeal might materially advance the ultimate termination of the litigation." 16 Charles Alan Wright et al., *Federal Practice and Procedure* § 3930 (3d ed. Apr. 2022 Update); *see also Knipe*, 583 F. Supp. 2d at 600 ("whether an interlocutory appeal would materially advance the termination of this litigation" "is closely tied to the requirement that the order involve a controlling question of law") (citation omitted). A question of law is "controlling" if "[r]eversal . . . would terminate the majority of [a party's] remaining claims." *Larsen v. Senate of Com. of Pa.*, 965 F. Supp. 607, 609 (M.D. Pa. 1997); *see also Newton v. Merrill Lynch, Pierce, Fenner & Smith, Inc.*, 259

F.3d 154, 165 (3d Cir. 2001) (where a decision is "likely dispositive of the litigation," granting the appeal "would be appropriate"). In addition, an issue is controlling if its resolution could have precedential value in other suits or would lead to the "saving of time of the district court and of expense to the litigants." *Katz*, 496 F.2d at 755.

Consistent with these principles, courts across the country have previously granted motions for certification of cross-cutting *Daubert* rulings where § 1292(b)'s criteria are satisfied. *See, e.g.*, *Bell v. Fore Sys., Inc.*, No. CIV.A. 97-1265, 2002 WL 32097540, at *5 (W.D. Pa. Aug. 2, 2002) (certifying in limine ruling excluding expert damages opinion as unreliable because, if erroneous, the ruling "would clearly be reversible on appeal"); *Larson*, 2005 WL 1048099, at *2 ("The fact that these [Rule 702] rulings affect not one, but *twelve*, remaining cases makes the issues 'extraordinary' . . . .").

Interlocutory review is all the more appropriate here. The issues presented are important and case-dispositive: a decision excluding Plaintiffs' expert evidence on general causation would terminate all of the 1,000-plus cases pending in this MDL proceeding. As the *Zantac* court explained, "[i]n a products liability MDL, the plaintiff must have admissible primary evidence with which to establish general causation"; otherwise, their claims cannot proceed. 2022 U.S. Dist. LEXIS 220327, at *670 (granting defendants summary judgment after excluding

plaintiffs' experts' general causation opinions). Reversal of the *Daubert* Order would also likely dispose of the consumer and economic-loss cases pending in the MDL, as the Court previously recognized. (Mar. 27, 2019 Status Conference Tr. 5:9-16 (filed Apr. 10, 2019), ECF No. 77 (stating that the threshold question of general causation "carries over into the other cases that are pending because, you know, if the contamination is not dangerous, then maybe you don't have such a great argument that you should get your money back for paying for it.").) In short, the entire MDL turns on the answer to the general causation question.

Moreover, resolution of these issues now rather than later could save the Court and the parties tremendous amounts of time and effort. Interlocutory review could "materially advance" this litigation by avoiding the necessity of further expensive and burdensome discovery, motion practice and complex trials. Indeed, such an outcome would further the very purpose for which this MDL was created. *In re Valsartan N-Nitrosodimethylamine (NDMA) Contamination Prods. Liab. Litig.*, 363 F. Supp. 3d 1378, 1381 (J.P.M.L. 2019) ("Centralization will . . . prevent inconsistent pretrial rulings, including with respect to . . . *Daubert* motions; and conserve the resources of the parties, their counsel, and the judiciary.").

And finally, resolution of these issues will provide needed clarity to issues that arise with some frequency in this Circuit (including in the multiple mass tort MDL proceedings pending here), making certification all the more appropriate.

In short, § 1292(b) was designed precisely for cases like this one. If the Court will not reconsider its order (which would likewise facilitate appeal and final resolution of the general causation question), Defendants respectfully submit that it should enter an order certifying the general causation question for interlocutory review.

CONCLUSION

For the foregoing reasons, Defendants request that the Court reconsider its order denying Defendants' motions to exclude Plaintiffs' general causation experts. In the alternative, Defendants request that the Court certify the question for interlocutory appeal.

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Respectfully submitted,

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CERTIFICATE OF SERVICE

I HEREBY CERTIFY that on December 20, 2022, I electronically filed the foregoing with the Clerk of the Court by using the CM/ECF system, which will send a notice of electronic filing to all CM/ECF participants in this matter.

/s/ *Jessica Davidson Miller*
Jessica Davidson Miller (DC Bar No. 457021)

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY
CAMDEN VICINAGE

IN RE: VALSARTAN, LOSARTAN, AND IRBESARTAN PRODUCTS LIABILITY LITIGATION **This Document Relates to All Actions**	MDL No. 2875 Honorable Robert B. Kugler, District Court Judge **[PROPOSED] ORDER GRANTING DEFENDANTS' MOTION FOR RECONSIDERATION OR, IN THE ALTERNATIVE, TO CERTIFY THIS MATTER FOR INTERLOCUTORY APPEAL**

ORDER

THIS MATTER, having been opened to the Court by Defendants for entry of an order reconsidering the Court's *Daubert* ruling, and the Court having considered the submissions of the parties and having heard oral argument, and for good cause shown:

IT IS on this ___ day of _____, 2023

ORDERED as follows:

Defendants' Motion is Granted in its entirety.

On reconsideration, the Court GRANTS Defendants' motions to exclude Plaintiffs' experts' general causation opinions in this litigation.

_____

Hon. Robert B. Kugler, U.S.D.J.