

# NO. 09-0073

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IN THE SUPREME COURT OF TEXAS

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MERCK & CO., INC.,

PETITIONER,

VS.

FELICIA GARZA ET AL.,

RESPONDENTS.

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ON APPEAL FROM THE COURT OF APPEALS FOR THE FOURTH  
JUDICIAL DISTRICT OF TEXAS AT SAN ANTONIO

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**MERCK'S REPLY TO RESPONSE TO PETITION FOR REVIEW**

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## ARGUMENT

Each of the arguments advanced by the Garzas in their response rests on one of two faulty premises: (1) that the requirements for scientific reliability enunciated in *Havner* do not apply to clinical trials, or (2) that *Havner* does not require that epidemiological evidence show, at a minimum, a statistically significant more than doubling of the risk at the plaintiff's dose and duration. But, as discussed more fully in Merck's petition, *Havner's* requirements apply whenever plaintiffs seek to prove causation inferentially through evidence that exposure to a substance increases the risk of injury, and that is exactly what the Garzas attempted to do with the clinical trial evidence in this case. Moreover, *Havner* holds that inferential evidence of causation, such as an epidemiological study, can meet the more-likely-than-not burden of proof only when it is statistically significant and demonstrates that the risk of injury in the exposed population is more than double the risk in the unexposed population.

Regardless, the Garzas' arguments simply highlight the importance to the jurisprudence of the causation and evidentiary sufficiency issues presented by this case. If allowed to stand, the court of appeals' opinion will sanction a reversion to an ipse dixit evidentiary regime in virtually every pharmaceutical drug case. The Court should not permit an intermediate appellate court to distort and subvert the requirements of its landmark *Havner* opinion for an entire class of cases, leaving intact only the "sound

bite,” not the “bite,” of its carefully-crafted holding. The Court should grant Merck’s petition.<sup>1</sup>

**I. *Havner*’s scientific reliability requirements apply to all forms of epidemiological evidence, including clinical trials.**

The Garzas insist that the court of appeals’ general causation analysis is consistent with *Havner* because “clinical trials and epidemiological studies are light years apart” and the *Havner* court “expressly limited its reach to epidemiological studies.” (Resp. 6, 10.) The Garzas mischaracterize epidemiological studies and misread *Havner*.

First, clinical trials unquestionably are epidemiological studies. “Epidemiological studies may be characterized as observational or experimental.” DAVID E. LILIENFELD & PAUL D. STOLLEY, FOUNDATIONS OF EPIDEMIOLOGY 151 (3d ed. 1994). “Most epidemiological studies are observational—that is, they ‘observe’ a group of individuals who have been exposed to an agent of interest” and “compare them with another group of individuals who have not been so exposed.” Michael D. Green et al., *Reference Guide on Epidemiology*, in REFERENCE MANUAL ON SCIENTIFIC EVIDENCE 333, 339 (2d ed. 2000) [hereinafter “Reference Guide”].<sup>2</sup> Consequently, the phrase

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<sup>1</sup> The Garzas seek to influence the Court’s consideration of the legal issues in this case with an inflammatory rendition of the facts. While Merck acknowledges that the Starr County jury found in the Garzas’ favor, the Garzas’ factual rendition is both misleading and irrelevant to the issues presented.

<sup>2</sup> See also *Magistrini v. One Hour Martinizing Dry Cleaning*, 180 F. Supp. 2d 584, 590-91 (D.N.J. 2002) (“There are two categories of epidemiological studies: experimental studies and observational studies. Experimental studies, in the form of randomized trials, clinical trials, or true experiments, generally involve two groups, one of which is exposed to the agent in question while the other is not. In observational studies, individuals who have been exposed to the agent at issue are observed and compared to a group of individuals who have not been so exposed.”); *Caraker v. Sandoz Pharms. Corp.*, 188 F. Supp. 2d 1026, 1031 (S.D. Ill. 2001) (“There are essentially three types of study designs used by epidemiologists in attempting to determine whether there is an association between exposure to an agent and development of a disease: (1) randomized trial or randomized clinical trial, (2) [observational] cohort studies, and (3) [observational] case-control studies.”).

“epidemiological studies” often is used as shorthand for observational epidemiological studies. Another type of epidemiological study, however, is the clinical trial, in which study participants are “randomly separated, each group exposed either to an agent or placebo in precise dose, and evaluated for the incidence of the effect under study.” See Michael D. Green, *Expert Witnesses and Sufficiency of Evidence in Toxic Substances Litigation: The Legacy of Agent Orange and Bendectin Litigation*, 86 NW. U. L. REV. 643, 646-47 (1992) [hereinafter “Green”]. The goal of both observational studies and clinical trials is “[t]o determine whether an agent is related to the risk of developing a certain disease or an adverse health outcome.” Reference Guide at 338-40.<sup>3</sup>

Contrary to the Garzas’ assertions, Merck does not contend that clinical trials and observational epidemiological studies are entitled to equal weight. Clinical trials are superior to observational studies, as they enable researchers to minimize relevant differences between participants that might account for different outcomes between the exposed and unexposed groups. *Id.* at 338. The fact remains, however, that clinical trials, like all forms of epidemiology, do not constitute *direct* proof of general causation. See Green at 646 & n.15 (describing epidemiology as one of five inferential methods of establishing causation); *Caraker*, 188 F. Supp. 2d at 1031 (“Epidemiology cannot objectively prove causation; rather, causation is a judgment for epidemiologists and others interpreting the epidemiological data.”). Nor can they prove what caused any

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<sup>3</sup> Although the Garzas claim that the Reference Guide characterizes clinical trials as fundamentally different from epidemiological studies (Resp. 8-9), they neglect to mention that the passages they quote are from a section of the guide entitled, “What Different Kinds of Epidemiologic Studies Exist? Experimental and Observational Studies of Suspected Toxic Agents.” Reference Guide at 338. Thus, the Reference Guide confirms, rather than refutes, that clinical trials are epidemiological evidence.

particular claimant's injury. See Steve Gold, *Causation in Toxic Torts: Burdens of Proof, Standards of Persuasion, and Statistical Evidence*, 96 YALE L.J. 376, 380 (1986) [hereinafter "Gold"] ("[I]n an individual case, epidemiology cannot conclusively prove causation."); Reference Guide at 381-82 ("[S]pecific causation . . . is beyond the domain of the science of epidemiology."); see also *Havner*, 953 S.W.2d at 718 ("We recognize, as does the [Reference Guide], that a disease or condition either is or is not caused by exposure to a suspected agent and that frequency data, such as the incidence of adverse effects in the general population when exposed, cannot indicate the actual cause of a given individual's disease or condition."). Instead, they at best "can establish only a certain probability that a randomly selected case of disease was one that would not have occurred absent exposure, or the 'relative risk' of the exposed population." Gold at 380.

Second, while it is true that *Havner* focused on observational epidemiological studies, that is because the evidence at issue in *Havner* consisted "to a considerable extent" of such studies. 953 S.W.2d at 715. The Court never stated that its holding was limited to observational studies, nor did it state that a clinical trial is the type of controlled scientific experiment that proves causation directly and thus falls outside the bounds of *Havner*. To the contrary, the Court articulated a reliability standard that applies whenever a claimant attempts to prove causation inferentially, e.g., with epidemiological evidence. In fact, *Havner* relies on the federal regulation concerning clinical trials, further confirming that the Court was familiar with clinical trials and did not intend to exclude them from *Havner*'s reach. *Id.* at 720 (citing 21 C.F.R. § 314.126).

**II. *Havner* requires at least two studies showing, at a minimum, a statistically significant doubling of the risk at Mr. Garza’s dose and duration.**

In arguing that *Havner* does not require epidemiological evidence to show a statistically significant more than doubling of the risk, the Garzas join the court of appeals in rewriting *Havner* to distort its holdings and undermine its restrictions on the use of junk science. (Resp. 11.) Like the court of appeals, the Garzas recite language from *Havner* stating that a relative risk of more than 2.0 is *not necessarily sufficient* to suggest that a relative risk of more than 2.0 is *not required*. (*Id.*) Moreover, the Garzas ignore language in *Havner* expressly reserving the question of whether there is any circumstance in which a relative risk of 2.0 or less might suffice if “coupled with other credible and reliable evidence” of causation.<sup>4</sup> 953 S.W.2d at 719. As discussed more fully in the petition, the language quoted by the Garzas, when examined in its proper context, actually emphasizes that a relative risk of 2.0 is a *minimum* requirement that epidemiological evidence must meet in order to be capable of satisfying the more-likely-than-not burden of proof. (Pet. 9-10.) *See Havner*, 953 S.W.2d at 717-18 (“[W]e are persuaded . . . that there is a rational basis for relating the *requirement* that there be more than a ‘doubling of the risk’ to our no evidence standard of review and to the more likely than not burden of proof.”) (emphasis added); *see also* Reference Guide at 384 (“The threshold for concluding that an agent was more likely than not the cause of an

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<sup>4</sup> If the bare assertion of an expert witness that the likelihood of Mr. Garza’s heart attack’s being caused by Vioxx was greater than average is sufficient to support an inference of causation, then it is difficult to fathom a case in which *Havner*’s more than 2.0 requirement would ever apply. Given Mr. Garza’s numerous risk factors for having a heart attack, it strains credulity past the breaking point to say that Dr. Simonini’s two-clot theory gives the jury a credible basis to decide that Mr. Garza more likely than not died due to his brief use of Vioxx.

individual's disease is a relative risk of greater than 2.0. . . . A relative risk greater than 2.0 would permit an inference that an individual plaintiff's disease was more likely than not caused by the implicated agent.”).

### **III. The court of appeals' “totality of the evidence” review failed to consider the totality of the evidence.**

The Garzas contend that the court of appeals correctly conducted a “totality of the evidence” review, which they claim is all that *Havner* requires. (See Resp. 10-12.) The Garzas then assert, somewhat contradictorily, that the court of appeals “could have supported its finding of legal sufficiency solely on the [deposition] testimony of Dr. Topol.” (*Id.* at 12.) According to the Garzas, Dr. Topol's testimony “that the risk of Vioxx for heart attacks can occur at any time after the initiation of the medicine,” coupled with his reliance on clinical trials and peer-reviewed studies, constitutes legally sufficient evidence of general causation. (*Id.*) The Garzas fail to explain, however, how Dr. Topol's testimony constitutes *any* evidence of causation when nothing in the record, including the studies upon which he relied, supports the conclusion that 25 milligram Vioxx use for less than 30 days doubles the risk of heart attack.<sup>5</sup> See *Havner*, 953 S.W.2d at 714 (“If the foundational data underlying opinion testimony are unreliable, an expert will not be permitted to base an opinion on that data because any opinion drawn from that data is likewise unreliable.”). Although the Garzas contend that numerous clinical studies support the court of appeals' judgment (Resp. 12-13), that contention rests

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<sup>5</sup> None of the studies relied upon by the Garzas showed any statistically significant increased relative risk with 25 mg Vioxx taken for less than 30 days, much less the *Havner*-required relative risk of greater than 2.0. (See, e.g., Pet. at 12 n.9.)

on their mistaken belief that *Havner* neither applies to clinical trials nor requires that epidemiological evidence show a statistically significant doubling of the risk at the plaintiff's dose and duration. (*See id.* at 10, 12-13.) The Garzas do not, because they cannot, point to any study in this case that actually meets *Havner*'s requirements.

The Garzas fail to respond at all to Merck's argument that the court of appeals erroneously ignored contrary evidence showing that Dr. Topol's opinions were scientifically unreliable. (*See* Pet. 13-14.) The court of appeals' "totality of the evidence" review should have addressed the conclusions of the underlying studies themselves;<sup>6</sup> the FDA's conclusion, reached after analyzing those same studies, that short-term Vioxx use does not appear to confer an increased risk of CV events; and the testimony of Drs. Evans and Pratt that there is no statistically significant study showing that Vioxx doubles the risk of heart attack at Mr. Garza's dose and duration. Had the court of appeals taken this evidence into account, it would have been forced to conclude that Dr. Topol's opinion had no scientific basis and thus was no evidence of causation.

**IV. The Garzas did not exclude other plausible causes of Mr. Garza's heart attack with reasonable certainty.**

Although the Garzas insist that they carried their burden of proving specific causation, they retreat from the two-clot theory advanced, without any scientific support,

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<sup>6</sup> In particular, the court of appeals failed to consider the following: (1) more than 100 clinical trials, including placebo-controlled clinical trials, showed no statistically significant difference in adverse CV events (*see* 7 RR 24-26, 104, 112-13, 117-20; 13 RR 9-10); (2) Mr. Garza was not similar to those in the clinical trials upon which the Garzas relied for proof of causation, including the VIGOR study, which compared 50 mg Vioxx use to 100 mg Naproxen use in patients with rheumatoid arthritis (*see* 12 RR 114-15, 118); and (3) most of those trials were active comparator studies—i.e., studies comparing Vioxx users to users of other drugs, with no placebo control group—which inherently are less reliable than placebo-controlled studies. (*See* 7 RR 61-65; 8 RR 36-37; 11 RR 44-46; 23 RR 84-85; 26 RR 51-53.)

by Dr. Simonini.<sup>7</sup> Instead, the Garzas claim that they proved specific causation with evidence that (1) Vioxx is capable of causing blood clots, (2) blood clots are a common cause of heart attacks, (3) Mr. Garza died of a heart attack caused by blood clots, (4) cardiac tests in the weeks before he died showed that Mr. Garza was at low risk for a heart attack, (5) people with heart disease are particularly at risk for blood clots and heart attacks after taking Vioxx, and (6) “[n]umerous tests have shown that Vioxx can cause serious adverse cardiac events soon after a patient begins taking it.” (Resp. 13-14.) This evidence, which the Garzas mischaracterize, does not exclude with reasonable certainty the likely possibility that Mr. Garza’s long history of severe heart disease, rather than his short-term Vioxx use, caused his heart attack. Instead, it is precisely the kind of post hoc ergo propter hoc reasoning that *Havner* rejected. *Havner*, 953 S.W.2d at 719 (“[E]vidence of causation from whatever source must be scientifically reliable. Post hoc, speculative testimony will not suffice.”). While Dr. Simonini opined that Vioxx caused Mr. Garza’s heart attack, there is no reliable support for his opinion. *See E.I. du Pont de Nemours & Co. v. Robinson*, 923 S.W.2d 549, 559 (Tex. 1995) (expert opinions that fail to rule out other causes are “little more than speculation”).

#### CONCLUSION

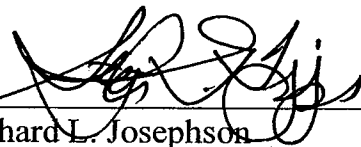
This Court should grant the petition, reverse the judgment of the court of appeals, and render judgment in favor of Merck.

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<sup>7</sup> The court of appeals correctly held in its original opinion that there was no scientific evidence proffered to show that Vioxx poses an increased risk of multiple clots at Mr. Garza’s dose and duration. (Pet. App. A at 5.)

Respectfully submitted,

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**CERTIFICATE OF SERVICE**

I certify that a copy of this petition for review was sent by certified mail, return receipt requested, with a courtesy e-mail copy to Mr. Dubose, to all counsel of record for the respondents on the 11th day of March, 2009.

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