Karch's Drug Abuse Handbook

Third Edition

Edited by

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9 Legal Aspects of the Opioid Epidemic

Section Editors: Eric Lasker and Robert E. Johnston

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9.1 LEGAL ASPECTS OF THE OPIOID EPIDEMIC

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9.1.1 Introduction

> "The federal court is probably the least likely branch of government to try and tackle [the opioid epidemic], but candidly, the other branches of government, federal and state, have punted," Judge Dan Polster during the first hearing of the Opioid Multidistrict Litigation in January 2018.

The rise in prescriptions for opioid medications has created a public health crisis in the United States. By 2016, more people had died from opioid overdoses than died during the entire Vietnam War. Opioid overdose is the leading cause of death for Americans under 50. The crisis affects people

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from all walks of life and shows no sign of slowing. At least 100 people die of opioid overdoses every day.

Federal and state governments have declared the opioid epidemic a national health emergency. The epidemic has given rise to legislation to mitigate the impact on Americans, government regulation and enforcement actions, and massive nationwide litigation involving an increasing number of corporate and individual defendants in the chain of distribution of opioids, from manufacturers to physicians. This chapter outlines the evolution of the opioid crisis, the government's efforts to combat its effects and hold those who allegedly contributed to the epidemic responsible, and the litigation arising from it. It also analyzes medical malpractice claims involving opioids and precautionary measures physicians can take to help avoid becoming embroiled in the multifaceted aspects of the opioid epidemic.

9.1.2 Opioid Overview

9.1.2.1 Medical Uses

Opioids have long been used to treat pain and other ailments. Poppy plants have been cultivated since as early as 3400 BC, leading to the development of morphine in the early 1800s.[2] Opioids are compounds that work by interacting with opioid receptors in brain cells to reduce the perception of pain, signaling to the brain that a person is not in pain.[3] Opioids can be derived from the poppy plant (e.g., morphine or codeine) or can be manufactured synthetically (e.g., hydrocodone, OxyContin, and fentanyl).[4]

Like other narcotics, opioids are used to manage chronic and acute pain and are regarded as among the most effective drugs for pain relief.[5] "Their use in the management of acute severe pain and chronic pain related to advanced medical illness is considered the standard of care in most of the world."[6]

Although opioids are commonly used to treat patients who have cancer or are approaching the end of life, they are also used for treatment of moderate to severe pain associated with other serious medical conditions. "Several medical professional organizations acknowledge the utility of opioid therapy and many case series and large surveys report satisfactory reductions in pain, improvement in function and minimal risk of addiction."[7] However, the overtreatment of patients and epidemic-level opioid abuse and addiction have caused public officials and medical practitioners to reconsider their widespread use.[8]

9.1.2.2 Risks of Adverse Effects

Despite their well-accepted benefits in relieving pain,[9] opioids may have serious adverse side effects requiring warning.[10] Common adverse effects include sedation, dizziness, nausea, vomiting, constipation, physical dependence, tolerance, and respiratory depression.[11] Extended use may cause increases in the amount of medication necessary to achieve the same pain-relieving effects. In turn, dependence may occur, and abrupt cessation of longer-term use often causes withdrawal symptoms. Withdrawal symptoms include diarrhea, nausea, vomiting, muscle pain, anxiety, and irritability.[12] In addition to these adverse effects, very high doses of opioids can slow a person's breathing and heart rate, which can lead to death.[13]

Among the most serious adverse effects are overdose and psychological addiction.[14] Addiction is characterized as an urge to use opioids even when they are no longer medically required.[15] One of the factors leading to addiction is the phenomenon of tolerance, which results when a particular dose of an opioid no longer provides the same pain-relieving effects, leading patients to seek higher doses to achieve the same analgesic effects.[16]

Awareness of these risks of opioid addiction has increased dramatically. When they were initially marketed, opioids were not regarded as addictive. Indeed, an early study of opioids' risk of addiction, performed by Dr Hershel Jick and Jane Porter, concluded that addiction was rare in patients treated with narcotics.[17] This study, which included nearly 12,000 patients, found "only four cases of reasonably well documented addiction in patients who had no history of addiction."[18] The study did not, however, identify how long the patients were treated with opioids, the purpose of the treatment, or dosage.[19] In 2017, Dr David Juurlink published a letter taking the position that the 1980 Jick and Porter Study had contributed to the opioid epidemic:

> The crisis arose in part because physicians were told that the risk of addiction was low when opioids were prescribed for chronic pain. A one-paragraph letter that was published in the *Journal* in 1980 was widely invoked in support of this claim, even though no evidence was provided by the correspondents. … we found that a five-sentence letter published in the *Journal* in 1980 was heavily and uncritically cited as evidence that addiction was rare with long-term opioid therapy. We believe that this citation pattern contributed to the North American opioid crisis by helping to shape a narrative that allayed prescribers' concerns about the risk of addiction associated with long-term opioid therapy.[20]

Since the 1980s, the medical community and the public have become much more aware of the risk of opioid addiction. Thus, physicians are exercising more caution in prescribing increasing dosage or renewing patient prescriptions of opioids.[21] "The past several decades in the United States have been characterized by attitudes that have shifted repeatedly in response to clinical and epidemiological observations [regarding opioid use], and events in the legal and regulatory communities."[22] One unintended consequence of the reduction in opioid prescriptions is that opioid users may seek illegal and more powerful opioids, such as heroin and fentanyl, because of their addiction.[23]

9.1.2.3 Current Opioid Epidemic

In response to the rapid increase in the use of prescription and non-prescription opioids in the United States from the mid- to late 1990s to the present,[24] the director of the Center for Disease Control and Prevention (CDC) stated: "We have an emergency on our hands. The fast-moving opioid overdose epidemic … is accelerating."[25] Although the causes of

the crisis are multifaceted and complex, the statistics of the crisis demonstrate that opioid use is at crisis level. In 2016, more people died from opioid overdoses than all U.S. deaths during the entire course of the Vietnam War.[26] Opioid overdose is the leading cause of death for Americans under 50, and over 100 Americans die daily from an opioid overdose.[27] By 2016, "the number of overdose deaths involving opioids (including prescription opioids and illegal opioids like heroin and illicitly manufactured fentanyl) was five times higher than in 1999."[28] More troubling, as of 2018, 40% of all U.S. opioid overdose deaths involved a prescription opioid.[29] President Trump responded to the epidemic in late 2017 by declaring the problem a national health emergency.[30]

Government agencies such as the Department of Health and Human Services (HHS) and the CDC attribute the opioid crisis to multiple factors. According to the HHS, beginning in the mid- to late 1990s, pharmaceutical companies marketing opioids allegedly downplayed the risk of opioid addiction and sought to assure the medical community that opioids were both safe and effective pain relievers.[31] Dr David Juurlink noted that many of these companies relied upon the letter by Dr Jick and Ms Porter stating that opioids were not addictive in order to promote widespread marketing and sales of the drug. In turn, healthcare providers prescribed opioids at increasing rates.[32]

According to the HHS and the CDC, pharmaceutical distributors shipped and supplied massive quantities of opioids, often without reporting sales to authorities. Pharmacies often allegedly "turned a blind eye" to the large amount of opioids sold to the public and frequently did not question suspicious prescriptions from doctors.[33] Researchers report that the increases in opioid prescriptions were associated with dramatic increases in opioid-related overdose deaths and addiction.[34]

9.1.3 Government Efforts to Curb the Opioid Epidemic

Widespread concern about the opioid epidemic prompted state and federal governments to enact various prevention measures, including legislation, agency action, educational outreach, and increased accessibility to naloxone, an overdose-reversal drug.[35]

9.1.3.1 Legislation

Federal and state legislators have proposed and enacted legislation to combat the epidemic by investing in prevention, detection, surveillance, and treatment for the abuse of opioids. In 2016, Congress passed the Comprehensive Addiction Recovery Act (CARA) in its initial effort to curb the opioid epidemic. CARA increased federal funding to states for increased access to opioid treatment providers and to require federal and state agencies to disseminate more information to consumers about the risks of prescription opioid abuse.[36] Senator Robert Portman (R-OH), the author of the Senate version of CARA, stated:

> This is a historic moment, the first time in decades that Congress has passed comprehensive addiction legislation, and the first time Congress has ever supported long-term addiction recovery. This is also the first time that we've treated addiction like the disease that it is, which will help put an end to the stigma that has surrounded addiction for too long.[37]

Since 2016, similar legislation seeking to combat the epidemic by investing in prevention, detection, surveillance, and treatment of opioid addiction has been proposed.[38] In early 2018, both the House and the Senate introduced identical "CARA 2.0" bills, (S. 2456) and (H.R. 5311), which would include increased funding for national education campaigns, increased access to medication-assisted treatment, expanded first responder training, and increased access to naloxone.[39] On October 24, 2018, President Trump signed the SUPPORT for Patients and Communities Act (H.R. 6) (SUPPORT Act), which is a comprehensive opioid legislation based on the House and Senate's opioid bills, including elements of CARA 2.0. The SUPPORT Act focuses on "improving the federal response to the opioid epidemic via changes to Medicaid and Medicare, expansion of treatment resources for health care providers and enhancement of recovery supports for patients."[40]

In 2018, Congress introduced a variety of additional bills targeting opioid addiction, which were still pending as of this publication, including the Stop Counterfeit Drugs by Regulating and Enhancing Enforcement Now Act (SCREEN Act), sponsored by U.S. Representative Frank Pallone Jr. of New Jersey.[41] The Act would allow the U.S. Food and Drug Administration (FDA) to destroy and/or refuse to import drugs identified as "articles of concern," such as heroin and fentanyl. In addition, the bill would allow the FDA to use emergency recalls prohibiting the distribution of opioid drugs and debar companies that continue to import drugs illegally. The bill would also authorize $110 million in spending for innovation of new pain treatments and provide enhanced access to opioid abuse treatment.[42]

Another pending bipartisan bill introduced in early 2018 is the Durbin–Kennedy Opioid Quota Reform Act of 2018. The Drug Enforcement Agency (DEA) is responsible for establishing annual quotas determining the exact amount of each drug that is permitted to be produced in the United States each year. Currently, the DEA's manufacturing quotas are based upon the amount of the drug sold in the previous year and expected demand, but some consider the DEA's quota for opioids to be inflated because opioids are overprescribed.[43] The Act would require the DEA to consider public health factors, such as overdose and death rates, in setting opioid manufacturing quotas, thereby enabling the DEA to adjust manufacturing quotas to limit opioid diversion and abuse. [44]

Finally, the Senate Committee on Health, Education, Labor, & Pensions (HELP) released a draft bill that would, among other things, authorize grants for communities to set up comprehensive opioid recovery centers, require the HHS to issue guidance on best practices for operating recovery facilities, and allow the National Institutes of Health (NIH) to approach pharmaceutical companies and universities to conduct opioid-related research.[45] Some state legislatures

have proposed the imposition of taxes on opioid sales in an effort to curb the epidemic.[46] It remains to be seen which, if any, of the proposed legislation described here will be enacted and whether the existing and proposed laws will be effective in tackling the opioid epidemic.

9.1.3.2 Regulatory Action

In addition to legislative changes, government agencies and the executive branch have taken steps to combat the epidemic. In 2018, President Trump emphasized that ending the epidemic is a national priority.[47] In late March 2018, he announced a four-point plan to combat the epidemic. First, the plan seeks to reduce the supply of opioids by requiring harsher punishment for manufacturers and criminally negligent doctors, pharmacies, and distributors, including making opioid trafficking a capital offense subject to the death penalty. Second, the plan would reduce demand and improper prescribing by utilizing advertising to help deter the use of opioids. Third, the plan would help addicts by enabling more people to obtain naloxone and creating more treatment programs. Finally, President Trump's plan would include measures to combat "the driving forces" of the opioid crisis by curbing overprescription and expanding addiction treatment systems.[48]

9.1.3.2.1 Department of Justice

The U.S. Department of Justice (DOJ), the HHS, the DEA, and other government agencies have also responded to the epidemic by participating in litigation, developing multistep plans, and creating task forces. DOJ officials have made numerous public statements regarding the crisis, and the DOJ's involvement in the consolidated multidistrict litigation against opioid manufacturers, distributors, and pharmacies, discussed in Section 9.4.2.1, indicates that it may play an even bigger role in opioid-related litigation, particularly litigation targeting opioid manufacturers and distributors. In April 2018, DOJ filed a motion to participate in settlement discussions and participate as friend of the court in the federal opioid litigation against pharmaceutical manufacturers and distributors.[49] DOJ contended:

> The United States has a unique interest and expertise regarding the subjects at issue in this litigation and can provide information and expertise to assist the parties and the Court in reaching a comprehensive and effective resolution of the issues in this case. The United States will lend its knowledge and understanding of the federal government and its agencies for the benefit of the litigation and provide the nationwide view of this crisis of national scope whenever it is called upon by the Court.[50]

In June 2018, the motion was granted as unopposed.[51] DOJ has also repeatedly stated its intention to utilize the False Claims Act to hold those responsible for the opioid epidemic accountable. For example, former Attorney General Sessions stated in 2017 that DOJ would "make it a high priority of the Department to root out and prosecute fraud in federal programs and to recover any monies lost due to fraud or false claims."[52]

9.1.3.2.1.1 DOJ's Opioid Fraud and Abuse Detection Unit

In addition to expressing its goals and strategies to combat the opioid epidemic, DOJ has also taken action to curb the epidemic through the creation of specialized units and task forces, such as the Opioid Fraud and Abuse Detection Unit. In 2018, DOJ placed 12 prosecutors in geographic areas that experience high levels of opioid prescription abuse by healthcare providers. The prosecutors' primary stated goal is to curb the unlawful sale of opioids and in turn, alleviate the addiction problem in the United States.[53] DOJ adopted a hybrid approach to combatting the opioid crisis through prosecution of both drug traffickers and those participating in healthcare fraud, including physicians, drug treatment centers, and pharmacists. DOJ has partnered with the DEA, FBI, HHS, and other state and federal agencies to craft this program.[54]

DOJ asserts that although doctors and pharmacists have a license to dispense controlled substances, they are allowed to do so only within the bounds of a legitimate practice. Under the Controlled Substances Act (CSA), it is a crime for anyone to distribute controlled substances without registration.[55] Even if an entity has a registration, however, the registration allows prescriptions only for legitimate medical purposes that are consistent with the professional standard of care.[56] This initiative requires doctors to exercise due diligence in writing prescriptions. Prescribers who defraud healthcare benefit programs such as Medicare and Medicaid by charging for services that were not performed or overcharging for services related to opioids will also be identified and prosecuted.[57] For example, physicians who prescribe medically unnecessary opioid treatment to a Medicare beneficiary, which is then reimbursed by Medicare Part D, will be identified and prosecuted by the Opioid Fraud and Abuse Detection Unit.

DOJ's actions are based on reports that doctors often charge for medically unnecessary procedures, services not actually rendered, or "upcoded" services when evaluating patients to prescribe opioids.[58] Further, doctors may prescribe unnecessary services, such as magnetic resonance imaging, to their addicted patients to make more money.[59] DOJ plans to use "red flags" to identify doctors and physicians who violate federal statutes.[60] Physicians should be aware that these "red flags" include high patient numbers, cursory exams, high cash prices, high percentages of doctors' patients who are prescribed controlled substances, prescription of multiple controlled substances,[61] and treatment of out-of-state patients, among other factors.[62]

The CSA requires pharmacists to identify overprescribing. In prosecuting pharmacists, DOJ will look for similar red flags to those for physicians. Pharmacists must determine whether the prescription is for legitimate medical purposes and within the usual course of that practice.[63] In addition, other red flags for pharmacists include multiple patients with identical prescriptions, high percentages of pharmacies' prescriptions for controlled substances from a single doctor, prescriptions of high dosages/quantities

compared with medical conditions, failure to use drug monitoring programs/data collection sites, or providing high volumes of prescriptions of controlled substances compared with peer pharmacies.[64] DOJ also looks for doctors or pharmacies providing "buffer drugs," which consists of ordering two drugs (only one of which is an opioid), or billing for improperly dispensed controlled substances.[65]

9.1.3.2.1.2 DOJ's Prescription Interdiction & Litigation Task Force DOJ is also creating another task force called the Prescription Interdiction & Litigation (PIL) Task Force. PIL will utilize both civil and criminal law enforcement tools, such as the False Claims Act (FCA), "to reverse the tide of opioid overdoses in the United States."[66] The task force will target opioid manufacturers and distributors. PIL will include senior officials from the offices of the Attorney General and Executive Office for U.S. Attorneys, the Civil Division, Criminal Division, and the DEA. In addition to the FCA, the task force plans to use the CSA to bring claims against responsible parties. PIL will also help investigate and support municipalities in bringing claims against manufacturers and distributors of opioids while expanding efforts by the Opioid Fraud and Abuse Unit through working with DEA and HHS to investigate illegal practices. The PIL aims to (1) improve the coordination of data sharing within the federal government to better identify fraud and violations of the law; (2) evaluate regulatory changes to the role governing opioid distribution; and (3) evaluate potential legislative changes.[67]

9.1.3.2.2 Drug Enforcement Administration

The DEA is also involved in combatting the epidemic by targeting opioid distributors for failure to report suspicious orders. The CSA requires drug distribution companies to report suspicious orders of narcotics to the DEA, including unusually large or unusually frequent orders. Distributors who fail to report may be fined or have their DEA registrations revoked. For example, Mallinckrodt Pharmaceuticals agreed to pay $35 million to resolve DEA probes into its monitoring and reporting of suspicious orders of controlled substances.[68] As discussed later, a rule was proposed in 2018 that would allow the DEA to place limits on pharmaceutical companies or distributors if it suspects opioid drugs are being siphoned to others in the chains of distribution who may sell them for illegal purposes.[69] The purpose of the rule is "to strengthen controls over diversion of controlled substances and make other improvements in the quota management regulatory system for the production, manufacturing, and procurement of controlled substances."[70] For example, in 2018, the DEA suspended opioid sales by a wholesale distributor for failing to identify suspicious orders to pharmacies. It was the first time in 6 years that the DEA had cut off sales by a narcotic distributor.[71]

9.1.3.2.3 Food and Drug Administration

The U.S. FDA has also been actively involved in combatting the opioid epidemic. The FDA requested in 2017 that Endo Pharmaceuticals remove its opioid pain medication, oxymorphone hydrochloride, from the market. The FDA indicated that the benefits of the drug may no longer outweigh its risks. This was the first time that the FDA had requested a manufacturer to remove a currently marketed opioid pain medication from the market due to public health concerns of possible addiction and abuse.[72]

FDA Commissioner Scott Gottlieb announced in 2018 that internet service providers and social media companies should take action to track and prevent illegal sales of opioids. Specifically, because fentanyl is frequently sold online, the FDA hopes to collaborate with online companies tracking data regarding sellers and purchases of the drug.[73] The FDA also released Draft Guidance in 2018 outlining proposed methods for drug companies to develop new medications to treat opioid addiction. The Draft Guidance focuses on the creation of modified-release drugs that can be implanted or injected.[74] The FDA announced in early April 2018 that it would spend $10 million in the fiscal year 2019 to expand access to naloxone by changing its status from prescription to over-the-counter.[75]

9.1.3.3 Criminal Prosecutions and Government Investigations

Federal prosecutors have charged opioid sales managers for violations of the Anti-Kickback Statute. For example, John Kapoor of Insys Therapeutics, Inc. was arrested and charged with racketeering and fraud in October 2017 for allegedly bribing doctors to prescribe a fentanyl-based painkiller spray for off-label uses.[76] Luzerne County (Pennsylvania) also filed a federal lawsuit alleging that Purdue Pharma, Endo Pharmaceuticals Inc., Janssen Pharmaceuticals, Teva Pharmaceutical Industries, and other opioid manufacturers violated the Racketeer Influenced and Corrupt Organizations Act (RICO) by illegally marketing the highly addictive fentanyl spray.[77] Congress has begun its own investigation of fentanyl distributors through the Subcommittee on Oversight and Investigations of the House Energy and Commerce Committee.[78] Witnesses from opioid distributors testified at a May 8, 2018 hearing regarding the excess availability of opioids in certain West Virginia counties.[79] Following the November 2018 elections, it is anticipated that Congress will engage in even more aggressive oversight.[80]

The federal government has also increased its prosecution of physicians under the CSA, which provides criminal sanctions for individuals who distribute or dispense Schedule I or II substances (most opioid drugs are Schedule II substances).[81] Physicians are generally provided with an exception from the applicability of section 841(a)(1), which provides for criminal sanctions, pursuant to 21 U.S.C. § 802(21), so long as their prescriptions are "for a legitimate medical purpose."[82] Where, however, a physician knowingly prescribes outside the course of professional practice or without a legitimate medical purpose, criminal sanctions may be imposed under the CSA.[83]

Based on a review of data contained in the National Practitioner Data Bank between 2011 and 2014, one commentator has determined that federal criminal cases against physicians increased from 88 cases in 2011 to 371 cases by 2014, a quadrupling of the number of cases brought against physicians under the CSA.[84] Many of these prosecutions have focused on prescribers of pain medicines.[85] Dr Paul Volkman, for example, received four life sentences based on the fact that four of his patients at the Tri-State Health Clinic in Portsmouth, Ohio died after taking pain medicines distributed by his dispensary at the clinic.[86] Dr Dewey MacKay was sentenced in 2013 to serve 240 months in prison for prescribing opioid pain medication that allegedly caused the death of one of his patients.[87] In 2010, Dr Stephen Schneider and his nurse/wife Linda were sentenced to 30 and 33 years in prison, respectively, for their prescription of pain medication allegedly resulting in numerous deaths at a pain management clinic in Kansas.[88]

The doctors in these examples were prosecuted under an enhanced sentencing provision added to the CSA in 1986 that provides mandatory minimum sentences of 20 years and mandatory maximum sentences of life for offenses in which "death or serious bodily injury results from" the distribution of the controlled substance.[89] In 2014, the United States Supreme Court determined that the enhancement statute could only be applied where a jury finds that there is evidence beyond a reasonable doubt that the controlled substance provided by the distributor was the "but-for" cause of death or injury.[90] The defendant in *Burrage* had provided illicit heroin to Joshua Banka, who died after a 24-hour "drug binge" that included marijuana, stolen oxycodone (which was "crushed, cooked and injected"), and heroin that he had procured from Burrage during the binge.[91] Alprazolam, clonazepam, and hydrocodone were also found in Banka's residence. Two experts testified for the prosecution that the heroin had played a contributing role with the other drugs to cause Banka's death, but neither would testify that Banka would have survived had he not taken the heroin.[92] The trial court instructed the jury that they could apply the enhancement statute if heroin had contributed to Banka's death, and Burrage was convicted and sentenced using the enhancement statute.[93] Justice Scalia, writing for the court and joined by all the Justices but Ginsburg and Sotomayor, who concurred, held that but-for causation was the background principle against which "Congress legislate[s]" and that the ordinary meaning of the phrase "results from" indicated a Congressional intention to require but-for causation.[94] Accordingly, the enhancement statute could not be applied where there was no evidence from which a jury could conclude beyond a reasonable doubt that the heroin the defendant supplied was the but-for cause of death.

As a result of the court's decision in *Burrage*, several of the convictions of physicians discussed here have been revisited. In the *MacKay* case, the physician's sentence of 240 months (20 years) was reduced to 36 months.[95] The impact on the Schneiders was even more significant. The trial court concluded that the enhanced sentence for all but one of the death counts had to be vacated because it could not conclude that the jury would have reached a different result if a "but-for" causation instruction had been given.[96] As to the other count, the court held that the evidence was sufficient for the jury to have found but-for causation beyond a reasonable doubt and conclude that the instruction error was, therefore, harmless.[97]

Several commentators have criticized the Supreme Court's *Burrage* decision. Some criticize Justice Scalia's view that the plain meaning of the "resulting from" language is, in fact, but-for causation and that many states have adopted a view that causation can be based on contributory effect, even if but-for causation cannot be shown.[98] Other commentators have bemoaned the fact that *Burrage* increases the prosecutorial burden for death "resulting from" cases such that an effective deterrent to overprescription of opioids has been removed from the government's arsenal.[99] It remains to be seen, however, whether *Burrage* has, in fact, trimmed prosecutorial zeal for charging physicians in opioid cases involving death. It also remains to be seen whether the mandatory enhancements under 841(b)(1)(C) will remain the law should civil justice reform wipe away the concepts of mandatory maximum and minimum sentences. It remains the law, however, that physicians can be prosecuted and punished under the CSA for their prescribing practices of opioids that are not in accord with professional standards. The only question is how long a sentence can be imposed.

9.1.4 Litigation

The opioid crisis has given rise to a wide variety of litigation, including lawsuits brought by state attorneys general, city mayors, Indian Nations, and private parties against pharmacies, doctors, manufacturers, distributors, and others. In August 2019, the first bench trial concluded in Oklahoma state court, resulting in the first ruling holding a drug company responsible for the opioid crisis. Judge Thad Balkman ordered that Johnson & Johnson pay the state over $572 million, which he calculated to be the cost of the first year of a plan to abate the public nuisance caused by the opioid crisis.[100] He later acknowledged that he had made a $107 million math error, which will be corrected in the future. Oklahoma's sole (and novel) claim for relief against the defendants was for causing a public nuisance pursuant to 50 O.S. 1981 § I et seq.[101] The state had sought over $17 billion to combat the epidemic over the next three decades, but the judge held that the state did not present sufficient evidence of the amount of time and costs necessary to abate the epidemic beyond the first year of an abatement plan. The case was originally brought by the state against Purdue, Teva, and Johnson & Johnson, but the state settled with other defendants before the case went to trial in May.[102] On September 25, Johnson & Johnson filed an appeal with the Oklahoma Supreme Court, arguing that the ruling "disregard[ed] a century of precedent."[103] As of November

2019, the appeal remains pending before the Oklahoma Supreme Court.

9.1.4.1 Overview of Allegations

Many of the claims in these cases are similar regardless of whether the defendant is a distributor or a manufacturer of opioids. Typical claims against manufacturers include unjust enrichment, negligence, false advertising, violations of public nuisance laws, fraud, deceptive marketing, racketeering, corruption, and violations of federal and state laws regarding controlled substances and unfair competition. Claims against distributors may additionally include diversion, failure to report suspicious orders to DEA, and violations of the RICO. Claims against pharmacies include, among others, violations of the CSA and FCA. As explained in more detail later, these claims show that the government and private parties are asserting a plethora of civil legal theories against numerous parties involved in the manufacture and distribution of opioids.

9.1.4.2 Manufacturers and Distributors

Private parties, along with cities, states, and Indian tribes, have sued manufacturers and distributors of opioids under a variety of theories, many of which overlap. At the most basic level, plaintiffs allege that opioid manufacturers and/or distributors failed to communicate to patients and doctors both (1) the efficacy of the drugs and (2) the risk of overdose, addiction, and death. Plaintiffs typically assert false advertising or misrepresentation as legal theories to support such claims.[104] Plaintiffs also allege that manufacturers, in particular, overstated the benefits and downplayed the risks of opioids for decades, which in turn led to overprescription of the drugs, overuse, addiction, and death.[105] Plaintiffs also assert violations of state consumer protection laws, alleging that manufacturers misled consumers regarding the safety and efficacy of their products.[106] Plaintiffs also claim fraud, including Medicaid fraud, based on allegations that manufacturers made false statements to obtain reimbursements.[107]

One of the more unusual claims that plaintiffs allege is public nuisance, as was the case in the first bench trial mentioned earlier. Generally, public nuisance is "an unreasonable interference with a right common to the general public," including conditions that endanger public health or safety.[108] This doctrine is typically used by a government entity in the context of interference with real property or infringement of public rights. Government entities bringing suit in the context of opioid litigation argue that because the opioid epidemic has resulted in harm to the community, subverts public order, and causes inconvenience to the public in general, public nuisance is an appropriate basis for their claims.[109] For example, the City of Miami sued manufacturers, distributors, and pharmacies in April 2018, alleging that the "Defendants … made fraudulent and negligent misrepresentations, were negligent and grossly negligent, created a public nuisance, and were unjustly enriched."[110] States, cities, and Native American tribes across the country have pled this legal theory in opioid-related litigation. Although Johnson & Johnson's appeal from the first bench trial remains pending, we may expect plaintiffs to bring more public nuisance claims in the future given Judge Balkman's ruling.

Plaintiffs often assert the additional legal theory of "diversion" against opioid distributors. Plaintiffs contend that distributors have allowed diversion of the drugs because they were aware (or should have been aware) that particularly high amounts of opioids were sold to particular communities, leading to oversupply and abuse. They claim that distributors should have noticed such diversion as a "red flag" and should have taken precautions to prevent the distribution to those communities.[111] This theory may be asserted as a violation of federal and state laws intended to prevent diversion.[112] The Cherokee Nation, for example, filed such a suit in April 2017 against distributors, including McKesson Corporation, Cardinal Health, AmerisourceBergen, CVS, Walgreens, and Walmart. The basis of the plaintiffs' diversion claim is that the distribution companies allegedly filled suspicious orders from retailers that were unusually large or unusually frequent and in violation of the FCA and state law. The complaint alleges that distributors allowed massive quantities of opioids to be diverted to the black market, which exacerbated the epidemic of opioid abuse in the Cherokee Nation.[113]

In addition to claims of diversion, plaintiffs, including Native American Nations and states, allege that both distributors and manufacturers should be held liable for unjust enrichment due to additional profits they made at the expense of plaintiffs.[114]

9.1.4.2.1 Multidistrict Litigation

Given the explosion of opioid lawsuits across the country, the Judicial Panel on Multidistrict Litigation (JPML) in late 2017 created a multidistrict litigation (MDL) in the Northern District of Ohio to handle pretrial matters in many similar opioid cases filed around the country in a consolidated fashion. The JPML tasked Judge Dan Polster of the Northern District of Ohio with structuring and managing about 300 lawsuits involving plaintiffs such as local governments, hospitals, unions, and Native American tribes with suits involving claims against drug manufacturers, distributors, and pharmacies. The allegations by plaintiffs in the MDL include that opioid manufacturers overstated benefits and understated risks in marketing the prescription medications to doctors. Plaintiffs also allege that distributors failed to monitor, detect, and/or investigate suspicious orders of opioids. Manufacturer defendants in the MDL include Actavis Generics, Allergan plc, Cephalon, Inc., Endo International plc, Janssen Pharmaceuticals, Johnson & Johnson, Purdue Pharma L.P., Teva Pharmaceutical Industries Ltd., and Watson Pharmaceuticals, Inc.[115] Distributor defendants include AmerisourceBergen Corporation, McKesson Corporation, and Cardinal Health, Inc., which together allegedly distributed more than 80% of the drugs at issue.

Despite defense objections to consolidation of these cases, the JPML held that the cases brought against opioid manufacturers and distributors shared common issues of fact, such as the manufacturers' and distributors' knowledge of alleged diversion and alleged improper marketing. The JPML concluded that MDL was an appropriate process for the complex cases.[116] Plaintiffs' lawyers argue that damages could amount to hundreds of billions of dollars.[117]

The Northern District of Ohio was chosen as the district to oversee the MDL because of its strong connection to the opioid epidemic as well as Judge Polster's experience with opioid litigation.[118] Judge Polster has aggressively advocated for early settlement. In late March 2018, Judge Polster compelled the disclosure of alleged competitive business information, which is normally protected from disclosure during the discovery phase of litigation, from AmerisourceBergen, Cardinal Health Inc., and McKesson Corporation. Judge Polster reasoned that the chances of early resolution of the MDL litigation would be enhanced by requiring these disclosures early. He directed the parties to prepare certain cases to proceed in the MDL and set three consolidated cases for a 3-week bellwether trial starting March 18, 2019. Plaintiffs' lawyers frankly noted: "We're very pleased because trial dates tend to force settlement – that's a truism in our world."[119]

Although the plaintiffs who initially moved to consolidate the litigation into an MDL were cities, states, and counties, plaintiffs in the MDL now include Native American tribes, hospitals, and private individuals. For example, the New York Attorney General sued Insys Therapeutics, Inc. for misrepresenting that its spray version of fentanyl was safe for non-cancer patients and appropriate for treating mild pain. Although Insys's product was approved by the FDA in 2012, the Attorney General claims that Insys encouraged sales representatives to recommend higher doses of the drug than were medically necessary.[120] Ohio's Attorney General also brought suit against opioid distributors McKesson, AmerisourceBergen, Cardinal Health, and Miami-Luken, Inc. for allegedly selling opioids in violation of state and federal laws meant to stop diversion. The Attorney General sued drug manufacturers in both state court and multidistrict litigation.[121]

In October 2019, the first MDL bellwether case settled hours before trial was set to begin.[122] Two Ohio counties, Summit and Cuyahoga, accepted a settlement deal of approximately $260 million from distributors AmerisourceBergen, Cardinal Health, and McKesson and manufacturer Teva Pharmaceuticals.[123] Other defendants had settled earlier. However, there remain thousands more plaintiffs in the MDL, and cases remain on track for trial. The deals still await final approval.

Ironically, a month prior to settlement, some of the drug companies had urged Judge Polster to recuse himself from presiding over the trial because of his encouragement for parties to settle and for commenting to the press about the litigation.[124] Once Judge Polster refused to recuse himself, the petitioners sought a writ of mandamus with the Sixth Circuit to compel him to step aside. The Sixth Circuit rejected the motion, explaining that Judge Polster "pushed for settlement not because he had prejudged the case, but because that was the most expedient way to conclude the dispute."[125] The Sixth Circuit provided some advice to MDL judges involved in high-profile litigation, however:

> Judge Polster's statements to the press and in court might call into question his impartiality. But we must take his statements in context. Judge Polster equally placed blame on all parties … While we may not have chosen to make the statements, grant the interviews, or participate in the programs that form the basis for this petition, particularly in a case of such enormous public interest and significance, and while we do not encourage Judge Polster to continue these actions, we nevertheless conclude that Petitioners have not established that they are entitled to a writ of mandamus requiring Judge Polster's recusal on the basis of this conduct.[126]

Judge Polster himself commented that he had been active in encouraging settlement, but explained:

> It goes without saying that if even a small fraction of the 2,000 cases in the MDL requires a months-long trial, the federal judiciary will be overwhelmed and most of the defendants would be forced into bankruptcy, simply because of litigation costs. … Ordinarily, the resolution of a social epidemic should be the responsibility of our other two branches of government, but these are not ordinary times.[127]

Further highlighting the extraordinary and novel nature of this litigation, Judge Polster approved plaintiffs' motion for a negotiation class, thereby permitting lawyers for a group of 49 cities and counties to negotiate class-wide settlements, on a voluntary basis, with defendants who make, distribute, or sell opioids nationwide.[128] This is the first time that Federal Rule of Civil Procedure 23 has been used to create such a class.[129] If 75% of voting class members support a proposed settlement, class counsel will ask the court to approve the settlement, which will then become binding on the class.[130] It remains to be seen whether such a class will achieve settlement more efficiently than through a bellwether trial process.

9.1.4.3 Prescribers and Pharmacies

Although manufacturers and distributors are the most significant targets of litigation, prescribers and pharmacies have not entirely avoided the opioid litigation. Plaintiffs have more recently brought claims against prescribers, pharmacies, and pharmacists for their role in the supply chain that facilitates people's access to prescription opioids.[131]

In 2018, Webb County, Texas sued the three largest pharmacy benefit management firms (PBMs) – CVS Caremark, Express Scripts, and OptumRx – as well as smaller PBMs that operate in Texas. Plaintiffs allege that the PBMs hid their financial relationships with drug makers, gave opioids better positions on their formularies, and

purposely included more addictive opioids in their formularies to generate larger profits.[132] Plaintiffs also allege that PBMs drove the opioid epidemic on the basis of increasing profits from such drugs.[133] The defense refutes these claims, arguing that "PBMs play a less significant role and one that's harder to ascribe liability to under traditional tort principles."[134]

9.1.4.4 Medical Malpractice

Perhaps the most expected type of litigation in the opioid epidemic context is medical malpractice litigation. Medical malpractice occurs when a hospital, doctor, or other healthcare professional, through a negligent act or omission, causes an injury to a patient.[135] Medical negligence is commonly defined as the failure of a physician to exercise the skill, care, and diligence generally exercised by physicians in the same medical community and under the same or similar circumstances.[136] The plaintiff in a medical malpractice suit must establish 1) that there is a physician–provider relationship that gives rise to a duty of care; 2) the applicable standard of care; 3) that the physician breached that standard of care; 4) that the breach was the cause of the plaintiff's injury; and 5) that the plaintiff incurred damages.[137] The prescription of opioid medications by physicians as pain management carries with it a high risk of litigation. This section outlines standard-of-care practices that may help decrease the risk of a medical malpractice suit and discusses some common lawsuits involving the prescription of opioid medications.

9.1.4.4.1 Standard of Care in Medical Malpractice Cases Involving Prescription of Opioid Medications

In determining whether a physician has breached the standard of care in lawsuits involving the prescription of opioid medications, courts may look to generally accepted clinical practices. Examples of these clinical practices are outlined by the Federation of State Medical Board of the United States in the Model Guidelines for the Use of Controlled Substances for the Treatment of Pain and by the Substance Abuse and Mental Health Services Administration (SAMHSA).[138] The practices for prescribing opioid medications include evaluating the patient, developing a treatment plan, obtaining informed consent, conducting periodic review, and complying with controlled substances laws and regulations.[139]

9.1.4.4.1.1 Evaluation To reduce the risk of litigation, physicians should conduct a thorough patient evaluation before prescribing an opioid medication. The physician should question the patient regarding the nature and intensity of the pain, the effect that the pain has on the patient, and past and current treatments.[140] The physician should also obtain a thorough medical history, including the patient's past use of drugs – both illicit and prescribed.[141] Many states have developed Prescription Drug Monitoring Programs (PDMPs), which prescribers should check to determine whether a patient is obtaining prescriptions for drugs from multiple physicians.[142]

Courts consider the adequacy of the physician's evaluation a key component in determining whether the physician breached the standard of care. Courts have refused to find against physicians where the physician "spoke with [the] patient, took a detailed history, and on the basis of all the circumstances, prescribed medications accordingly."[143]

9.1.4.4.1.2 Developing a Treatment Plan Physicians prescribing opioid medications should develop written treatment plans with their patients.[144] The plan should clearly state realistic goals to be reached in terms of both pain relief and improved physical and psychosocial function.[145] Importantly, physicians should only prescribe opioid medications if the expected benefits for pain relief outweigh the risks to the patient.[146] In making this determination, the physician should consider the severity of the patient's pain, the patient's reliability in taking medications, and the dependence-producing potential of the medication.[147] At least one court has found a physician liable for a patient's addiction to morphine where there was evidence that other, non-addictive drugs would have been equally effective in treating the patient's condition.[148]

Once an appropriate medication is selected, the physician should also carefully consider the appropriate dosage and duration of the prescription.[149] Many organizations have released handbooks that include guidelines on safe opioid dosage.[150] If possible, the patient should only receive opioid prescriptions from one physician and one pharmacy throughout the treatment to reduce the risk of abuse.[151]

9.1.4.4.1.3 Informed Consent As with any treatment, physicians must obtain informed consent from their patients before proceeding with an opioid treatment, including discussion of the risks and benefits of the treatment.[152] Because the failure to obtain a patient's informed consent may be considered a breach of the standard of care, obtaining a patient's informed consent is critical in avoiding medical malpractice liability. The informed consent agreement should be in writing and should be signed by both the patient and the physician.[153] The agreement should include the risks of the medication, the need to adhere to a single treatment regimen, that the patient agrees to obtain the medication from only one physician and to take it as prescribed, that the patient is responsible for safeguarding the medication, and the consequences of failure to adhere to the treatment plan, which may include refusing to treat the patient further, referral to a rehabilitation center, or referral of the patient's identity to tracking agencies to prevent doctor-shopping.[154]

9.1.4.4.1.4 Monitoring the Patient Prescribing physicians must monitor patients throughout treatment with opioid prescriptions, which may include speaking with family members and other close contacts about patients' progress. Regular follow-up appointments should be required to monitor the therapy and its effect on the patient's health.[155]

Monitoring subjective symptoms as well as objective symptoms, including body weight, pulse rate, and temperature, can identify early warning signs of opioid abuse and allow necessary treatment modifications.[156]

Failure to monitor opioid patients may form the basis for medical malpractice lawsuits. Physicians across the country have faced both civil and criminal charges for failing to monitor patients and ignoring warning signs that patients were abusing opioid medications.[157] For example, a New Mexico jury found a physician guilty of malpractice for allowing his patient to become addicted to morphine when the physician failed to meet regularly with a patient while continuing to prescribe opioid medications.[158] The monitoring might have to continue even after the physician has stopped the prescription. A judge in Georgia found that physicians breached their duty of care by failing to monitor the patient's respiratory function after his last dose of opioid medication, ultimately leading to the patient's death.[159]

9.1.4.4.1.5 Complying with Controlled Substances Laws and Regulation Executing the prescription order correctly is vital to prevent manipulation of the opioid prescription. The CSA requires that prescriptions for controlled substances be signed and dated on the day they are issued, and that the prescription include details such as the name and address of the patient, the name and address of the physician, the name and quantity of the drug, and directions for use, among others.[160] There are additional federal requirements for Schedule II classified drugs – the category into which many prescription opioid drugs fall.[161] DOJ makes available a Practitioner's Manual, which sets out the requirements involved in prescribing opioid medications.[162] State regulations often impose additional requirements.[163] For example, one New Jersey state court found a physician liable for medical malpractice when he prescribed postdated and undated prescriptions for narcotics in violation of federal regulations for Schedule II narcotics, which resulted in the patient's addiction.[164]

9.1.4.4.2 Types of Medical Malpractice Suits Involving Opioid Medications

In recent years, lawsuits involving the prescription of drugs have increased as the plaintiffs' bar broadened its circle of target defendants beyond pharmaceutical companies to include treating physicians as well.[165] Lawsuits involving the prescription of drugs are now the fourth most common kind of medical malpractice claim and often involve the prescription of opioids, even in some cases for a physician's failure to uncover fraud in obtaining the prescription.[166] The damages alleged in these lawsuits include overdose, addiction, and third party injury.[167] We may also see an increase in lawsuits involving the use of naloxone as it is becoming more readily available.

9.1.4.4.2.1 Overdose Cases Opioid-related medical malpractice claims cases against prescribing physicians often involve overdoses,[168] and the pool of potential plaintiffs is ever-increasing. The number of deaths resulting from opioid overdoses doubled from 21,089 in 2010 to 42,249 in 2016.[169] The media has reported on numerous cases involving doctors who allegedly negligently prescribed opioids, resulting in an overdose. For example, one suit against a Philadelphia area doctor resulted in a million-dollar settlement after the doctor prescribed nearly 200 narcotic pain and anxiety pills every week to a patient who ultimately overdosed and died.[170] The doctor testified that he did not perform routine physician checks such as ordering blood work or urine tests, reviewing records from other doctors, or properly diagnosing the patient's pain, nor did he take any measures to protect the patient when he suspected abuse of the drugs.[171] In a California case, a doctor was convicted of murder for recklessly prescribing drugs to patients after they disclosed their drug addictions and two admitted to dealing the drugs they were prescribed.[172] Notably, that physician was subject to both criminal and civil liability.[173]

9.1.4.4.2.2 Addiction Cases Patients also pursue malpractice actions against physicians when they become addicted to opioid medication. Under the learned intermediary doctrine, a drug manufacturer has a duty to warn of a drug's known dangerous propensities, including the risk of addiction, but it is the physician who has the duty to convey that warning to the patient.[174] Many manufacturers properly avoid liability because of this doctrine, making it more likely that physicians will be the targets of these suits.[175] For example, a Massachusetts jury found that a physician failed to meet the standard of skill and care required of him when he administered morphine to a patient over 3 years in increasing frequency until she became addicted.[176] The physician originally prescribed morphine without any physical examination of the patient or assessment of her pain and without conducting a medical history.[177] The jury found that the physician continuously increased the dosage and frequency of morphine, ultimately causing the patient to become addicted.[178] Similarly, a North Carolina court denied summary judgment for a defendant physician when there was evidence that a physician prescribed the narcotic pantopon, morphine, and other addictive drugs for over 12 years to a patient at increasing doses.[179] The physician did not evaluate the potential of using non-addictive substances to treat the patient's pain and failed to keep accurate records of the prescriptions.[180]

9.1.4.4.2.3 Fraud in Obtaining Prescriptions Cases Courts are split on whether a physician may be held liable for a patient's opioid addiction or overdose when a patient procures the drug by fraud. For example, a Mississippi court held that a patient could not maintain a malpractice action against a doctor for addiction to OxyContin when he obtained the drug "by misrepresenting his medical history and ongoing treatment to those from whom he sought care" and utilized ten doctors and seven pharmacies in multiple cities in order to obtain the drugs.[181]

In other jurisdictions, however, courts have held physicians liable for negligent behavior even when the patient engaged in fraudulent behavior. In a South Carolina case,

a jury found that the physician was negligent and reckless in overprescribing narcotic painkillers to the patient and failing to monitor the patient for addiction, but the court subsequently reduced the punitive damages award, where the patient deliberately overdosed on the pain medication.[182]

9.1.4.4.2.4 Third Party Injury Cases Third parties may bring medical malpractice cases against physicians for negligently prescribing opioids to a patient, which resulted in the injury or death to the third party. For example, in West Virginia, plaintiffs sued the prescribing physician after an opioid patient caused a car accident under the influence of the medication, killing a man and injuring his wife and children.[183] Plaintiffs alleged that the doctor negligently prescribed codeine and other addictive drugs for 17 years, causing the patient to become addicted.[184] The court held that the physician breached his duty of care by continuing to prescribe opioids over several years in spite of knowledge that the patient was a drug and alcohol abuser instead of taking action to rehabilitate the patient.[185]

9.1.4.4.2.5 Naloxone Cases Narcan®, a form of naloxone, stops or reverses opioid overdoses when given in a timely manner.[186] Given the popularity of Narcan® to reverse opioid overdose, the recent FDA approval of a Narcan® nasal spray,[187] and the U.S. Surgeon General's public health advisory encouraging greater availability and awareness of Narcan,®[188] it is possible that more suits will be filed alleging that healthcare workers negligently administered, or negligently failed to administer, Narcan®. For example, in a California medical malpractice suit against a hospital and its doctors, plaintiffs alleged that the hospital was negligent in failing to administer sufficient Narcan® during their decedent's opioid overdose.[189] The court dismissed the case, holding that the plaintiffs could not show that the doctors failed to comply with the standard of care in administering Narcan® during the decedent's overdose.[190] Nonetheless, it is likely that more cases involving the administration of Narcan® will be brought in the future.

9.1.5 Conclusion

The opioid epidemic has given rise to legislation, government regulation and enforcement actions, and massive nationwide litigation. Individuals and state governments are increasingly turning to courts to hold doctors, pharmacists, pharmaceutical companies, and insurance companies liable for opioid misuse, abuse, addiction, and overdose, with varying degrees of success. It must be expected that the plaintiffs' bar will continue to seek out new legal theories and targets to compensate patients and others affected by opioid abuse.

NOTES

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9.2 DAUBERT AND TESTING CLAIMS OF ADVERSE DRUG EFFECTS IN THE COURTROOM

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> There is something fascinating about science. One gets such wholesale returns of conjecture out of such a trifling investment of fact.
>
> **Mark Twain, Life on the Mississippi (1874)**

In today's litigious society, no textbook on the potential adverse health effects of drugs would be complete without a discussion of how claims of alleged adverse drug reactions are evaluated in the courtroom. While there are many examples of licit and illicit drugs that have scientifically established adverse effects, there are also many examples of medically indicated drugs that have been pulled from the market, in whole or in part, based upon perceived risks that are not borne out by the objective scientific data. Over the past 30 years, the courts have been inundated with scientifically-unfounded claims that pharmaceuticals or medical devices caused adverse health effects, starting with the allegations in the 1980s that the morning sickness drug Bendectin caused birth defects and continuing in the 1990s, 2000s, and beyond with, for example, claims of autoimmune disease from silicone breast implants and claims of strokes and cardiovascular diseases from the postpartum lactation drug Parlodel®. These cases have led the courts to develop important evidentiary rules that – when properly applied – prevent such unfounded claims from reaching the jury.

Ever since the United States Supreme Court's landmark ruling in the Bendectin case *Daubert v. Merrell Dow Pharmaceuticals, Inc.*,[2] judges have been tasked with the obligation to serve as gatekeepers to keep scientifically unreliable and irrelevant expert testimony out of the courtroom. The standards set forth in *Daubert*, which the Supreme Court has described as "exacting,"[3] have had a significant impact on numerous areas of legal dispute, but perhaps no area has been more affected than toxic tort and pharmaceutical product liability litigation. Under *Daubert* and its progeny, *General Electric v. Joiner*[4] and *Kumho Tire Co., Ltd. v. Carmichael*,[5] a plaintiff can no longer get a product liability claim before a jury based solely on an expert's subjective opinion that the plaintiff's injury was caused by a particular drug. Rather, the plaintiff must demonstrate that the expert's opinion is scientifically valid, both on the general causation question of whether the drug could potentially cause the injury in any patient and the specific causation question of whether the drug in fact did cause the particular plaintiff's injury.[6]

Daubert has imposed a significant obligation on trial courts, and many judges have struggled to understand the scientific principles that they must follow in their new role.[7] In addition, there have been "consistent efforts by recalcitrant judges to stop or roll back" the "radical changes wrought by the 'Daubert revolution.'"[8] Plaintiffs' counsel and like-minded legal observers have sought to take advantage of this uncertainty by arguing that the Supreme Court provided ambiguous guidance regarding the admissibility of medical causation testimony and that courts should defer to the judgment of medical experts so long as they follow the same "differential diagnosis" reasoning in their expert testimony as they do in their clinical practice.[9] These arguments are wrong. The guidance provided by the Supreme Court is clear: expert testimony that a drug caused an adverse event is admissible only if it is based on the scientific method, *i.e.*, evidence properly derived through the generating and testing of hypotheses. This guidance provides a simple framework for courts considering the variety of evidence generally put forth by causation experts in drug product liability litigation, whether it be epidemiology, animal research, chemical analogies, anecdotal information, or differential diagnosis.

In this chapter, we review the Supreme Court's adoption of the scientific method as the standard for admissibility of expert testimony and analyze how a court's proper understanding of the scientific method can guide it in evaluating the different types of causation evidence presented in pharmaceutical product liability litigation, both with respect to general and specific causation. Throughout this discussion and in the concluding section, we will draw on our firm's experience as national defense counsel in a series of product liability cases involving the prescription drug Parlodel®, in which these evidentiary issues have been analyzed in depth in judicial opinions across the country. The Parlodel® litigation has been described in another textbook as "the first significant products liability causation debate of the 21st century" and one that "will serve as a guide to understanding the significant causation issues that will continue to be involved, at increased rates of complexity, in the 21st century products cases."[10]

9.2.1 The Supreme Court's Directive: Expert Testimony Must Be Derived by the Scientific Method

In *Daubert*, the Supreme Court held that scientific testimony is not admissible unless it satisfies the dual requirements of scientific reliability and relevance. Scholarly debate regarding *Daubert* has often focused on the four factors suggested by the Court in determining scientific reliability: (1) testing, (2) peer review, (3) error rate and standards, and (4) general acceptance. However, a rote discussion of these factors misses the point. These factors are relevant only insofar as they assist the trial court in applying the overarching directive of *Daubert* that expert testimony must be based on the scientific method. The Supreme Court explained that "in order to qualify as 'scientific knowledge' an inference must be derived by the scientific method."[11] The Court defined the scientific method as follows: "Scientific methodology today is based on generating hypotheses and testing them to see if they can be falsified; indeed, this methodology is what

distinguishes science from other fields of human inquiry."[12] Moreover, "[s]cientific validity for one purpose is not necessarily scientific validity for other, unrelated purposes."[13] In other words, expert testimony is admissible only if empirical testing validates the specific theory to which the expert opines.[14]

Daubert also explains that while admissible expert testimony must be based on the scientific method, "there are important differences between the quest for truth in a courtroom and the quest for truth in the laboratory."[15] "[S]cientific conclusions are subject to perpetual revision. Law, on the other hand, must resolve disputes finally and quickly."[16] Accordingly, expert testimony must be judged based on the current state of scientific knowledge, not on the possibility that additional knowledge may emerge in the future. The Court recognized that the requirement of existing empirical evidence "on occasion will prevent the jury from learning of authentic insights and innovation" but held that this "is the balance struck by Rules of Evidence designed not for the exhaustive search for cosmic understanding but for particularized resolution of legal disputes."[17]

Four years after *Daubert*, the Supreme Court provided further guidance on how judges should use the scientific method in evaluating expert testimony. In *Joiner*, the plaintiffs' experts contended that their opinion (that PCBs can cause lung cancer) should be admitted because they relied on epidemiology and animal studies, which are standard tools used by scientists in testing causal hypotheses. The Court rejected this contention, explaining that a faithful application of the scientific method requires more: "whether animal studies can ever be the proper foundation for an expert's testimony was not the issue. The issue was whether *these* experts' opinions were sufficiently supported by the animal studies on which they purported to rely."[18] In other words, expert testimony must be based on empirical testing that *validates* the conclusions reached.[19]

The *Joiner* Court held that the research cited by plaintiffs' experts did not validate their conclusions because the epidemiological studies did not report a statistically significant causal link between PCBs and lung cancer, lacked proper controls, and examined substances other than PCBs, and because the animal studies involved massive doses of PCBs and a different type of cancer and could not be properly extrapolated to humans. Plaintiffs' experts could not support their opinions under the scientific method because their conclusions ultimately rested on subjective leaps from the scientific evidence. "[N]othing in either *Daubert* or the Federal Rules of Evidence requires a district court to admit evidence that is connected to existing data only by the *ipse dixit* of the expert. A court may conclude that there is simply too great an analytical gap between the data and opinion proffered."[20]

Two years later, in *Kumho Tire*, the Supreme Court held that the *Daubert* requirements of reliability and relevance apply to all expert testimony, including experience-based testimony. Even in areas where the four factors proposed in *Daubert* are inapplicable, the Court explained that the overarching question remains the same: "Is the expert's testimony supported by a methodology that has been objectively validated and supports the conclusions offered?"[21] In evaluating this question, the Court instructed that courts should consider whether the expert "employs in the courtroom the same level of intellectual rigor that characterizes the practice of the expert in the relevant field."[22]

9.2.2 Evaluating General Causation Evidence Under the Scientific Method

General causation opinions in drug product liability litigation may be based on a wide variety of evidence of differing scientific value, including, *inter alia*, epidemiology, animal studies, chemical analogies, case reports, and regulatory findings and other secondary sources. Some legal observers have argued that a medical expert's evaluation of this evidence involves a "complex inferential process" and that the expert accordingly should be allowed to simply lump this evidence together and reach "a subjective judgment about the strength of the evidence."[23] However, *Daubert* clearly requires more. Under *Daubert*, a trial court must consider each of these categories of evidence in light of the scientific method, and the expert's testimony may only be admitted if the expert can establish, through scientific evidence, that her causal hypothesis has been reliably tested and validated.

Further, a causation expert cannot satisfy her *Daubert* burden by arguing that the scientific research necessary to test her hypothesis has not been or cannot be performed. *Daubert* requires trial judges to evaluate expert testimony based on the science that exists at the time, not the possibility of new scientific discoveries in the future or guesswork as to what those discoveries might show.[24] As Judge Posner of the United States Court of Appeal for the Seventh Circuit explained, "the courtroom is not the place for scientific guesswork, even of the inspired sort. Law lags science, it does not lead it."[25]

9.2.2.1 Epidemiology

Controlled epidemiological studies are generally considered the most reliable evidence for testing a hypothesis that a particular substance causes a particular injury in humans.[26] Epidemiological studies can be especially important in cases where the drug or substance at issue is widely used or where there is a measurable background rate of the alleged injury regardless of exposure. In these situations, epidemiology may be the only way to test the hypothesis that observed injuries in exposed individuals are reflective of an increased risk and a causal connection rather than pure statistical chance.[27] While the absence of epidemiology may not be fatal to a plaintiff's case, numerous courts have held that a plaintiff seeking to establish causation without such evidence will face a high evidentiary hurdle.[28] A reliable causation opinion also cannot "simply ignore the epidemiology that exists."[29] Courts have also rejected expert testimony that is based upon a cherry-picking of isolated

epidemiologic findings without explanation for the expert's failure to consider contrary epidemiologic findings.[30]

When a causation expert relies on epidemiological studies to support her opinions, a trial court must analyze those studies to determine whether they provide a proper foundation for the expert's testimony under the scientific method. The finding in an epidemiological study of an *association* between a substance and an injury is not equivalent of *causation*.[31] There are three reasons that a positive association may be observed in an epidemiological study: (1) chance, (2) bias, and (3) real effect.[32] As the Supreme Court recognized in *Joiner*, epidemiological research cannot provide a scientifically reliable basis for an affirmative causation opinion if it is statistically insignificant or inadequately controlled for bias.[33]

Epidemiologists attempt to account for the possibility of chance by calculating "confidence intervals" around point estimates of potential increased risk derived from epidemiological studies. An epidemiological study is considered to show a statistically significant association with an increased risk if the confidence interval of upper and lower bound estimates of risk does not include the possibility of no increased risk in the exposed population. The possibility of no increased risk is referred to as the "null" hypothesis, which is generally indicated by a relative risk or odds ratio of 1.0.[34] The generally accepted confidence interval in epidemiological studies is 95%, meaning that a study is not statistically significant unless the "null" hypothesis of no increased (or decreased) risk can be excluded with 95% confidence.[35] If an epidemiological study is not statistically significant, it cannot provide scientifically reliable evidence of an association, let alone causation.[36] Further, numerous courts have held that epidemiological evidence can only support a conclusion that a substance is more likely than not the cause of disease if it establishes a doubling of the risk of the disease.[37] The reasoning behind this requirement is that if exposure does not at least double the risk of injury, then more than half of the population suffering from injuries allegedly caused by the substance would have been injured anyway through pure chance (based on the background risk of injury) thereby disproving "more likely than not" legal causation. Courts have also cautioned against reliance on statistically significant subgroup analyses, given the likelihood that numerous subgroup analyses will result in spurious statistical associations in some endpoints through chance alone.[38]

Bias in epidemiology is any systematic error that makes the two groups being compared different in more ways than just the variable being studied.[39] Common sources of bias include confounding factors (other factors associated with the studied factor that might account for a perceived increased risk), selection bias (uncontrolled differences between the studied populations), and information bias (systematic error in measuring data that results in differential accuracy of information).[40] A court must consider each of these sources of bias in interpreting an epidemiological study because bias can produce an erroneous association.[41] Thus, for example, courts have excluded expert causation testimony based on purported statistically significant epidemiologic evidence where the study failed to account for other confounding exposures that could have accounted for the apparent association.[42] Courts have rejected expert opinions that relied upon epidemiological studies where the subjects were not blinded to the study hypothesis.[43] Courts have rejected expert testimony based on epidemiological studies that failed to adequately address the possibility that injured subjects would be more likely to recall a preceding exposure than healthy controls ("recall bias").[44] Courts have also rejected expert testimony that relied upon epidemiological studies that failed to articulate selection criteria for participants in the study and thus could not account for selection biases "that could lead to erroneous inferences regarding causation."[45]

The existence of a well-controlled epidemiological study that reports a statistically significant increased association with a specific injury does not, by itself, provide scientifically reliable evidence establishing causation.[46] "The strong consensus among epidemiologists is that conclusions about causation should not be drawn, if at all, until a number of criteria have been considered."[47] In analyzing the scientific reliability of epidemiological evidence under *Daubert*, a number of courts have been guided by a set of criteria published by the noted epidemiologist Sir Austin Bradford Hill in 1965 ("the Bradford Hill criteria").[48] The Bradford Hill criteria can be summarized as follows: (1) strength of association, (2) consistency and replication of findings, (3) specificity with respect to both the substance and injury at issue; (4) evidence of a dose-response relationship, (5) temporal relationship, (6) biological plausibility, and (7) consideration of alternative explanations.[49]

In light of these criteria, courts have rejected statistically significant epidemiological research under *Daubert* where the reported relative risk is only slightly elevated[50] and have suggested that epidemiological research reporting a relative increased risk of less than three times indicates only a weak association (strength of association).[51] Courts have also rejected isolated, statistically significant epidemiological findings that are not replicated in other epidemiological research (consistency).[52] Courts have rejected epidemiological studies reporting statistically significant associations with allegedly similar substances or allegedly similar injuries (specificity).[53] And courts have rejected alleged associations in epidemiological studies that did not demonstrate a dose response relationship (dose response).[54] Moreover, courts have not accepted the mere incantation of the name of Bradford Hill as establishing the reliability of a causation hypothesis.[55] These criteria must be applied faithfully or they can also generate unreliable conclusions,[56] as demonstrated by two review papers published in 1989–1990 that both purported to use the Bradford Hill criteria to assess the epidemiological evidence regarding an association between alcohol consumption and breast cancer, but reached dramatically different conclusions.[57] Courts also have excluded causation opinions where the expert applied the Bradford

Hill analysis without first establishing that an association existed between the specific drug and the injury at issue.[58]

Causation experts sometimes attempt to bolster individually weak epidemiological studies by relying on "meta-analyses" in which otherwise insignificant or inconsistent findings are pooled to generate a single purportedly significant finding. This approach was rejected by courts in the Bendectin litigation,[59] and rightfully so. While meta-analyses can provide useful information if conducted pursuant to proper scientific methodology, they have frequently reported causal relationships that do not survive scientific scrutiny.[60] By pooling data from different studies, meta-analyses can paper over biases and other weaknesses in the underlying studies, disregard inconsistent findings, and improperly combine divergent population groups. As one commentator has explained, "[m]eta-analyses begin with scientific studies, usually performed by academics or government agencies, and sometimes incomplete or disputed. The data from these studies are then run through computer models of bewildering complexity, which produces results of implausible precision."[61] After finding that meta-analyses were frequently contradicted by subsequent large, randomized controlled trials, another investigator cautioned: "The popularity of meta-analysis may at least partly come from the fact that it makes life simpler and easier for reviewers as well as readers. However, over simplification may lead to inappropriate conclusions."[62] Pursuant to *Daubert*, a court must look behind the "bewildering complexity" of meta-analysis and protect against "inappropriate conclusions" by requiring the expert to establish the reliability and relevance both of the different pieces of information going into the meta-analysis and the calculations used to combine the information into a single result.

9.2.2.2 Animal Research

Animal research may be a useful tool for raising suspicions that can then be tested in humans, but there are significant differences in humans and laboratory animals that limit the degree to which animal research can validate a causation hypothesis in humans.[63] There are numerous examples of apparent positive findings in animal studies that have subsequently been found inapplicable to humans. The most commonly cited example, perhaps, is saccharine, which was linked to bladder cancer in rats over 20 years ago but was later removed from the National Toxicology Program list of potential human carcinogens after years of subsequent research failed to find any health risk in humans. Similarly, scientists have determined that a common insecticide, carbaryl, causes fetal abnormalities in dogs because dogs lack a specific enzyme involved in metabolizing carbaryl. Humans have the enzyme at issue and are accordingly not believed to be at risk.[64] Because of numerous such problems of extrapolation, courts repeatedly have held that animal studies alone cannot prove causation in humans.[65]

At a minimum, extrapolations from animal studies to humans are not considered reliable in the absence of a credible scientific explanation why such extrapolation is warranted.[66] In evaluating whether animal studies can form a reliable foundation for a causation opinion, trial courts should consider such factors as: (1) whether the results followed a dose response curve; (2) whether the animal studies involved massive doses, (3) whether the studies involved different routes of administration, (4) whether the studies are conducted in intact animals (as opposed, *e.g.,* to isolated animal parts), (5) whether the results have been replicated in different animal species, and (6) whether the animal models have been shown to be reliable predictors of human experience.[67]

Animal toxicology studies are not designed to establish whether a substance is safe in humans but rather to allow scientists to study the types of effects a substance can produce under specified conditions.[68] Accordingly, animal studies are often conducted with the goal of inducing the greatest number of adverse effects. This is accomplished in a number of ways, including the use of extremely high doses and exposures through special routes designed to deliver the substance directly to a particular organ without allowing for normal absorption and metabolization.[69] While these models are useful and appropriate in the laboratory as a means to generate hypotheses for further testing, they create additional problems for extrapolating study findings to humans.

The existence of a dose-response relationship has been described as the most fundamental and pervasive concept in toxicology.[70] All substances, even water, become toxic at a high enough dose. Conversely, however, "it has long been recognized that acute toxicological responses are associated with thresholds; that is, there is some dose below which the probability of an individual responding is zero."[71] As stated by the oft-described father of chemical pharmacology, Paracelsus (1493-1541), "What is there that is not poison? All things are poison and nothing [is] without poison. Solely a dose determines that a thing is not a poison."[72] Accordingly, even leaving to one side the issue of interspecies variations, the fact that a high-dose study results in adverse effects in animals cannot be extrapolated into a scientifically reliable conclusion that the substance can cause such effects at normal exposure levels in humans.[73] To the contrary, because toxic effects in humans are generally expected to appear in the same range on the basis of dose per unit of body surface as in experimental animals, a finding of adverse events in animals at only very high doses may be more indicative of the safety of the substance in normal use.[74]

The route by which a substance enters the body can also have a significant effect on its toxicity. Animal researchers frequently administer chemical agents through special routes, including, *inter alia*, (1) intraperitoneal, (2) subcutaneous, (3) intramuscular, and (4) intravenous.[75] These routes of administration may bypass the normal mechanisms through which potential toxins are removed before reaching the general circulation. For example, many substances are biotransformed and detoxified by the liver; while these substances may demonstrate toxic effects when

injected intravenously, intramuscularly, or subcutaneously, they are perfectly safe if ingested orally.[76] Likewise, animal researchers also use genetically designed or physically altered animals in which normal protective body mechanisms are removed.[77] These types of animal studies can be useful in studying how an animal's normal body mechanisms interact and how substances can affect isolated physiological systems, but they do not reflect real world risks, even in the species being studied.

In conducting its *Daubert* inquiry, a trial court also must determine whether the findings in the animal studies "fit" the opinions being offered in the case. Thus, an expert cannot rely on animal research that relates to a different injury than the one at issue. For example, animal carcinogenicity studies indicate that animals "react differently and in much more diverse ways than man" and that "compared to humans much more variation occurs in the cancer sites in animals."[78] However, in cases in which a chemical has been associated with cancers in both animal studies and epidemiological studies, "the target organ is usually identical."[79] In *Joiner*, the Supreme Court thus rejected animal research in part because the animals had developed a different type of cancer than the cancer at issue in the plaintiff.[80]

9.2.2.3 Chemical Analogies

Causation opinions derived from chemical analogies rely on the hypothesis that a substance's effects can be predicted based on the established effects of similarly structured compounds. Trial courts should be very wary of such "guilt-by-association" evidence,[81] particularly where there is scientific research involving the actual substance at issue that demonstrates differences between it and its purported chemical cousins. Because even small changes in molecular structure can radically change a particular substance's properties and propensities, research in analogous substances does not reliably test the causal hypothesis at issue.[82]

The difficulty in relying on chemical analogies has been demonstrated by attempts to create computerized programs to assess the toxicity of chemical agents based on structure-activity relationships ("SARs"). These computerized models are far more sophisticated than the simplistic chemical analogies often relied on by causation experts in toxic tort litigation, and often rely on additional information regarding a substance beyond its chemical structure. Even so, while these models ultimately may prove helpful in setting research priorities or generating hypotheses, they have failed to provide reliable predictions as to a chemical's toxic effect.[83] As reported in one survey article, two prediction toxicity exercises conducted under the aegis of the National Toxicology Program have found that models that attempt to predict carcinogenicity "based solely on information derived from chemical structure" have been particularly unreliable, with the first exercise reporting that "overall accuracy in terms of positive or negative predictions was in the range 50–65%" and the ongoing second exercise reporting even higher error rates in preliminary results.[84] Moreover, "[a] clear limitation of almost all the prediction systems ... was their excessive sensitivity, *i.e.*, incorrectly predicting many non-carcinogens as positive."[85] Efforts to predict toxicity based on structure activity relationships have resulted in similar problems.[86]

9.2.2.4 Case Reports/Case Series

Case reports and case series are anecdotal observations of adverse effects occurring in coincidence with exposure to a given substance. If a sufficient body of similar case reports appear in the literature, they can spur epidemiological or other controlled research to test the hypothesis that a causal link exists.[87] However, as most courts have properly recognized, case reports themselves do not test the causal hypothesis and accordingly cannot support a causation opinion under *Daubert*.[88] Case reports are merely anecdotal accounts of observations in particular individuals; they are not controlled tests, frequently lack analyses, and frequently make little attempt to screen out alternative causes for a patient's condition.[89] As discussed above, when the substance at issue is widely used, it is statistically certain given general background rates of injury that there will be case reports in which an exposure and an injury coincidentally coincide. Accordingly, the existence of such case reports is of little scientific value.[90]

Adverse drug experience reports ("ADEs") – reports made by third parties, usually physicians, concerning an adverse medical event in a patient taking a particular drug – are also widely rejected as scientifically reliable evidence of causation.[91] The spontaneous adverse event reports that a manufacturer may be required to submit to a federal or state regulator (for example, ADE reports required by the FDA) often have an even more attenuated "fit" with a plaintiff's alleged injury than case reports published in the literature. Spontaneous reports, such as those sent to the FDA, are required to be sent based on a temporal association between a reported event and the use of a substance, irrespective of whether there is a causal relationship involved. These reports are not reliable scientific evidence of medical causation, and their use by a regulator to carry out authorized regulatory purposes does not imbue them with any greater scientific reliability.[92]

In drug product liability cases, causation experts may rely on so-called "causality assessments" of individual case reports. Causality assessments are algorithms used in some European pharmacovigilance regulatory schemes that seek to impose some structure on evaluation of individual case reports by creating standardized questions to be used in the review of such reports, such as:

- Was the adverse event a known consequence of the drug?
- Did the event occur in temporal proximity to the use of the drug?
- Did the symptoms disappear upon withdrawal of the drug ("dechallenge")?
- Did the symptoms reappear following reintroduction of the drug ("rechallenge")?

- Are there alternative causes for the adverse event?

Reviewers then grade individual case reports using such terms as "not possible," "unlikely," "possible," and "probable."[93] Causality assessments are used by some regulatory agencies as a signaling tool, but "they have no objective reliability which would render them useful in a wider environment."[94] "None of the available causality assessment systems has been validated … In other words the uncertainty [inherent in case reports] is not reduced, but categorized (at best in a semiquantitative way)."[95] Studies of standardized causality assessments have repeatedly found significant disagreements between graders using the same assessment methodology.[96] Accordingly, causality assessments carry no greater scientific weight than other case reports and likewise cannot provide the type of evidence required under *Daubert*.[97]

Some case reports include information regarding purported dechallenges or rechallenges, *i.e.*, reports that a patient's condition improved when the substance was removed or worsened when the substance was reintroduced. Where the dechallenge/rechallenge report is merely an after-the-fact account of an anecdotal observation, it suffers from similar reliability problems as other case reports. Many medical conditions result in fluctuations in symptomology in the ordinary course, and apparent temporal associations with exposure may be due to pure chance. Even if the dechallenge or rechallenge is conducted prospectively with the intent of testing a causal hypothesis, a perceived effect in one person has limited scientific value at best.[98] Because the data are limited to a single observation, a trial court must be particularly diligent in determining whether the dechallenge/rechallenge was conducted under strict controls to account for potential confounding influences. Prospective dechallenge/rechallenge experiments – sometimes referred to as "single subject" or "n of 1" experiments – have numerous limitations that preclude general causation conclusions.[99] "[W]ithout strong assumptions regarding how an intervention on one individual relates to its effects on others, the results from a single-subject design provide little useful information ... [and e]xamination of a single subject cannot verify those assumptions."[100] As courts have explained, a prospective dechallenge/rechallenge report "constitutes but one single, uncontrolled experiment."[101]

9.2.2.5 Secondary Source Materials

In addition to actual scientific or anecdotal data, causation experts will sometimes rely on secondary source materials that cite to the primary evidence, such as regulatory materials, textbooks, and internal company documents. These secondary materials do not add any additional scientific knowledge and are no more reliable than the evidence they cite.[102] They do not test a causal hypothesis; they merely report the findings of others.

In particular, regulatory findings do not provide relevant "peer review" for a causation opinion, because they are based on a risk-utility analysis that involves a much lower standard of proof than that which is demanded by a court of law.[103] For example, one article reported that the vast majority of regulatory withdrawals of approvals for drugs in Spain during the 1990s were based solely on case reports.[104] As one commentary observed, "law, societal considerations, costs, politics, and the likelihood of litigation challenging a given regulation all influence the level of scientific proof required by the regulator decision-maker in setting regulatory standards and make such standards problematic as reference points in litigation."[105]

9.2.2.6 The Scientific Method vs. Weight of the Evidence

One key issue in the assessment of general causation expert testimony is whether trial courts should defer to the expert's inchoate "weighing of the evidence" or instead require the expert to demonstrate that the individual lines of evidence upon which he relies are independently reliable evidence of causation. As a number of courts have noted, when predicated on individually unreliable pieces of evidence, the weight of the evidence methodology is inherently faulty because "[i]t amounts to a hollow whole of hollow parts."[106] Nonetheless, a number of courts have erroneously accepted "weight of the evidence" testimony.

In *Milward v. Acuity Specialty Products Group, Inc.*, the First Circuit Court of Appeals held that an expert witness could reliably opine as to whether benzene could cause a rare type of acute myeloid leukemia based upon his inchoate "weight of the evidence" assessment where none of the individual lines of evidence reliably supported a causation opinion.[107] The First Circuit explained that the plaintiffs' expert's "weight of the evidence" approach employed the methodology of abductive inference or inference to the best explanation, whereby – rather than drawing conclusions through logical inferences from known propositions or from a range of known particulars – conclusions "are drawn about a particular proposition or event by a process of eliminating all other possible conclusions to arrive at the most likely one, the one that best explains the available data."[108] The central flaw in the First Circuit's holding is that:

> [T] here is no way for a court to so evaluate the "weight of the evidence" approach followed by the Milwards' expert. An "inference to the best explanation" cannot be tested, it cannot be falsified, and it cannot be validated against known or potential rates of error. Ultimately, then, the court is left with nothing but the expert's self-serving assurances that he has weighed the evidence in a scientifically appropriate manner.[109]

In *Joiner*, the U.S. Supreme Court rejected a similar undefined weighing of evidence that was independently insufficient to support causation.[110] The Fifth and Tenth Circuits, along with numerous courts in other jurisdictions, also have expressly rejected causation opinions in which experts sought to aggregate individually unreliable lines of scientific evidence into a purportedly reliable "weight of the evidence."[111]

9.2.3 Causation Opinions Based On Clinical Reasoning

The question of whether clinical reasoning can reliably support a causation opinion must be considered separately with respect to general causation and specific causation. Doctors do not in their ordinary clinical practice reach scientifically reliable determinations regarding general causation; they make individualized treatment decisions based on the exigencies of the moment. Accordingly, clinical reasoning cannot reliably support a general causation opinion. On the other hand, clinical reasoning through a differential diagnosis may provide reliable support for a specific causation opinion, so long as the diagnosis is reached in a manner that it is faithful to the scientific method. Differential diagnoses conducted for tort litigation purposes raise unique issues of reliability, however, because they generally are conducted *post hoc* and not in the context of medical treatment.

9.2.3.1 Clinical Reasoning and General Causation

Doctors in their day-to-day practice are required to make treatment decisions for individual patients based upon the clinical information before them. These clinical judgments do not provide a reliable basis for a general causation opinion.[112] Courts have recognized that "[t]he ability to diagnose medical conditions is not remotely the same … as the ability to deduce … in a scientifically reliable manner, the causes of those medical conditions."[113] Doctors do not conduct scientific testing in their daily practice to determine whether particular substances can cause particular injuries. Indeed, few doctors have more than rudimentary training in the scientific methods used to determine causation.[114] Instead, they reach working diagnoses and make conservative medical judgments based on their Hippocratic oath to "first, do no harm."[115] Thus, for example, if a patient reports a recent exposure to a new medication or chemical substance, the doctor may order the patient to avoid further exposures based not on a scientific determination of causality but simply as a no-risk prophylactic measure.[116]

While doctors may reach tentative opinions regarding causation in the course of providing treatment, their opinions are not reached pursuant to the scientific method, but are instead based on inferential leaps that allow them to provide immediate therapeutic care. Clinical causation opinions based on differential diagnosis are "a mixture of science and art, far too complicated for its accuracy to be assessed quantitatively or for a meaningful error rate to be calculated."[117] Moreover, differential diagnosis only "follow[s] the causal stream up to a point where intervention is possible" because, typically, physicians "do not care about a disease's etiology ... unless understanding causation would assist in diagnosis and treatment."[118] As one court explained,

> Doctors in their day-to-day practices stumble upon coincidental occurrences and random events and often follow human nature, which is to confuse association and causation. They are programmed by human nature and the rigors and necessities of clinical practices to conclude that temporal association equals causation, or at least that it provides an adequate proxy in the chaotic and sometimes inconclusive world of medicine. This shortcut aids doctors in their clinical practices because the most important objective day-to-day is to help their patients and "first do no harm," as their Hippocratic oath requires. Consequently, they make leaps of faith. … [This type of] clinical impression is not the sort of scientific methodology that *Daubert* demands.[119]

Plaintiffs' counsel seeking to rely on clinical reasoning to support a general causation opinion will often cite to the language in *Kumho Tire* that an expert must "employ[] in the courtroom the same level of intellectual rigor that characterizes the practice of the expert in the relevant field."[120] This argument is misplaced, because, as explained above, "the relevant field[s]" for a general causation opinion are epidemiology and toxicology, not clinical medicine.[121] Plaintiffs' counsel will also argue that differential diagnosis is a well-recognized, scientifically reliable technique. But differential diagnosis is a reliable methodology only for "ruling out" alternative causes of injury from a list of possible causes; it does not "rule in" a substance as a potential cause in the first instance.[122] Courts therefore recognize that absent of a reliable general causation opinion, a differential diagnosis opinion is insufficient evidence of causation.[123]

9.2.3.2 Clinical Reasoning and Specific Causation

Although insufficient for purposes of general causation, a differential diagnosis may provide a scientifically reliable basis for a specific causation opinion – *i.e.*, that an established toxin in fact caused a plaintiff's injury. "In performing a differential diagnosis, a physician begins by 'ruling in' all scientifically plausible causes of the plaintiff's injury. The physician then 'rules out' the least plausible causes of injury until the most likely cause remains. The final result of a differential diagnosis is the expert's conclusion that a defendant's product caused (or did not cause) the plaintiff's injury."[124] However, an expert's bare assertion that he applied a differential diagnosis is not sufficient to satisfy *Daubert*. "[A]n expert does not establish the reliability of his techniques or the validity of his conclusions simply by claiming that he performed a differential diagnosis on a patient."[125] A trial court must determine whether the differential diagnosis is based on a reliable methodology. Accordingly, the expert must demonstrate that the differential diagnosis was based on a sufficient and valid clinical investigation.[126] The expert also must have a scientifically reliable basis for excluding alternative causes of the plaintiff's injury, including the possibility that the injury was idiopathic.[127] If the expert is the plaintiff's own treating physician, the same rigorous *Daubert* analysis applies to his or her proffered specific causation opinion.[128]

In analyzing the reliability of a specific causation opinion based on differential diagnosis, trial courts must ensure that the expert employs "the same level of intellectual rigor" in

the courtroom as a treating physician would employ in the ordinary care of patients.[129] An expert cannot simply look for all possible causes of a person's illness from the universe of potential causes and declare that each of them – including the exposure at issue – should be considered actual but-for causes for purposes of tort liability.[130] Even if an expert can show reliable scientific evidence supporting some level of increased risk from a drug, the expert cannot reliably point to the drug as the cause of an individual plaintiff's injury if that plaintiff has other independent risk factors that are more strongly associated with the injury in question. For example, assume that there is scientifically reliable epidemiological evidence showing a 3 times statistically significant increased risk of stroke in patients who used a given drug X. That evidence may be sufficient to support an expert's specific causation opinion with regard to a plaintiff who has no other risk factor for stroke. However, it would not be sufficient to support a specific causation opinion with regard to a patient who also suffers from uncontrolled hypertension and has smoked a pack of cigarettes a day for the past 20 years given the greater risks posed by those comorbid conditions. Where a plaintiff has other established risk factors that could have caused the plaintiff's injury, the expert must explain how he ruled out these other potential causes to reliably support an opinion that the injury was due instead to a drug exposure.[131]

A trial court also needs to evaluate an expert's differential diagnosis in light of the artificial circumstances in which it is reached. Unlike differential diagnoses conducted by doctors in their day-to-day practice, a differential diagnosis in a litigation context is often conducted in support of an already asserted legal claim of causation. This raises myriad possibilities of bias, both intentional and unintentional.

Consider a hypothetical example of typical large-scale drug product liability litigation. Based on anecdotal reports of adverse events and possibly pressure from special interest organizations like Public Citizen, the FDA recommends labeling changes or withdraws approval of a drug.[132] The same day, if not before, plaintiffs' firms will begin advertising for potential plaintiffs through various forms of media, including the internet, television, radio, and print media. Provided that the drug has been used by a relatively large number of patients, there will be a ready population of patients that had adverse events while taking the drug based solely on statistical chance due to the background rates of such events regardless of drug use. Accordingly, plaintiffs' counsel can quickly gather a large pool of potential plaintiffs.

Plaintiffs' counsel will then start weeding through that pool to exclude individuals with obvious alternative causes for their injuries and patients whose injury did not emerge in temporal proximity to their ingestion of the drug. At first blush, this might appear to be a reliable method for determining those individuals whose injuries were more likely due to the drug. That interpretation, however, is based on the false premise that medicine can always find a cause for an injury. In fact, there are many conditions for which medicine frequently cannot find a cause.[133] In other words, there is often a measurable background rate of *idiopathic* injuries, *i.e.*, injuries with unknown causes. In addition, "[t]emporal proximity is generally not a reliable indicator of a causal relationship."[134] Plaintiffs' counsel's weeding out process, accordingly, often merely identifies the statistically-expected population of patients who coincidentally had adverse events of unknown cause while taking the drug.

At the same time plaintiffs' counsel are reviewing their potential plaintiff population, they will also be looking for an expert witness to provide a specific causation opinion. Generally, plaintiffs' counsel will select an expert who is already prepared to offer a favorable general causation opinion. Plaintiffs' counsel will also select an expert witness who is pre-disposed towards providing a favorable specific causation opinion. This does not mean that the expert is intentionally biased or insincere in his opinion, but it does mean that the expert will enter the process with a preconceived assumption of causality.

By the time the expert and plaintiff are brought together for purposes of a differential diagnosis, the result is effectively preordained. The expert will start his examination from the premise that the substance at issue is dangerous and a likely cause of injury regardless of potential alternative causes. The plaintiff will not present with obvious alternative causes of injury sufficient to shake the expert from his initial presumption. Moreover, in cases where the expert is not the patient's treating physician, the expert will not test his initial diagnosis through ongoing observation and medical treatment.

This "differential diagnosis" bears little resemblance to a differential diagnosis conducted by treating physicians in their regular practice, and cannot provide the type of objective validation that *Daubert* requires for admissibility of an expert specific causation opinion. Trial courts must recognize that there is an inherent "selection bias" at work in mass drug product liability litigation and carefully evaluate the expert's specific causation opinion with this artificial background in mind.

9.2.4 The Parlodel® Litigation

During the 1990s and 2000s, a number of product liability cases involving the prescription drug Parlodel® worked their way through the courts. The Parlodel® litigation resulted in a body of *Daubert* case law that squarely addresses the issues of medical causation expert testimony discussed above and provides a detailed analysis of "all of the components of the 'causation' argument that are available to experts in the most contentious of products liability case[s]."[135]

A judicial consensus emerged that plaintiffs' experts' causation opinions in the Parlodel® litigation do not satisfy the requirements of *Daubert*. Three federal appellate courts, the Eighth, Tenth, and Eleventh Circuits, unanimously affirmed district court opinions excluding the causation opinions of plaintiffs' experts, and four other

published district court opinions excluding this testimony were not appealed.[136] A few earlier district court opinions, two of which were drafted by the same magistrate judge, have gone the other way.[137] The Parlodel® opinions thus provide a useful *Daubert* case study of courts that properly evaluated medical causation testimony based on the scientific method and those that do not.

9.2.4.1 Plaintiffs' Allegations Regarding Parlodel®

Parlodel® (bromocriptine mesylate) is an FDA-approved drug used for a variety of indications, including Parkinson's Disease, amenorrhea/galactorrhea (lack of menses), infertility, and acromegaly (a growth disorder). From 1980 to 1994, Parlodel® was also approved for the prevention of postpartum lactation ("PPL") in women who elected not to breast-feed. The manufacturer of Parlodel® withdrew the drug from the market for this PPL indication following receipt of a number of case reports of strokes, seizures, and myocardial infarctions and an FDA advisory committee determination that there was limited need for pharmaceutical treatment for PPL. The FDA withdrew its approval of Parlodel® for the PPL indication in 1995, based on its conclusion that the limited utility of the drug for PPL did not outweigh the possible risks.[138]

Plaintiffs' experts allege that Parlodel® causes vasoconstriction (a narrowing of blood vessels) which they allege can cause stroke, seizures, and myocardial infarction. Plaintiffs' experts' concede that the epidemiological studies conducted on the drug have not established a causal link with these injuries and that there is a body of controlled clinical research in humans that has found that Parlodel® has the exact opposite effect of causing vasodilation (a widening of blood vessels). Plaintiffs' experts also concede that controlled intact animal research has not shown a causal link between Parlodel® and strokes, seizures, or myocardial infarctions in animals. Plaintiffs' experts base their causation opinion on anecdotal case reports (including alleged dechallenge/rechallenge reports), animal research involving limited endpoints, chemical analogies, a variety of secondary source materials, and differential diagnoses.[139]

9.2.4.2 Opinions Admitting Plaintiffs' Experts' Causation Opinions

The district courts that have admitted plaintiffs' experts' causation opinions have relied primarily on differential diagnoses and the determination that lesser scientific evidence of general causation should be accepted because it allegedly would not be possible to conduct an epidemiological study of sufficient strength to adequately test plaintiffs' experts' causation hypothesis. Thus, one magistrate judge dismissed the lack of any direct scientific evidence supporting plaintiffs' experts' causation opinion, reasoning that "[s]cience, like many other human endeavors, draws conclusions from circumstantial evidence, when other, better forms of evidence [are] not available."[140] In a subsequent opinion, the same magistrate judge sounded a similar theme: "In science, as in life, where there is smoke, fire can be inferred, subject to debate and further testing."[141] The court was similarly deferential in its review of plaintiffs' experts' specific causation opinions. While noting that there were a number of alternative causes for the injuries at issue, the court found that the "debate creates a question about the weight to be accorded the plaintiffs' experts' opinions, but it does not affect the admissibility."[142]

Missing in these opinions is any recognition of the requirement in *Daubert* that the experts' causation opinions be based on the scientific method of testing and validating hypotheses. *Daubert* does not permit expert testimony to be admitted based on the smoke of anecdotal reports and inferences, nor does it allow courts to lower the bar of scientific reliability based on a perceived lack of relevant scientific evidence. In accepting plaintiffs' experts' lower showing of evidence, these courts abdicated their gatekeeping responsibility.

9.2.4.3 Opinions Excluding Plaintiffs' Experts' Opinions

By contrast, in the Parlodel® cases in which courts have evaluated plaintiffs' experts' opinions based on the scientific method, the experts' testimony has been excluded. These courts have conducted detailed analyses of each of the different categories of evidence discussed above, and their reasoning and conclusions are incorporated in that discussion. The overarching theme in these opinions is the courts' recognition that medical causation opinions are not admissible unless they are based upon scientifically tested and validated hypotheses.

As these courts have explained, *Daubert* does not establish a "best efforts" test.[143] An expert cannot satisfy *Daubert* by arguing that he has "used the best methodology available under the circumstance,"[144] or that he has "done the best [he] could with the available data and the scientific literature."[145] Rather, the expert must answer the "key question," whether the "theory being advanced by the expert is testable or has been tested, the methodology of which is what distinguishes science from other fields of human inquiry."[146] "The hallmark of [*Daubert*'s] reliability prong is the scientific method, *i.e.*, the generation of testable hypotheses that are then subjected to the real world crucible of experimentation, falsification/validation, and replication."[147] The "testing of hypotheses" is "a critical aspect of the application of the scientific method."[148] Expert opinions "reposed in the realm of 'may cause' or 'possibly could cause'" must be excluded.[149] "While hypothesis is essential in the scientific community because it leads to advances in science, speculation in the courtroom cannot aid the fact finder in making a determination of whether liability exists."[150]

These Parlodel® cases forcefully answer critics of *Daubert* who argue for a lower standard based on deferential review of medical causation testimony:

> The *Daubert* trilogy, in shifting the focus to the kind of empirically supported, rationally explained reasoning

> required in science, has greatly improved the quality of the evidence upon which juries base their verdicts. Although making determinations of reliability may present the court with the difficult task of ruling on matters that are outside its field of expertise, this is less objectionable than dumping a barrage of scientific evidence on a jury, who would likely be less equipped than a judge to make reliability and relevancy determinations.[151]

The scientific method serves as a bulwark against subjective judgments and inspired guesswork masquerading as scientific knowledge. Courts that ignore the scientific method in their review of medical causation opinions do a disservice to the legal system and disregard the Supreme Court's mandate.

9.2.5 Conclusion

Faced with the exacting standards of *Daubert*, plaintiffs' causation experts will often respond with a spaghetti-on-the-wall strategy in the hope that something will stick. The Supreme Court's adoption of the scientific method as the central guide to admissibility provides district courts with the solution they need to untangle the mess. For each strand in plaintiffs' expert's analysis, the questions are the same: Is the expert relying on evidence that has been tested and validated, and does the evidence fit the question at issue? Unless an expert can answer both of these questions in the affirmative, he should not be allowed to serve up his opinions to a jury.

As Supreme Court Justice Breyer explained in his concurring opinion in *Joiner*, the evidentiary safeguards imposed by the courts against unreliable science provide an important bulwark against unfounded litigation that can threaten access to needed healthcare:

> [M]odern life, including good health as well as economic well-being, depends upon the use of artificial or manufactured substances ... [I]t may, therefore, prove particularly important to see that judges fulfill their *Daubert* gatekeeping function, so that they help assure that the powerful engine of tort liability, which can generate strong financial incentives to reduce, or to eliminate, production, points toward the right substances and does not destroy the wrong ones.[152]

While this textbook has focused primarily on the dangers of *drug abuse*, the potential dangers of *litigation abuse* on the availability of medically-indicated pharmaceutical products also pose a threat to patient health that must not be ignored.

NOTES

1. Mr. Lasker and Ms. Barago are attorneys in the Washington, D.C. law firm Hollingsworth LLP, where they specialize in pharmaceutical and toxic tort litigation.
2. 509 U.S. 579 (1993).
3. *Weisgram v. Marley Co.*, 528 U.S. 440, 455 (2000).
4. 522 U.S. 136 (1997).
5. 526 U.S. 137 (1999).
6. *See*, *e.g.*, *Raynor v. Merrell Pharms. Inc.*, 104 F. 3d 1371, 1376 (D.C. Cir. 1997).
7. One survey of 400 state trial judges found that while a large majority of judges agreed that the role of "gatekeeper" was an appropriate one for a judge, most judges did not have a proper understanding of the scientific principles set forth in *Daubert*. *See* Sophia I. Gatowski, *et al.*, *Asking the Gatekeepers: A National Survey of Judges on Judging Expert Evidence in a Post-Daubert World*, 25(5) Law and Human Behavior 433 (2001).
8. David E. Bernstein, *The Misbegotten Judicial Resistance to the Daubert Revolution*, 89 NOTRE DAME L. REV. 27, 29-30 (2013); see also David E. Bernstein & Eric G. Lasker, Defending Daubert: It's Time to Amend Federal Rule of Evidence 702, 57(1) W & M Law Rev. 1 (2015).
9. *See*, *e.g.*, J. Kassirer & J. Cecil, *Inconsistency in Evidentiary Standards for Medical Testimony: Disorder in the Courts*, 288(11) JAMA 1382-87 (Sept. 2002); M. Berger, *Upsetting the Balance Between Adverse Interests: The Impact of the Supreme Court's Trilogy on Expert Testimony in Toxic Tort Litigation*, 64 SUM Law & Contemp. Probs. 289 (Spring/Summer 2001).
10. Terence F. Kiely, Science and Litigation: Products Liability in Theory and Practice 177 (CRC Press 2002).
11. 509 U.S. at 590.
12. *Id.* at 593. The Supreme Court cited to two philosophical texts on the nature of scientific evidence. *See id.* (citing C. Hempel, The Philosophy of Natural Science 49 (1966) ("[T]he statements constituting a scientific explanation must be capable of an empirical test"); K. Popper, Conjectures and Refutations: The Growth of Scientific Knowledge 37 (5th ed. 1989) ("[T]he criterion of the scientific status of a theory is its falsifiability, or refutability, or testability")).
13. *Id.* at 591.
14. The four factors discussed in *Daubert* provide different methods by which an expert's opinion can be analyzed for adherence to the scientific method. Two of the factors, testing and error rates, are integral parts of the scientific method itself. The other two factors, peer review and general acceptance, can provide independent support that the opinion was properly derived by the scientific method. Peer review, however, should not be mindlessly equated with publication. As the Supreme Court noted, publication "is but one element of peer review." *Daubert*, 509 U.S. at 593. Peer review, like general acceptance, refers more broadly to the concept that the theory at issue has been subjected to and found valid through empirical testing by the broader scientific community. *See generally* W. Anderson, *et al.*, *Daubert's Backwash: Litigation-Generated Science*, 34 U. Mich. J.L. Reform 619 (2001); E. Chan, *The "Brave New World" of Daubert: True Peer Review, Editorial Peer Review, and Scientific Validity*, 70 N.Y.U. L. Rev. 100 (1995).
15. *Daubert*, 509 U.S. at 596-97.
16. *Id.* at 597.
17. *Id.*
18. 522 U.S. at 145.
19. *See id.* at 146 ("conclusions and methodology are not entirely distinct from one another").
20. *Id.*
21. *See* 526 U.S. at 157 (noting with respect to challenged tire expert's testimony that "despite the prevalence of tire testing," plaintiffs did not "refer to any articles or papers that validate [the expert's] approach").

22. *Id.* at 152.
23. Kassirer & Cecil, *supra* note 9, at 1384, 1386; *see also* Berger, *supra* note 9.
24. 509 U.S. at 597.
25. *Rosen v. Ciba-Geigy Corp.*, 78 F.3d 316, 319 (7th Cir. 1996).
26. *See*, *e.g.*, *Soldo v. Sandoz Pharms. Corp.*, 244 F. Supp. 2d 434, 532 (W.D. Pa. 2003) (epidemiology is "the primary generally accepted methodology for demonstrating a causal relation between a chemical compound and a set of symptoms or a disease") (quoting *Conde v. Velsicol Chem. Corp.*, 804 F. Supp. 972, 1025-26 (S.D. Ohio 1992), *aff'd*, 24 F.3d 809 (6th Cir. 1994)); *Hollander v. Sandoz Pharms. Corp.*, 95 F. Supp. 2d 1230, 1235, n.14 (W.D. Okla. 2000) ("In the absence of an understanding of the biological and pathological mechanisms by which disease develops, epidemiological evidence is the most valid type of scientific evidence of toxic causation"), *aff'd*, 289 F.3d 1193 (10th Cir. 2002); *Breast Implant Litig.*, 11 F. Supp. 2d 1217, 1224-25 (D. Colo. 1998) (same, citing cases).
27. There has been some controversy regarding whether certain types of epidemiological studies should be considered inherently more reliable than others in establishing causation. Historically, courts have understood that randomized controlled clinical trials are less likely to report erroneous associations than observational epidemiological studies, like cohort or case control studies. *See In re Rezulin Prod. Liab. Litig.*, 369 F. Supp. 2d 398, 406 (S.D.N.Y. 2005); *see also* David H. Kaye & David A. Freeman, *Reference Guide on Statistics*, Reference Manual on Scientific Evidence (2d ed. 2000) at 94-95. However, research suggests that this understanding may be mistaken, *see* John Concato, *et. al.*, *Randomized, Controlled Trials, Observational Studies, and the Hierarchy of Research Design*, 342(25) New Eng. J. Med. 1887 (2000); John Concato, *Observational Versus Experimental Studies: What's the Evidence for a Hierarchy*?, 1 J. Am. Soc. Experimental NeuroTherapeutics 341 (2004). In a review of the most highly cited clinical research (defined as studies cited more than 1,000 times in the literature), a scientist concluded that 16% of the top-cited clinical research studies relating to medical interventions had been contradicted within the following 15 years and another 16% were followed by subsequent research suggesting that the initial findings may have been overstated. John P.A. Ioannidis, *Contradicted and Initially Stronger Effects in Highly Cited Clinical Research*, 294(2) JAMA 218 (2005). While epidemiological evidence can provide the best evidence of causation, as explained below, even the best study cannot establish that causation in fact exists.
28. *See*, *e.g.*, *Glastetter v. Novartis Pharms. Corp.*, 252 F.3d 986, 992 (8th Cir. 2001) (while not an absolute prerequisite, the lack of epidemiology "limited the available tools with which [plaintiff] could prove causation," and is a factor to be considered in evaluating the reliability of plaintiff's experts' methodology); *Siharath v. Sandoz Pharms. Corp.*, 131 F. Supp. 2d 1347, 1358 (N.D. Ga. 2001), *aff'd sub. nom Rider v. Sandoz Pharms. Corp.*, 295 F.3d 1194 (11th Cir. 2002).
29. *Perry v. Novartis Pharm. Corp.*, 564 F. Supp. 2d 452, 465 (E.D. Pa. 2008) (finding it "disquieting that [plaintiff's expert] fails to even mention [the only published epidemiology] study in his initial report."); *see also Gannon v. United States.*, 292 F. App'x 170, 174 (3d Cir. 2008) (expert testimony disallowed where expert, as well as Institute of Medicine, agreed epidemiologic evidence did not support causal relationship); *Norris v. Baxter Healthcare Corp.*, 397 F.3d 878, 882 (10th Cir. 2005) (where a large body of contrary epidemiological evidence exists, "it is necessary to at least address it with evidence that is based on medically reliable and scientifically valid methodology").
30. *See Arias v. DynCorp*, 928 F. Supp. 2d 10, 24-25 (D.D.C. 2013) (excluding opinion of expert who failed to explain why he credited one study and dismissed another); *Cano v. Everest Minerals Corp.*, 362 F. Supp. 2d 814, 850 (W.D. Tex. 2005) (rejecting testimony of expert who "sifted through the literature to pick and choose positive relative risks between ionizing radiation (of any type, source, and dose) and a particular Plaintiff's cancer").
31. *See* Michael D. Green, *Reference Guide on Epidemiology*, Reference Manual on Scientific Evidence (2d ed. 2000) at 336.
32. *See Magistrini v. One Hour Martinizing Dry Cleaning*, 180 F. Supp. 2d 584, 591 (D.N.J. 2002), *aff'd*, 68 Fed. Appx. 356 (3d Cir. 2003); *Caraker v. Sandoz Pharms. Corp.,* 188 F. Supp 2d 1026, 1032 (S.D. Ill 2001); *see also* Eddy A. Bresnitz, *Principles of Research Design* in Goldfrank's Toxicologic Emergencies 1827-28 (Goldfrank, *et al.* eds. 6th ed. 1998).
33. *See Joiner*, 522 U.S. at 145-46.
34. *See Turpin v. Merrell Dow Pharms., Inc.*, 959 F.2d 1349, 1353 n.1 (6th Cir. 1992).
35. *Id.*, at 723 (citing *DeLuca v. Merrell Dow Pharms., Inc.*, 791 F. Supp. 1042, 1046 (D.N.J. 1992), *aff'd*, 6 F.3d 778 (3d Cir. 1993)).
36. *See Joiner*, 522 U.S. at 145; *see also Wells v. SmithKline Beecham Corp.*, 601 F.3d 375, 380 (5th Cir. 2010) ("this court has frowned on causative conclusions bereft of statistically significant epidemiological support"); *Dunn v. Sandoz Pharms. Corp.*, 275 F. Supp. 2d 672, 681 (M.D.N.C. 2003) ("statistically insignificant results do not constitute proof" of causation); *Soldo*, 244 F. Supp. 2d at 533 ("Courts have emphasized that epidemiologic proof must be statistically significant.") (citing cases); *Caraker*, 188 F. Supp. 2d at 1034 (rejecting experts' causation opinions "inasmuch as they rely on selective use of statistically insignificant data from epidemiological studies"). Although some courts recently have questioned the necessity of statistically significant studies to support a causation opinion, they recognize that experts must adhere to the usual practice of their profession, which, for statisticians and epidemiologists, among others, entails finding a statistically significant association. *See In re Lipitor (Atorvastatin Calcium) Mktg., Sales Practices & Prods. Liab. Litig.*, 892 F. 3d 624, 642 (4th Cir. 2018) (district court correctly excluded opinion of statistician who did not adhere to the "norm" of first finding "a statistically significant association").
37. *See Magistrini*, 180 F. Supp. 2d at 591; *Siharath*, 131 F. Supp. 2d at 1356; *In re Breast Implant Litig.*, 11 F. Supp. 2d at 1225-26; *Hall v. Baxter Healthcare Corp.*, 947 F. Supp. 1387, 1403-04 (D. Or. 1996); *see also Daubert v. Merrell Dow Pharms., Inc,* 43 F.3d 1311, 1321 (9th Cir. 1995) ("*Daubert II*") ("A relative risk of less than two may suggest teratogenicity, but it actually tends to *dis*prove legal causation as it shows that Bendectin does not double the likelihood of birth defects"). *But cf. In re Hanford Nuclear Reservation Litig.*, 292 F.3d 1124, 1137 (9th Cir. 2002) (plaintiffs did not need to present epidemiological evidence showing a doubling of cancer risk from ionizing radiation at specific exposure levels because capability of ionizing radiation to cause cancer generally has been recognized by scientific and legal authority).

38. *See Newman v. Motorola, Inc.*, 218 F. Supp. 2d 769, 779 (D. Md. 2002), *aff'd* 62 Fed. R. Evid. Serv. 1289 (4th Cir. 2003).
39. *See Magistrini*, 180 F. Supp. 2d at 592.
40. *See Merrell Dow Pharms. v. Havner*, 953 S.W.2d 706, 719 (Tex. 1997); *see also* Bresnitz, *supra* note 32, at 1831-32; Michael D. Green, et al., *Reference Guide on Epidemiology*, Reference Manual on Scientific Evidence at 389, 392, & 395 (2d ed. 2000) (discussing sources of bias); David A. Grimes & Kenneth F. Schulz, *Bias and causal associations in observational research*, 359 The Lancet 248 (Jan. 19, 2002) (same, including real world examples of confounding errors).
41. *Magistrini*, 180 F. Supp. 2d at 591; *Caraker*, 188 F. Supp. 2d at 1032; *see also Havner*, 953 S.W.2d at 719 ("Bias can dramatically affect the scientific reliability of an epidemiological study.").
42. *See Nelson v. Tennessee Gas Pipeline Co.*, 243 F.3d 244, 252-54 (6th Cir. 2001) (expert's failure to account for confounding factors in cohort study or alleged PCB exposures rendered his opinion unreliable); *see also In re Bextra & Celebrex Mktg. Sales Practices & Prod. Liab. Litig.*, 524 F. Supp. 2d 1166, 1179 (N.D. Cal. 2007) (not scientifically reliable for expert to rely on study that failed to account for critical confounding factors).
43. *See Allison v McGhan Med. Corp.*, 184 F.3d 1300, 1315 (11th Cir. 1999) (noting that the women participating in the study at issue "were aware of the hypothesis, a factor which could have created bias, skewing the results and ultimately making the conclusions suspect").
44. *See Newman*, 218 F. Supp. 2d at 778; *see also Maras v. Avis Rent A Car Sys., Inc.*, 393 F. Supp. 2d 801, 808 (D. Minn. 2005) (rejecting expert testimony based on epidemiological study that, among other failures, may have been influenced by recall bias).
45. *In re TMI Litig.*, 193 F.3d 613, 707-08 (3d Cir. 1999); *see also Bouchard v. Am. Home Prods. Corp.*, 213 F. Supp. 2d 802, 809-10 (N.D. Ohio 2002) (excluding expert causation testimony to the extent based on epidemiological study tainted with selection bias).
46. *See*, *e.g.*, *Amorgianos v. Nat'l R.R. Passenger Corp.*, 137 F. Supp. 2d 147, 168 (E.D.N.Y. 2001), *aff'd*, 303 F.3d 256 (2d Cir. 2002).
47. *Havner*, 953 S.W.2d at 718.
48. *See Dunn*, 275 F. Supp 2d at 677-78; *Magistrini*, 180 F. Supp. 2d at 592-93; *Amorgianos*, 137 F. Supp. 2d at 168; *Castellow v. Chevron* USA, 97 F. Supp. 2d 780, 786-87 & n.2 (S.D. Tex. 2000); *In re Breast Implants*, 11 F. Supp. 2d at 1233 n.5; *Havner*, 953 S.W.2d at 718 & n.2.
49. *Id.*; *see also* Bresnitz, supra note 32, at 1827-28 (describing Bradford Hill criteria in detail); Grimes & Schulz, *supra* note 40 (same); Douglas L. Weed, *Underdetermination and Incommensurability in Contemporary Epidemiology*, 7(2) Kennedy Institute of Ethics Journal 107, 113-15 (1997) (same).
50. *See Allison*, 184 F.3d at 1315 (noting that statistically significant epidemiological study reporting an increased risk of marker of disease of 1.24 times in patients with breast implants was so close to 1.0 that it "was not worth serious consideration for proving causation."); *In re Breast Implants Litig.*, 11 F. Supp. 2d at 1227 (same).
51. *See Havner*, 953 S.W.2d at 719.
52. *See*, *e.g.*, *Miller v. Pfizer*, *Inc.*, 196 F. Supp. 2d 1062, (D. Kan. 2002) (expert failed to address "fact that other research is contrary to his conclusion), *aff'd*, 356 F.3d 1326 (10th Cir.), *cert denied*, 125 S. Ct. 40 (2004); *Havner*, 953 S.W.2d at 727 ("if scientific methodology is followed, a single study would not be viewed as indicating that it is 'more probable than not' that an association exists").
53. *See Joiner*, 522 U.S. at 145-46 (studies proffered as evidence of PCB-lung cancer link involved exposures to mineral oils or other potential carcinogens); *Burleson v. Tex. Dep't. of Criminal Justice*, 393 F.3d 577, 585-86 (5th Cir. 2004) (rejecting expert testimony where expert could not point to epidemiological studies demonstrating statistically significant link between thorium dioxide exposure and plaintiff's type of lung or throat cancer); *Allison*, 184 F.3d at 1315 (studies reported link to injuries not suffered by plaintiff); *Schudel v. Gen. Elec. Co.*, 120 F.3d 991, 997 (9th Cir. 1997) (studies involved exposures to organic solvents other than those at issue); *Magistrini*, 180 F. Supp. 2d at 603-04 (to same effect); *see also Wells*, 601 F.3d at 380 (rejecting as reliable causation evidence a study reporting "a class association, as opposed to a specific medication, finding"); *Jones v. Novartis Pharm. Corp.*, 235 F. Supp. 3d 1244, 1270 (N.D. Ala. 2017) (rejecting general causation opinion based on an association for an entire drug class, and not an association between the specific drug at issue and the injury alleged), *aff'd*, 720 F. App'x. 1006 (11th Cir. 2018).
54. *See Newman*, 218 F. Supp. 2d at 778 (no dose response relationship found in study involving cell phone use and cancer); *Kelley v. Am. Heyer-Schulte Corp.*, 957 F. Supp. 873, 879 (W.D. Tex. 1997).
55. *See Hollander,* 289 F.3d at 1204 (rejecting expert's causation testimony despite his claimed adherence to the Bradford Hill methodology): *Dunn,* 275 F. Supp. 2d at 677-78 (same).
56. *See Lust v. Merrell Dow Pharms. Inc.*, 89 F.3d 594, 598 (9th Cir 1996) ("the district court should be wary that the [expert's] method has not been faithfully applied"); *O'Conner v. Commonwealth Edison Co.*, 13 F.3d 1090, 1106-07 (7th Cir. 1994) (excluding opinion where expert did not follow his own expressed methodology for establishing causation); *Knight v. Kirby Inland Marine, Inc.*, 363 F. Supp. 2d 859, 864 (N.D. Miss. 2005) (expert's "Bradford-Hill analysis is only as reliable as the underlying data upon which it is based"); *Hall*, 947 F. Supp. at 1400 (quoting *Lust*).
57. *See* Weed (1997), *supra* note 49, at 115, 116-18 (discussing Robert A. Hiatt, *Alcohol Consumption and Breast Cancer*, 7 Medical Oncology Tumor Pharmacotherapy 143 (1990) (concluding that women with risk factors for breast cancer should limit alcohol use) and Ernst L. Wynder & Randall E. Harris, *Does Alcohol Consumption Influence the Risk of Developing Breast Cancer?* in Important Advances in Oncology 283 (V.T. Devita, S. Hellman, and S.A. Rosenberg eds. 1989) (concluding that there was no evidence of a causal link)).
58. *In re Lipitor*, 892 F. 3d at 642 (affirming exclusion of expert's general causation opinion where he deviated from the "norm" of relying on a statistically significant association before applying Bradford Hill analysis); *Jones*, 235 F. Supp. 3d at 1269 (holding that, before applying Bradford Hill criteria, expert needed to establish that an association "existed based on existing medical literature").
59. *See*, *e.g.*, *DeLuca v. Merrell Dow Pharms., Inc.*, 791 F. Supp. 1042, 1046-59 (D.N.J. 1992), *aff'd without op.,* 6 F.3d 778 (3d Cir. 1993); *see also Knight*, 363 F. Supp. 2d at 866 (rejecting causation opinion based on meta-analyses of cancer risks to chemical industry employees).

60. For examples, see Douglas L. Weed, *Interpreting epidemiological evidence; how meta-analysis and causal inference methods are related*, 29 Int'l J. Epidemiol. 387 (2000); Jacques LeLorier, *et. al.*, *Discrepancies Between Meta-Analyses and Subsequent Large Randomized, Controlled Trials*, 337(8) New Eng. J. Med. 536 (1997); Samuel Shapiro, *Is Meta-Analysis a Valid Approach to the Evaluation of Small Effects in Observational Studies?* 50(3) J. Clin. Epidemiol. 223 (1997); Samuel Shapiro, *Meta-analysis/Shmeta-analysis*, 140(9) Am. J. Epid. 771 (Nov. 1994).
61. Shapiro (1994), *supra* note 60, at 771.
62. LeLorier (1997), *supra* note 60, at 541; *see also* J. Berlin et al., *The Use of Meta-Analysis in Pharmacoepidemiology*, in Pharmacoepidemiology at 726 (5th ed. 2012) ("Combining a group of poorly done studies can produce a precise summary result built on a very weak foundation.").
63. *See*, *e.g.*, Irva Hertz-Picciotto, *Epidemiology and Quantitative Risk Assessment: A Bridge from Science to Policy*, 85(4) Am. J. Public Health. 484, 485 (1995) ("The uncertainty stemming from interspecies extrapolation is far larger than the uncertainty resulting from uncontrolled bias or errors in exposure information in epidemiological studies").
64. *See* Bernard D. Goldstein & Mary Sue Henifen, *Reference Guide on Toxicology*, Reference Manual on Scientific Evidence 420 n.48 (2d ed. 2000). For additional examples of the often dramatic differences in responses among animal species and between animals and humans, see David L. Eaton & Curtis D. Klaassen, *Principles of Toxicology* in Casarett & Doull's Toxicology: The Basic Science of Poisons 25-26 (Curtis D. Klaassen ed., 6th ed. 2001); Elaine M. Faustman & Gilbert S. Omenn, *Risk Assessment*, in Casarett & Doull's Toxicology: The Basic Science of Poisons, *supra*, at 88-90; Lorenz Rhomberg, *Risk Assessment and the use of information on underlying biological mechanisms: A perspective*, 365 Mutation Research 175, 179-80 (1996); Jan M. M. Meijers, *et al.*, *The Predictive Value of Animal Data in Human Cancer Risk Assessment*, 25 Regulatory Toxicology & Pharmacology 94 (1997).
65. *See Chapman v. Procter & Gamble Distrib., LLC*, 766 F.3d 1296, 1308 (11th Cir. 2014); *Johnson v. Arkema, Inc.*, 685 F.3d 452, 463 (5th Cir. 2012) (there is "very limited usefulness of animal studies when confronted with questions of toxicity") (citations omitted); *Siharath*, 131 F. Supp. 2d at 1367; *Wade-Greaux v. Whitehall Labs.,Inc.*, 874 F. Supp. 1441, 1483-84 (D.V.I. 1994), *aff'd without op.*, 46 F.3d 1120 (3d Cir. 1994).
66. *See Soldo*, 244 F. Supp. 2d at 565; *Siharath*, 131 F. Supp. 2d at 1366-67 (citing cases); *see also Newkirk v. ConAgra Foods, Inc.*, 727 F. Supp. 2d 1006, 1026 (E.D. Wash. 2010) (excluding expert who "offers no explanation for how and why the results of [rat] studies can be extrapolated to humans"), *aff'd*, 438 F. App'x 607 (9th Cir. 2011).
67. *See*, *e.g.*, *Joiner*, 522 U.S. at 144; *Hollander,* 289 F.3d at 1209; *Turpin,* 959 F.2d at 1358-61; *In re Rezulin Prod. Liab. Litig.*, 369 F. Supp. 2d at 406-07; *Caraker,* 188 F. Supp. 2d at 1037; *Wade-Greaux*, 874 F. Supp. at 1477.
68. *See* Eaton & Klaassen, *supra* note 64, at 27.
69. *See id.*; Karl K. Rozman & Curtis D. Klaassen, *Absorption, Distribution, and Excretion of Toxicants*, in Casarett & Doull's Toxicology: The Basic Science of Poisons, at 111.
70. *See* Eaton & Klaassen, *supra* note 64, at 17-18.
71. *Id.* at 21.
72. *Id.* at 13.
73. *See*, *e.g.*, Meijers, *supra* note 64, at 100 (concluding based on a comparison of animal and epidemiological studies for specific chemicals that "chemicals with little or no cancer potential in humans have been tested at too high concentrations in rodents ... which resulted in the observed carcinogenic effect").
74. *Id.* at 27. Federal regulatory agencies such as the Environmental Protection Agency thus use high dose animal research as a basis for establishing conservative regulatory safe exposure levels for humans (albeit at levels several multiples below that found to have no effect in animals). *See*, *e.g.*, Faustman & Omenn, *supra* note 64, at 92-94.
75. *See* Rozman & Klaassen, *supra* note 69, at 111; *see also* Meijers, *supra* note 64, at 95-98; Hertz-Picciotto, *supra* note 63, at 485.
76. *See* Eaton & Klaassen, *supra* note 64, at 14; Rozman & Klaassen, *supra* note 69, at 111-14.
77. *See*, *e.g.*, Rhomberg, *supra* note 64, at 181-83 (discussing carcinogenicity testing in animals engineered to be more susceptible to tumors).
78. Meijers, *supra* note 64, at 98.
79. *Id.*
80. *See Joiner*, 522 U.S. at 145; *see also Glastetter*, 252 F.3d at 991; *In re Accutane Prods. Liab.*, 511 F. Supp. 2d 1288, 1294 (M.D. Fla. 2007) (rat studies involving high doses of different chemical cannot support opinion of expert who fails to show data can be properly extrapolated to humans and who fails to differentiate dog studies with contrary results); *In re Baycol Prods. Litig.*, 532 F. Supp. 2d 1029, 1057-58 (D. Minn. 2007) (rejecting expert reliance on animal studies that neither involved drug in question nor even drugs in same class),), *aff'd*, 596 F.3d 884 (8th Cir. 2010); *Dunn*, 275 F. Supp. 2d at 683 (rejecting animal studies as basis for expert's opinion where expert failed to explain how results of animal studies could be extrapolated to humans).
81. *Caraker*, 188 F. Supp. 2d at 1038; *see also Soldo*, 244 F. Supp. 2d at 549 ("Other federal courts facing proffered expert testimony based on the effects of allegedly similar compounds have reached the same conclusion and rejected such contentions: these courts have found that consideration of the effects of *other* drugs can only lead away from the truth.") (citing cases).
82. *See McClain v. Metabolife Int'l, Inc.*, 401 F.3d 1233, 1246 (11th Cir. 2005); *Rider*, 295 F.3d at 1200-01; *Glastetter*, 252 F.3d at 990; *Schudel*, 120 F.3d at 996-97; *see also Jones*, 235 F. Supp. 3d at 1271-72 (rejecting general causation opinion where expert admitted differences among drugs in the class); *In re Accutane Prods. Liab.*, 511 F. Supp. 2d at 1294 (rejecting expert testimony based on Vitamin A data in case involving Accutane, which is a derivative of Vitamin A).
83. *See*, *e.g.*, Faustman & Omenn, *supra* note 64, at 86-87; A.M. Richard & R. Benigni, *AI and SAR Approaches for Predicting Chemical Carcinogenicity: Survey and Status* Report, 13(1) SAR and QSAR in Environmental Research 1 (2002); J. Ashby & R.W. Tenant, *Prediction of rodent carcinogenicity for 44 chemicals: results*, 9(1) Mutagenisis 7 (1994).
84. *See* Richard & Benigni, *supra* note 83, at 8, 10.
85. *Id.* at 8; *see also* Ashby & Tenant, *supra* note 83, at abstract ("Carcinogenicity tends to be overpredicted by this integrated technique" of basing predictions on chemical structure, genotoxicity and rodent toxicity.).
86. *See* James D. McKinney, *et al.*, *Forum: The Practice of Structure Activity Relationships (SAR) in Toxicology*, 56 Toxicological Sciences 8, 15 (2000) ("Given the huge range

and variability of possible interactions of chemicals in biological systems, it is highly unlikely that SAR models will ever achieve absolute certainty in predicting a toxicity outcome, particularly in a whole-animal system.").

87. *See* Howard Hu & Frank E. Speizer, *Influence of Environmental and Occupational Hazards on Disease*, in Harrison's Principles of Internal Medicine 19 (Braunwald, *et al*. eds. 15th ed. 2001) ("Case reports either sent to local authorities or published in the literature often prompt follow-up studies that can lead to the identification of new hazards"); David A. Grimes & Kenneth F. Schulz, *Descriptive Studies: what they can and cannot do*, 359 The Lancet 145 (Jan. 12, 2002) ("epidemiologists and clinicians generally use descriptive reports to search for clues of cause of disease – *i.e*., generation of hypotheses."); J.A. Arnaiz, *et al*., *The use of evidence in pharmacovigilence: Case reports as the reference source for drug withdrawals*, 57 Eur. J. Clin. Pharmacol 89-91 (2001).
88. *See Chapman,* 766 F.3d at 1308; *Wells*, 601 F.3d at 380; *McClain*, 401 F.3d at 1253-54; *Norris v. Baxter Healthcare Corp*., 397 F.3d 878, 885 (10th Cir. 2005); *Rider*, 295 F.3d at 1199; *Hollander*, 289 F.3d at 1211; *Glastetter*, 252 F.3d at 989-90; *Soldo*, 244 F. Supp. 2d at 541; *Caraker*, 188 F. Supp. 2d at 1034-35; *Brumbaugh v. Sandoz Pharm. Corp*., 77 F. Supp. 2d 1153, 1156 (D. Mont. 1999); *see also Siharath*, 131 F. Supp. 2d at 1361-62 (citing cases).
89. *See Rider*, 295 F.3d at 1199; *Glastetter*, 252 F.3d at 989-90; *Soldo*, 244 F. Supp. 2d at 539-40; *see also* Ellenhorn's Medical Toxicology: Diagnosis and Treatment of Human Poisoning 1 (Ellenhorn ed. 2d ed. 1997) ("Case reports demonstrate a temporal but not necessarily causative relationship between exposure and health effects. This information is often confounded by the inability to exclude other causes of illness.").
90. *See* Grimes & Schulz, *supra* note 87, at 148 (case reports, case series, and other descriptive studies "do not allow conclusions about cause of disease").
91. *See, e.g*., *In re Baycol Prods. Litig.*, 532 F. Supp. 2d at1037-41 (rejecting meta-analysis of ADE data to prove relative toxicities of drugs); *In re Meridia Prods. Liab. Litig.*, 328 F. Supp. 2d 791, 807 (N.D. Ohio 2004) (rejecting plaintiffs' comparison of adverse cardiovascular events reported to FDA with respect to Meridia® and Xenical® and the conclusion that twice as many ADEs for Meridia® compared to Xenical® reflects a doubling of risk), *aff'd sub nom. Meridia Prods. Liab. Litig. v. Abbott Labs*., 447 F.3d 861 (6th Cir. 2006); *Leathers v. Pfizer, Inc.*, 233 F.R.D. 687, 694 (N.D. Ga. 2006) ("[A]dverse incident reports generally do not, standing alone, render an expert's opinion reliable under *Daubert*.").
92. *See, e.g*., *McClain*, 401 F.3d at 1250, 1253-54 (reversing trial court's admission of expert testimony predicated on adverse event reports); *Swallow v. Emergency Med. of Idaho, P.A*., 67 P.3d 68, 72-74 (Idaho 2003) (affirming trial court's exclusion of adverse event reports and expert testimony predicated on those reports under *Daubert* and the state court standard regarding the admissibility of expert testimony, as "speculation based on a temporal concurrence of events").
93. *See* M.N.G. Dukes, *et al*., *Responsibility for Drug-Induced Injury: A Reference Book for Lawyers, the Health Professionals and manufacturers* 45-46 (2d ed. 1998); Ronald H.B. Meyboom, *et. al*., *Causal or Casual? The Role of Causality Assessments in Pharmacovigilance*, 17(6) Drug Safety 374, 375-81 (1997).
94. M.N.G. Dukes, *supra* note 93 at 46.
95. Meyboom, *supra* note 93, at 382.
96. *See* Meyboom, *supra* note 93, at 381; G. Miremont, *et al*., *Adverse drug reactions: physicians' opinions versus a causality assessment method*, 46 Eur. J. Clin. Pharmacol. 285, 288 (1994).
97. *See Glastetter v. Novartis Pharms. Corp*., 107 F. Supp. 2d 1015, 1037 n. 21 (E.D. Mo. 2000) ("like case reports ... a causality assessment involves only one individual, and, in any event, is not sufficient to establish causation"), *aff'd,* 252 F.3d 986 (8th Cir. 2001); *Soldo*, 244 F. Supp. 2d at 545 (plaintiff has failed to show that the causality assessment "methodology – adopted for foreign regulatory purposes – meets any of the *Daubert* criteria, nor has plaintiff shown any other indicia of reliability.").
98. *See Dunn*, 275 F. Supp 2d at 683; *Soldo*, 244 F. Supp. 2d at 541-42; *Caraker*, 188 F. Supp. 2d at 1035-36; *see also Revels v. Novartis Pharms. Corp*., No. 03-98-00231-CV, 1999 WL 644732, *5 (Tex. App. Aug. 26, 1999).
99. *See* David M. Reboussin & Timothy M. Morgan, *Statistical considerations in the use and analysis of single-subject designs*, Medicine and Science in Sports and Exercise 639, 640-642 (1996) (discussing limitations).
100. *Id*., abstract.
101. *Soldo*, 244 F. Supp. 2d at 541 (quoting *Revels*, 1999 WL 644732, at *5); *see also McClain*, 401 F.3d at 1254-55 ("de-challenge/re-challenge tests are still case reports and do not purport to offer definitive conclusions as to causation") (quoting *Rider*, 295 F.3d at 1200).
102. *See Soldo*, 244 F. Supp. 2d at 513, 542; *Caraker*, 188 F. Supp. 2d at 1039; *Siharath*, 131 F. Supp. 2d at 1370; *Glastetter*, 107 F. Supp. 2d at 1034 n.18.
103. *See McLain*, 401 F.3d at 1248-50; *Rider*, 295 F.3d at 1201; *Glastetter*, 252 F.3d at 991; *Hollander*, 289 F.3d at 1215; *Conde*, 24 F.3d at 814; *Dunn*, 2003 WL 21856420, at * 10; *Soldo*, 244 F. Supp. 2d at 513; *see also* Richard A. Merrill, *Regulatory Toxicology*, in Casarett & Doull's Toxicology: The Basic Science of Poisons 1041-43 (1975), (discussing federal regulator's conservative risk-utility analysis); Joseph V. Rodricks & Susan H. Rieth, *Toxicological Risk Assessment in the Courtroom: Are Available Methodologies Suitable for Evaluating Toxic Tort and Product Liability Claims?* 27 Regulatory Toxicology and Pharmacology 21, 27 (1998) ("The public health-oriented resolution of scientific uncertainty [used by regulators] is not especially helpful to the problem faced by a court").
104. *See* Arnaiz, *supra* note 87.
105. Rodricks & Rieth, *supra* note 1038, at 30.
106. *Caraker v. Sandoz Pharm. Corp*., 188 F. Supp. 2d 1026, 1040 (S.D. Ill. 2001); *see also Siharath*, 131 F. Supp. 2d at 1371 ("one cannot lump together lots of hollow evidence in an attempt to determine what caused a medical harm").
107. 639 F.3d 11, 23 (1st Cir. 2011).
108. *Id*. at 17 n.7.
109. Eric G. Lasker, *Manning the Daubert Gate: A Defense Primer in Response to Milward v. Acuity Specialty Products*, 79 DEF. COUNS. J. 128, 131 (April 2012).
110. 522 U.S. at 146.
111. *See, e.g*., *Hollander*, 289 F.3d at 1216 n.21 ("[Plaintiffs] maintain that even though each individual category of evidence may be insufficient, all of the evidence considered as a whole raises factual questions as to whether Parlodel® caused her stroke. [Plaintiffs] cite no legal authority in support of this approach, and in our view, this argument is

inconsistent with *Daubert*."); *Allen v. Pa. Eng'g Corp.*, 102 F.3d 194, 198 (5th Cir. 1996) ("We are also unpersuaded that the 'weight of the evidence' methodology these experts use is scientifically acceptable for demonstrating a medical link between Allen's EtO exposure and brain cancer."); *Magistrini*, 180 F. Supp. 2d at 608 ("Where, as here, elements of judgment pervade the methodology, it is essential that the expert set forth the method for weighing the evidence upon which his opinion is based. Absent that, this Court's role as gatekeeper to assess the reliability of the methodology applied in this case is nullified.").

112. *See Soldo*, 244 F. Supp. 2d at 508; *Siharath*, 131 F. Supp. 2d at 1362; *In re Breast Implant Litig.*, 11 F. Supp. 2d at 1230; *Hall*, 947 F. Supp. at 1413.
113. *Tamraz v. Lincoln Elec. Co.*, 620 F.3d 665, 673 (6th Cir. 2010) (plaintiff conflated proposed expert's expertise in diagnosis with expertise in etiology because "most treating physicians have more training in and experience with diagnosis than etiology" (citing Joe G. Hollingsworth & Eric G. Lasker, *The Case Against Differential Diagnosis: Daubert, Medical Causation Testimony, and the Scientific Method*, 37 J. Health L. 85, 98 (2004)).
114. *See* Hu & Speizer, *supra* note 87.
115. *See Siharath*, 131 F. Supp. 2d at 1371; *see also* Miremont, *supra* note 96, at 288 (explaining finding that physicians are more likely to attribute causation to a drug as being due to their "necessarily more pragmatic approach to patients and diseases").
116. *See* Kassirer & Cecil, *supra* note 9, at 1384.
117. John M. Conley & John B. Garver, III, *William C. Keady and the Law of Scientific Evidence*, 68 Miss. L.J. 39, 51 (1998).
118. Herbert A. Simon, *Artificial-Intelligence Approaches to Problem Solving and Clinical Diagnosis*, in Logic of Discovery and Diagnosis in Medicine 72, 87 (Kenneth F. Schaffner ed. 1985).
119. *Siharath*, 131 F. Supp. 2d at 1372.
120. 526 U.S. at 152.
121. *See Siharath*, 131 F. Supp. 2d at 1362; Michael B. Kent, Jr., *Daubert, Doctors and Differential Diagnosis: Treating Medical Causation Testimony as Evidence*, 66 Def. Couns. J. 525, 532-33 (1999); *see also Thomas v. Novartis Pharms. Corp.*, 443 F. App'x 58, 62 (6th Cir. 2011) (expertise in recognizing and treating an injury is not sufficient to establish a doctor is qualified to testify on the cause of an injury).
122. *See Norris*, 397 F.3d at 885; *Soldo*, 244 F. Supp. 2d at 524; *Siharath*, 131 F. Supp. 2d at 1362-63; *Glastetter*, 107 F. Supp. 2d at 1027.
123. *Chapman*, 766 F.3d at 1311 (differential diagnosis unreliable where expert "ruled-in and considered an etiology" that had not been established to cause plaintiff's disease); *Jones*, 235 F. Supp. 3d at 1277 (where there is no admissible general causation opinion in the case, "then an expert may not rely on a differential diagnosis to prove specific causation"); *In re Zoloft (Sertralinehydrochloride) Prods. Liab. Litig.*, 176 F.Supp.3d 483, 496 (E.D. Pa. 2016) ("the ruling-out process, by itself, cannot establish causation."), *aff'd*, 858 F.3d 787 (3d Cir. 2017).
124. *Glastetter,* 252 F.3d at 989 (differential diagnosis was invalid because the experts "lacked a proper basis for 'ruling in' [the drug] Parlodel as a potential cause of [stroke] in the first place").
125. *Guinn v. AstraZeneca Pharm. LP,* 602 F.3d 1245, 1253 (11th Cir. 2010).
126. *See Soldo*, 244 F. Supp. 2d at 551; *Garrison v. Novartis Pharm. Corp.*, 30 F. Supp.3d 1325, 1339 (M.D. Ala. 2014) (excluding specific causation testimony of plaintiff's expert where expert failed to conduct "a sufficiently thorough analysis to support his conclusive elimination of osteomyelitis as a specific cause of ONJ" and "glosses over" certain facts that "compromise the reliability of [expert's] firm conclusion that [plaintiff's] ONJ was solely caused by her exposure to bisphosphonates").
127. *See Daubert,* 43 F.3d at 1319; *Hall v. Conoco Inc.*, 886 F.3d 1308, 1311–12 (10th Cir. 2018); *Chapman*, 766 F.3d at 1311; *Soldo*, 244 F. Supp. 2d at 551-52; *Perry*, 564 F. Supp. 2d at 471; *Magistrini,* 180 F. Supp. 2d at 608-10; *Nelson v. Am. Home Prods. Corp.*, 92 F. Supp. 2d 954, 971 (W.D. Mo. 2000).
128. *Deutsch v. Novartis Pharm. Corp.*, 768 F. Supp. 2d 420, 472 (E.D.N.Y. 2011) ("[W]hen the treating physician seeks to opine on causation, that opinion 'is subject to the same standards of scientific reliability that govern the expert opinions of physicians hired solely for the purposes of litigation.'") (quoting *In re Aredia & Zometa Prods. Liab. Litig.*, 754 F. Supp. 2d 934, 936 (M.D. Tenn. 2010)).
129. *Kumho Tire*, 536 U.S. at 152.
130. *See Cano v. Everest Minerals Corp.*, 362 F. Supp. 2d 814, 846 (W.D. Tex. 2005).
131. *See In re Lipitor*, 892 F.3d at 645 (excluding specific causation opinion where expert failed to provide "a reasoned scientific analysis" for excluding other possible causes of plaintiff's diabetes); *Wills v. Amerada Hess Corp.*, 379 F.3d 32, 50 (2d Cir. 2004) (excluding expert's specific causation opinion that plaintiff's squamous cell carcinoma had been caused by polycyclic aromatic hydrocarbons where plaintiff was a smoker and heavy consumer of alcohol); *In re Trasylol Prods. Liab. Litig.*, No. 08-MD-1928, 2013 WL 3353833, at *9 (S.D. Fla. July 3, 2013) ("Where an expert testifies that a particular injury could have numerous causes and simply picks the cause that is most advantageous to a plaintiff's claim, such testimony is not admissible.") (quotations & alterations omitted); *Harvey v. Novartis Pharm. Corp.,* 895 F. Supp. 2d 1206, 1213 (N.D. Ala. 2012) ("Because [the expert] never offered a principled reason for ruling out osteomyelitis, his opinion that Zometa caused [plaintiff's] osteonecrosis would be nothing more than speculation and conjecture."); *Easter v. Aventis Pasteur, Inc.*, 358 F. Supp. 2d 574, 577 (E.D. Tex. 2005) (expert could not reliably point to thimerosal in vaccine as a cause of plaintiff's neurological injuries where plaintiff had autism that could not be linked to vaccine and was independently associated with such injuries).
132. As discussed *supra* at __, such regulatory action is not the equivalent of a finding of causation.
133. *See*, *e.g.*, Steven A. Kittner, *et al*, *Cerebral Infarction in Young Adults*, 50 Neurology 890-94 (1998) (despite neurologists' careful review, in 50.5% of cases, no probable cause of stroke in young adults could be identified).
134. *Guinn*, 602 F.3d at 1254 ("[t]he temporal connection between exposure to chemicals and an onset of symptoms, standing alone, is entitled to little weight in determining causation"); *Kilpatrick v. Breg, Inc.*, 613 F.3d 1329, 1343 (11th Cir. 2010) ("[P]roving a *temporal* relationship ... does not establish a *causal* relationship .... [S]imply because a person takes drugs and then suffers an injury does not show causation.").
135. Kiely, *supra* note 10. In addition to being used as a case study for legal scholars, the Parlodel® litigation was discussed in an article published in the Journal of the American Medical Association by an unsuccessful *amicus*

for plaintiffs appealing a Parlodel® *Daubert* exclusionary ruling to the Eleventh Circuit Court of Appeals in *Rider*. *See* J. Kassirer & J. Cecil, *supra* note 9.

136. *Rider*, 295 F.3d 1194; *Hollander*, 289 F.3d 1193; *Glastetter*, 252 F.3d 986; *Dunn*, 275 F. Supp. 2d 672; *Soldo*, 244 F. Supp. 2d 434; *Caraker*, 188 F. Supp. 2d 1026; *Brumbaugh,* 77 F. Supp. 2d 1153; *see also Revels*, 1999 WL 644732 (excluding Parlodel® causation opinions on Texas analog of *Daubert*).
137. *Brasher v. Sandoz Pharms. Corp.*, 160 F. Supp. 2d 1291 (N.D. Ala. 2001) (Putnam, M.J.); *Globetti v. Sandoz Pharms. Corp.*, 111 F. Supp. 2d 1174 (N.D. Ala. 2000) (Putnam, M.J.); *Eve v. Sandoz Pharms. Corp.*, 2001 U.S. Dist. LEXIS 4531 (S.D. Ind. Mar. 7, 2001); *see also Hyman & Armstrong, P.S.C. v. Gunderson*, 279 S.W.3d 93 (Ky. 2008).
138. *See Caraker*, 188 F. Supp. 2d at 1028, 1040.
139. *See generally Rider*, 295 F.3d 1194; *Glastetter*, 252 F.3d 986; *Caraker*, 188 F. Supp. 2d 1026.
140. *Globetti*, 111 F. Supp. 2d at 1180; *see also Eve*, 2001 U.S. Dist. LEXIS 4531, at *75 (quoting *Globetti*).
141. *Brasher*, 160 F. Supp. 2d at 1296; *see also id*. at 1297 ("Given the practical unavailability of other forms of scientific evidence, reliance on those that are available is all the more reasonable.").
142. *Id*. at 1299.
143. *Siharath*, 131 F. Supp. 2d at 1373.
144. *Id*. at 1371.
145. *Hollander*, 289 F.3d at 1213.
146. *Brumbaugh*, 77 F. Supp. 2d at 1156.
147. *Caraker*, 188 F. Supp. 2d at 1030.
148. *Soldo*, 244 F. Supp. 2d at 529.
149. *Glastetter*, 107 F. Supp. 2d at 1025.
150. *Dunn*, 275 F. Supp 2d at 684.
151. *Rider*, 295 F.3d at 1197.
152. *Joiner,* 522 U.S. at 148-49 (Breyer, J., concurring).