
No. 08-2555

State of Arkansas; State of Florida;
State of Idaho; State of Iowa; State of
Kentucky; State of Maine; State of
Minnesota; State of Missouri; State of
Montana; State of Nebraska; State of
New Hampshire; State of New Jersey;
State of New Mexico; State of North
Dakota; State of Oklahoma; State of
Oregon; State of South Carolina; State
of South Dakota; State of Utah;

Trial Lawyers Association, *
*
Amici on *
behalf of Appellant. *

No. 08-2711

In re: Prempro Products Liability *
Litigation. *

Donna Scroggin, *
*
Plaintiff/Appellee, *
*
v. *

Wyeth, and its divisions, *
*
Defendant/Appellant, *
*
Pharmacia & Upjohn Company, L.L.C., *
*
Defendant. *

Barr Laboratories, Inc.; Duramed *
Pharmaceuticals, *
*
Amici on *
Behalf of Appellant, *

State of Arkansas; State of Florida; *
State of Idaho; State of Iowa; State of *
Kentucky; State of Maine; State of *

Minnesota; State of Missouri; State of
Montana; State of Nebraska; State of
New Hampshire; State of New Jersey;
State of New Mexico; State of North
Dakota; State of Oklahoma; State of
Oregon; State of South Carolina; State
of South Dakota; State of Utah,

Amici on
behalf of Appellee.

No. 08-2713

In re: Prempro Products Liability
Litigation.

Donna Scroggin,

Appellee,

v.

Wyeth, and its divisions,

Defendant,

Pharmacia & Upjohn Company, L.L.C.,

Defendant/Appellant.

Barr Laboratories, Inc.; Duramed	*
Pharmaceuticals,	*
	*
Amici on	*
Behalf of Appellant,	*
	*
State of Arkansas; State of Florida;	*
State of Idaho; State of Iowa; State of	*
Kentucky; State of Maine; State of	*
Minnesota; State of Missouri; State of	*
Montana; State of Nebraska; State of	*
New Hampshire; State of New Jersey;	*
State of New Mexico; State of North	*
Dakota; State of Oklahoma; State of	*
Oregon; State of South Carolina; State	*
of South Dakota; State of Utah,	*
	*
Amici on	*
behalf of Appellee.	*

Submitted: May 13, 2009
 Filed: November 2, 2009

Before WOLLMAN, JOHN R. GIBSON, and MURPHY, Circuit Judges.

WOLLMAN, Circuit Judge.

Donna Scroggin was diagnosed with breast cancer eleven years after she began taking estrogen and progestin drugs manufactured by Wyeth Pharmaceuticals Inc. (Wyeth) and Pharmacia & Upjohn Co. (Upjohn).¹ She sued the companies in 2004

¹This opinion uses the names “Wyeth” and “Upjohn” to refer to the companies, their divisions, and their predecessor companies.

for failure to warn of the risk of breast cancer from combination hormone therapy. The trial was bifurcated, with liability determined first and punitive damages determined second.

A jury returned a verdict finding Wyeth and Upjohn liable and awarding Scroggin compensatory damages. The district court denied Wyeth's and Upjohn's motions for judgment as a matter of law on liability. Following the second phase of the trial, the jury awarded Scroggin punitive damages. Wyeth and Upjohn moved to strike Scroggin's expert witness's testimony and for judgment as a matter of law. The district court granted the motions, vacating the punitive damages award. The district court ruled in the alternative that, had it denied the motions, it would have granted a new trial to determine punitive damages.

Wyeth and Upjohn appeal from the entry of judgment against them on liability, arguing that Scroggin's claim was preempted, that the statute of limitations barred her claim, and that she failed to prove causation. Wyeth and Upjohn also contend that the district court erred in admitting Scroggin's expert evidence on specific causation and in instructing the jury on proximate causation. Scroggin appeals from the district court's order striking her expert evidence during the punitive damages phase of the trial, granting Wyeth's and Upjohn's motions for judgment as a matter of law, and vacating the jury's punitive damages award.

We affirm the jury verdict and its award of compensatory damages. We also affirm the disputed evidentiary orders and jury instruction. We affirm the judgment as a matter of law in favor of Upjohn, but reverse it as to Wyeth, adopting the district court's alternative holding and granting Wyeth a new trial on punitive damages.

I. Factual Background

In 1989, Scroggin began taking combination hormone replacement therapy drugs to relieve menopausal symptoms, including hot flashes and vaginal atrophy. Scroggin was prescribed Ogen, an estrogen product produced by Upjohn, and Provera, a progestin product produced by Upjohn. Dr. Irving Kuperman began treating Scroggin in 1989, and he continued the prescriptions. In 1992, Dr. Kuperman changed Scroggin's estrogen prescription to Premarin, a Wyeth-manufactured drug, and in 1996 he prescribed Prempro, a Wyeth-manufactured drug that combined estrogen and progestin. In 1999, Dr. Kuperman returned Scroggin to the Premarin/Provera combination. When she was diagnosed with ductal carcinoma breast cancer in both breasts in July 2000, her surgeon, Dr. Jim Hagans, discontinued hormone replacement therapy because it is contraindicated for breast cancer.

Scroggin underwent a double mastectomy that removed her breast tissue and the lymph nodes under each arm. After her incisions healed, she underwent six months of chemotherapy, experiencing intermittent nausea, anxiety, fatigue, hot flashes, difficulty sleeping, and continuing memory problems. Chemotherapy was followed by five years of medication to reduce the risk of her breast cancer returning. She remains at risk for recurrence and requires extensive annual examinations and lab work. Scroggin has chosen not to have reconstructive surgery.

In 2002, the National Institutes of Health (NIH) published the results of its Women's Health Initiative (WHI) study, linking the use of hormone replacement therapy to breast cancer. The WHI study results were widely publicized, and at some point after their publication Scroggin concluded that her breast cancer was the result of her long-term use of estrogen and progestin therapy.

A. Hormone Replacement Therapy

Hormone replacement therapy, consisting of estrogen plus progestin, is prescribed to combat the symptoms of menopause. Women's ovaries typically stop producing estrogen between the ages of forty-five and fifty-five, commencing the onset of menopause. Some women develop moderate to severe symptoms, including intense episodes of heat and sweating, known as hot flashes, as well as vaginal atrophy.

In 1942, Wyeth introduced Premarin, a conjugated equine estrogen intended to replace the estrogen naturally decreasing in women during menopause and reduce the associated symptoms. In 1959, Upjohn launched Provera, a progestin product approved for treatment of abnormal uterine bleeding. By the 1970s, studies showed a link between estrogen replacement drugs such as Premarin and endometrial cancer. It was later determined that prescribing progestin along with estrogen reduced this risk. Although the Food and Drug Administration (FDA) had not approved the combination of estrogen and progestin for treating menopausal symptoms, such combination hormone therapy became the standard of care. Provera was often lawfully prescribed for this off-label use in conjunction with Premarin. In 1994, Wyeth became the first pharmaceutical company to combine estrogen and progestin into one package with the launch of Prempro. In 1995, Prempro became the first pharmaceutical that combined the two hormones into a single tablet. As of 2008, Premarin and Provera were the most common forms of estrogen and progestin replacement drugs.

B. Wyeth

Premarin is among Wyeth's most profitable products. The company has described Premarin as "our most important asset and our most important priority" and has equated the Premarin marketing efforts with a "Holy War, a Crusade." At trial,

Scroggin argued that this devotion led Wyeth to implement a policy of “dismiss and distract” when it came to the risks associated with the drug. Scroggin asserted that Wyeth intentionally ignored the breast cancer risk and avoided its study at the same time as it vigorously promoted Premarin and Prempro. According to Scroggin, Wyeth’s “dismiss and distract” policy began in 1975.

1. Wyeth’s Reaction to Estrogen Replacement Therapy Being Linked to Endometrial Cancer

In 1975, the FDA’s Obstetrics and Gynecology Advisory Committee concluded that there was a link between endometrial cancer and estrogen replacement therapy drugs such as Premarin. The Committee held public hearings, the evidence presented at which suggested a 7.6% increased risk for endometrial cancer among women taking estrogen replacement drugs. This risk decreased to 5.6% for exposure of less than five years and increased to 13.9% for exposure greater than seven years. Following the hearings, the FDA notified Wyeth that Premarin’s label would have to be changed to warn consumers of the risk of endometrial cancer

In response to these hearings and other reports of an endometrial cancer link, Wyeth penned a “Dear Doctor” letter in December 1975. The letter declared that “it would be simplistic indeed to attribute an apparent increase in the diagnosis of endometrial carcinoma, solely to estrogen therapy.” The letter went on to state that Wyeth “is vitally concerned about the ultimate resolution of conflicting evidence in this area” and suggested that using the drug as described in the package’s labeling would minimize any potential risk and allow for continued use.

Wyeth’s letter “in[c]ensed the FDA at all levels, including the Commissioner.” Within weeks, FDA officials met with Wyeth executives to discuss the FDA’s position that the letter misrepresented the available scientific data. The FDA’s Director of Bureau of Drugs stated that he expected Wyeth to provide a sound medical

and scientific response to the new information, but instead Wyeth misrepresented scientific findings. Wyeth failed to propose studies to confront the questions that the new data raised and failed to refute or confirm the studies that were then available. The FDA deemed Wyeth's letter a borderline violation of the Food, Drug, and Cosmetic Act and issued a Drug Information Bulletin to "stat[e] objectively the findings linking estrogens in endometrial cancer." Shortly thereafter, the FDA required a boxed warning² of the endometrial cancer risk with every Premarin prescription.

2. Wyeth's Reaction to Hormone Replacement Therapy Being Linked to Breast Cancer

By 1976, the medical community began questioning whether there was a connection between estrogens and breast cancer. In an internal memo dated June 14, 1976, Wyeth doctors recognized that "there is valid concern as to whether or not the use of exogenous estrogen leads to an increase in the incidence of breast cancer," but the memo ultimately concluded that "[e]strogen use does not appear to bring about an increased risk of breast cancer." The following month, Dr. Robert Hoover of the National Cancer Institute at the NIH sent a manuscript of his forthcoming study on menopausal estrogens and breast cancer to Wyeth.³ Dr. Hoover had concluded that estrogens may be a risk factor for breast cancer, and the study found a 2.0 relative

²A boxed warning is defined as "an alert to medical practitioners about potentially serious adverse drug reactions, contraindications, or other special problems with a given drug, contained in a ruled box at a site specified within the label format by the FDA." PDR Medical Dictionary 2145 (3d ed. 2006).

³This evidence, along with certain other evidence relied upon in this section, was admitted for a limited purpose. The jury was instructed to consider it solely to determine whether Wyeth was on notice of a duty to test.

risk⁴ for women using estrogen for fifteen years or more. Dr. Hoover's letter stated that his study's findings were cause for grave concern and that more intensive study was necessary.

Faced with the upcoming publication of Dr. Hoover's study in the New England Journal of Medicine, Wyeth prepared to defend Premarin. Internal correspondence stated that it was crucial to formulate a plan to "mitigate the possible adverse effects" of the study. The correspondence suggested prioritizing the "refutation, or mitigation of the effects" of Dr. Hoover's study, concluding that Wyeth could not "afford to wait for the axe to start its descent before we give serious attention to how we might blunt its edge." Internal documents also showed a concern that the breast cancer risk was being overstated and that the study might affect Premarin's labeling requirements. A Wyeth-sponsored case-control study⁵ on mammary cancer was considered, but never materialized. Prescriptions for estrogen in combination with progestin were on the rise, and as a Wyeth document stated, "the number of published, well-designed studies [was] small or practically non existent."

In the late 1980s and early 1990s, additional studies linked hormone replacement therapy to an increased risk of breast cancer. In 1989, Dr. Leif Bergkvist

⁴Relative risk is the risk of an outcome in one group compared with the risk in another group. The baseline risk is 1.0, meaning that a relative risk of 1.0 or less indicates no greater incidence of the event. A relative risk of 2.0 would indicate a doubling of the baseline risk or a 200% increased risk.

⁵Stedman's Medical Dictionary 1852 (28th ed. 2006) defines case-control study as

an epidemiologic method that begins by identifying people with the disease or condition of interest (the cases) and compares their past of exposure to identified or suspected risk factors with the past history of similar exposures among those who resemble the cases but do not have the disease or condition of interest (the controls).

published the results of his long-term study of the risk of breast cancer following estrogen and estrogen-progestin replacement. Although the study had a small sample size, it nonetheless concluded that treatment with estrogens “seems to be associated with a slightly increased risk of breast cancer, which is not prevented and may even be increased by the addition of progestins.” This conclusion was contrary to the prevailing view that progestins might decrease the risk of breast cancer in much the same way that they decreased the risk of endometrial cancer.

In 1990, Wyeth obtained information that Dr. Graham Colditz would present the results of a study showing that Premarin increased the risk of breast cancer by thirty percent in current users. The presentation was scheduled to take place at a meeting of the Society of Epidemiologic Research. Wyeth prepared talking points in advance of the meeting, planning to “effectively position[] the risks vs. benefits so there is some counterbalance to potential negative news.” Wyeth implemented a similar plan in response to the International Agency for Research on Cancer’s (IARC)⁶ announcement that it would evaluate the carcinogenic risks of estrogen replacement therapy. Justin Victoria, Wyeth’s Associate Director of Regulatory Affairs, proposed the formation of a task force to “ensure that IARC does not develop a position on a definitive relationship between breast cancer and estrogen replacement therapy as well as to ensure that conjugated estrogens are not singled out from other estrogen replacement therapies as any different in terms of carcinogenic risk.”

Throughout the 1990s, Wyeth remained vigilant in disassociating its product from cancer. In accordance with company policy, Wyeth denied the Eastern Cooperative Oncology Group’s 1993 request for a supply of Premarin to conduct a study of hormone replacement therapy in women who have breast cancer. Presumably, the request was denied because estrogen is contraindicated for breast

⁶ The IARC is an agency within the World Health Organization charged with identifying cancer-causing agents in the environment.

cancer, but a later memo referred to a custom at Wyeth of denying requests for Premarin for studies involving breast cancer. In 1994, a Wyeth executive responded to the suggestion that a respected oncologist chair an upcoming meeting of Wyeth consultants with “[n]o way having an oncologist chair this. NO NO NO NO & NO.” In 1995, a British scientist requested mammograms used in previous Wyeth studies for a study on breast density in estrogen and progestin users. Wyeth agreed on condition that there be “no review of issues currently under discussion in literature elsewhere reviewing HRT and breast cancer” and that the Premarin Study Review Committee “has an absolute and final right to comment on the content, emphasis and conclusions of any publication(s)” and if there are “any significant differences of opinion raised” the scientist “will agree to accept the views of the Premarin Study Review Committee.”

In 1996, an NIH-sponsored study, authored by Dr. Steven Cummings, concluded that “the risk of breast cancer associated with hormone replacement therapy may have been substantially underestimated.” Wyeth received an advanced abstract of the study and established a breast cancer task force in response. Wyeth’s response plan involved the following strategy: “shift attention to other cancers;” characterize the study as “just one more paper;” and highlight flaws in the study’s methodology. The task force’s stated goal for an upcoming meeting of the American Society of Clinical Oncology was to “[o]vershadow [the] Cummings data” by directing media attention elsewhere. Handwritten notes regarding the study state “keep US press busy” and “dismiss/distract.”

Wyeth also engaged in the lawful, though questionable, practice of commissioning ghost written articles. In 2000, Wyeth tapped Dr. John Eden to author “Breast Cancer and Progestins,” but the true author was a technical writing company, hired to produce the manuscript for Wyeth’s approval and Dr. Eden’s editing. Wyeth submitted a project assignment with references, a timetable, and topics to address, such as “why progestins may not be responsible for the incidence of breast cancer in

hormone replacement therapy (HRT) users.” The finished product was published in the Journal of Obstetrics and Gynecology, apparently without the publication’s knowledge of the article’s origins and with no reference to Wyeth. Other authors then cited to the article, including Wyeth’s own Dr. Ginger Constantine, facilitating its absorption into the collection of reliable medical data.⁷

3. Wyeth’s Interactions with the FDA Regarding Hormone Replacement Therapy

Wyeth sought FDA approval of Prempak, a combination product containing Premarin and a progestin tablet, in the 1980s. Wyeth did not support its application with its own study, but instead relied on the then-available studies to substantiate the efficacy and safety of Prempak. The FDA denied the application, concluding that the studies were inadequate and that Wyeth was unable to assure “the long term safety of the combination treatment for human use.”

By the early 1990s, Wyeth was well aware of the FDA’s position that the data on estrogen use in combination with progestin was insufficient. In an internal memo dated August 22, 1990, Justin Victoria explained that the FDA had denied Wyeth’s applications for combination packaging, informing Wyeth that it could not approve a combination without an adequate, well-controlled clinical trial that evaluated the overall benefits and risks of the combination. The memo stated that the FDA “remain[ed] unconvinced of the overall safety and effectiveness of combined estrogen/progestin therapy.” Wyeth and Upjohn also attended the 1990 and 1991 meetings that the FDA held to address, among other issues, the concern that hormone replacement therapy was associated with an increased risk of breast cancer. Both meetings concluded that the current available evidence was insufficient and inconclusive, as some studies showed an increased risk and others did not. Scroggin’s

⁷For a recent report regarding the use of ghost-written articles, see Natasha Singer, Medical Papers By Ghostwriters Pushed Therapy, N.Y. Times, Aug. 5, 2009, at A1.

regulatory expert and a former Chief Medical Officer with the FDA, Dr. Suzanne Parisian testified at trial that the FDA would have expected Wyeth to take these meetings seriously and that Wyeth should have viewed the 1990 meeting as a red flag. Wyeth, however, considered the meeting a success, celebrating it as a “non-event.”

In 1991, Wyeth sought FDA approval of its Premarin marketing plan and the plan’s centerpiece, a magazine. In a February 21, 1991, letter to Wyeth, the FDA’s Acting Director of the Division of Drug Advertising and Labeling stated that the FDA “view[ed] this campaign in its entirety to be a form of extremely insidious hidden persuasion” and a “marketing ploy masquerading as concern for the health of post-menopausal women.” The letter described the magazine as a “house organ,” faulting it as misleading for failing to clearly state Wyeth’s sponsorship and for stating that the magazine was provided by a pharmacy. Moreover, the letter criticized the magazine’s articles as misleading. The letter remarked that the campaign “**intentionally** misleads the reader into thinking that her physician is somehow responsible for providing it to her.” Wyeth subsequently altered the campaign.

In 1994, the FDA approved Prempro, a combination packaging of estrogen and progestin, on the condition that Wyeth perform a post-marketing study on the risk of breast cancer. Dr. Parisian testified that the FDA cannot force a pharmaceutical company to perform safety tests and suggested that approval was granted as a means of compelling the study. Such a study would take eight or nine years to complete.

Following the FDA’s approval of Prempro, Wyeth requested that its support of the following two studies satisfy its obligation to study the breast cancer risk: the WHI study and the Women’s International Study of Long-Duration Oestrogen After Menopause. The WHI study was underway and was evaluating whether combination use of estrogen and progestin provided long-touted cardiovascular benefits. Although

the FDA had previously expressed skepticism that the WHI study could evaluate the breast cancer risk, it approved Wyeth's proposal.

C. Upjohn

Evidence presented at trial did not show that Upjohn tried to undermine evidence linking breast cancer to hormone replacement therapy or its progestin, Provera. Instead, Scroggin argued that Upjohn failed to study whether hormone replacement therapy increased the risk of breast cancer and that it ignored the growing evidence indicating that such a risk existed.

1. Upjohn's Reaction to Hormone Replacement Therapy Being Linked to Breast Cancer

As early as 1963, Upjohn was aware that Provera might exacerbate existing breast cancer.⁸ In 1970, Upjohn withdrew Provest, an oral contraceptive containing estrogen and progestin, after a study showed that progestin caused mammary nodules in beagle dogs. Recognizing that Provest's withdrawal might alarm doctors prescribing combination hormone therapy drugs, Upjohn issued a "Dear Doctor" letter that assured that there was "no reason to predict human extrapolation of this finding," but that there was also no way of disproving it. The letter distinguished Provest, a contraceptive used for a prolonged period of time for which there were adequate replacements, from Provera, a "therapeutic agent[] for specific gynecological disorders." The letter concluded that Provera's benefits outweighed the possible risks and that continued use "poses no unwise risk in this regard to you or your patients."

In 1990, Upjohn hired the Degge Group to gather and review all available scientific data concerning the risk of breast cancer with hormone replacement therapy

⁸Scroggin established at trial that Upjohn would have been aware of the same medical literature and research as Wyeth.

involving progestin. The goal was to determine what was known and what areas needed further research. The Degge Group found that the evidence was inconclusive, and it identified and recommended areas for further research. The Degge Group published the results of its research in 1992, in Fertility and Sterility, an obstetrics and gynecology medical journal. Upjohn, however, did not conduct follow up studies or research.

By 1992, Upjohn still did not know the extent of the risk of breast cancer with progestin use as part of hormone replacement therapy. Between 1982 and 1994, Upjohn conducted thirty-four studies to prove that Provera protected the endometrium. The studies were monitored for breast cancer, but they were not designed to be large enough or long enough in duration to be capable of evaluating the breast cancer risk.

Until 1995, there remained a prevailing view that progestin's addition to estrogen replacement therapy might reduce the incidence of breast cancer in much the same way that it reduced the risk of endometrial cancer. In 1995, however, a publication by Dr. Colditz examined available data from 1978 through 1992 and concluded that there was no benefit. In fact, the study found a slightly higher risk with the addition of progestin. Dr. Colditz "observed a significant elevation in the risk of breast cancer among women using conjugated estrogen alone," a relative risk of 1.32; for estrogen and progestin, the relative risk was 1.41; and for progestin alone, the relative risk was 2.24.

2. Upjohn's Interactions with the FDA Regarding Hormone Replacement Therapy

In 1966, Upjohn applied for FDA approval of Provera's use with estrogens for treatment of menopause. The FDA denied the application because Upjohn failed to justify the requested indication with adequate clinical data. In 1986, Upjohn submitted a supplemental application to the FDA, again seeking to expand Provera's

indications for use of the drug to oppose the endometrial effects of estrogen in menopausal women receiving estrogen replacement therapy. The FDA denied the application because Upjohn failed “to provide substantial evidence consisting of adequate and well-controlled studies . . . that Provera will have the effect it is represented to have under the conditions of use prescribed, recommended, or suggested in its proposed labeling.”

Although Provera was not approved for use in treating menopausal symptoms, Upjohn advertised it as such. In 1984, the FDA called for the immediate cancellation of Provera advertisements appearing in Contemporary OBGYN. The advertisements promoted Provera’s off-label use with estrogen replacement therapy and failed to mention its indicated use, treatment for abnormal uterine bleeding. Upjohn agreed to limit its advertisements to the approved indication. Notwithstanding that agreement, the FDA found it necessary to request immediate cancellation of a similar advertisement in 1985, and another advertisement in 1990, that claimed Provera was “the other half of hormone replacement therapy.” In 1991, Upjohn submitted proposed promotional materials to the FDA for approval. The FDA limited the material because it was potentially misleading. The FDA reminded Upjohn of their previous discussions “regarding material which suggests that Provera is indicated for use in postmenopausal replacement therapy for the prevention of endometrial hyperplasia.”

In 1998, Provera was finally approved “for the reduction of endometrial hyperplasia in postmenopausal women” who are receiving estrogen. Testimony at trial revealed that Upjohn did not conduct any breast cancer studies from 1960 until the time of trial.

D. The Women's Health Initiative Study

The WHI study began in 1991. The study consisted of multiple components, one of which was an evaluation of the use of estrogen and progestin in postmenopausal women. Primarily, this component evaluated whether estrogen and progestin use decreased the incidence of cardiovascular disease. Secondly, the study assessed numerous safety issues, including the risk of breast cancer. The study was organized as a randomized placebo-controlled trial, meaning that one group of women received the drugs and the other a placebo. The average age of the participants was sixty-three, and it included women who were already on hormone replacement therapy, as well as women who began treatment at the start of the study. The study had a predetermined stopping point if the incidence of breast cancer exceeded a certain point. In 2002, three years short of its scheduled completion, the NIH terminated the study, finding an unacceptably high incidence of invasive breast cancer among the participants.

In July 2002, the initial results of the WHI study were published in the Journal of the American Medical Association. The study reported a relative risk of breast cancer of 1.24 over 5.6 years of estrogen and progestin use. Stated differently, the estrogen plus progestin group was twenty-four percent more likely to develop breast cancer than the control group. This result was consistent with estimates from pooled epidemiological data. Wyeth's Dr. Constantine described the relative risk of increased incidence of breast cancer as small and Scroggin's medical expert, Dr. Don Austin, described it as slightly elevated. The study also found that the risk of breast cancer decreased after stopping the hormone therapy.

These initial results, however, contained variables not accounted for in the 1.24 relative risk. Dr. Austin testified that the 1.24 number was misleading, particularly for women using hormone replacement therapy for long periods of time. He noted that although randomized clinical trials assist in showing causal relationships, they

may not be accurate in reporting the size of the risk. The 1.24 relative risk was based on the “intent to treat” group, meaning the women who had signed up to participate in the study, but it did not account for those who had dropped out during the course of the study. According to the WHI, all of the women had been enrolled for 3.5 years, with an average enrollment of 5.2 years, and a maximum enrollment of 8.5 years. Forty-two percent of estrogen plus progestin users and thirty-eight percent of the placebo group ceased participating during the course of the study. The initial WHI results, however, calculated the relative risk as if these women had remained in the study.

In 2006, Dr. Garnet Anderson, who had worked on the WHI study, published a report that accounted for these variables. When she accounted for confounding variables, the relative risk was 1.96. She found that women who had been taking hormone replacement therapy prior to commencement of the study had a relative risk of 2.78 and that women who were taking the medication for more than five years had a relative risk of 2.5. When Dr. Anderson analyzed only the women who remained in the study and adhered to the treatment, she found a relative risk of 3.56.

Dr. Austin testified that “the true value is somewhere between 1.18 and 10.73, but the best estimate is 3.56.” Dr. Colditz asserted that the relative risk is somewhere between 2.0 and 4.0 depending on use and duration. Both Dr. Colditz and Dr. Austin agreed that estrogen plus progestin use causes breast cancer. Additionally, the IARC has classified estrogen plus progestin as a carcinogen of the breast.

E. Wyeth’s and Upjohn’s Breast Cancer Warnings

The FDA requires drug information to be sent directly to the physician as well as provided to the patient with each prescription. In 1992, both the physician labeling and patient information sheet for Premarin provided the following warning: “Some studies have suggested a possible increased incidence of breast cancer in those women

on estrogen therapy taking higher doses for prolonged periods of time. The majority of studies, however, have not shown an association with the usual doses used for estrogen replacement therapy.” Similar language was included in the physician label and patient information sheet accompanying Prempro prescriptions.⁹ The Premarin labeling did not provide any information concerning the combined use of estrogen plus progestin. Both Dr. Parisian and Dr. Kuperman testified that this label did not convey a significant risk of breast cancer associated with the use of estrogen or progestin.

The Prempro information sheet included this additional information:

Most studies have not shown a higher risk of breast cancer in women who have ever used estrogens. However, some studies have reported that breast cancer developed more often (up to twice the usual rate) in women who used estrogens for long periods of time (especially more than 10 years), or who used high doses for shorter time periods. The effects of added progestin on the risk of breast cancer are unknown. Some studies have reported a somewhat increased risk, even higher than the possible risk associated with estrogens alone. Others have not. Regular breast examinations by a health professional and monthly self-examination are recommended for all women. Regular mammograms are recommended for all women over 50 years of age.

Dr. Parisian testified that the Prempro warning was confusing and did not clearly convey a risk to patients. She also testified that it falsely implied that Wyeth had conducted studies to analyze the risk. Dr. Kuperman testified that the warning provided no clear indication of a breast cancer risk and instead implied that the risk was unresolved and that there was likely a low correlation.

⁹The Prempro label had the following modification: “Some studies have reported a moderately increased risk of breast cancer (relative risk 1.3 to 2.0) in those women on estrogen replacement therapy taking higher doses, or in those taking lower doses for prolonged periods of time, especially in excess of 10 years.”

In 1999, the Prempro label continued to provide the warning contained in the Premarin label, but added, “[t]he effect of added progestins on the risk of breast cancer is unknown, although a moderately increased risk in those taking combination estrogen/progestin therapy has been reported.” The label provided an example of a clinical trial and concluded that “[t]he overall incidence of breast cancer in this clinical trial does not exceed that expected in the general population.”

Upjohn’s Provera provided no warning of breast cancer, and none was required by the FDA until 1999. At that time, the label informed patients of the results of the study on beagle dogs and concluded that the “significance with respect to humans has not been established.”

F. Current Status of Hormone Replacement Therapy

Premarin, Provera, and Prempro continue to be prescribed today, and the FDA still considers the drugs safe and effective. The FDA now requires, however, the drugs’ labels to reflect the results of the WHI study, and all three medications now contain a boxed warning of the risk of breast cancer. Following the release of the WHI results, the number of prescriptions dropped significantly. This drop in prescriptions was accompanied by a corresponding reduction in the number of cases of breast cancer diagnosed in the United States. Likewise, a retrospective review has since shown that breast cancer increased as prescriptions for hormone replacement therapy increased.

Dr. Kuperman’s prescription habits have also changed. Although he testified that he has always warned of the known risks and prescribed the lowest effective dose, he now relies on the WHI study and subsequent studies to provide a more accurate assessment of the risks to his patients. As a result of the study, Dr. Kuperman aims to keep the duration of estrogen plus progestin use to less than five years, and he no

longer prescribes hormone replacement therapy for durations of ten or fifteen years. Instead, he tries to wean patients off hormone replacement therapy. Following the study results, Dr. Kuperman told Wyeth sales representatives who had routinely visited his office that he had a negative opinion of Prempro and no longer wanted samples. Since 2002, his prescriptions for estrogen plus progestin have decreased.

G. Procedural Background

After a nearly three-week-long trial, the jury found that Wyeth and Upjohn had inadequately warned about a known or knowable risk of breast cancer from ingestion of Premarin, Provera, and Prempro and that this failure to warn was the proximate cause of Scroggin's breast cancer. The jury awarded Scroggin compensatory damages in the amount of \$2.7 million. Following a three-day trial, the jury found Wyeth liable for \$19.36 million and Upjohn liable for \$7.76 million in punitive damages. The district court granted Wyeth's and Upjohn's motions for judgment as a matter of law as to punitive damages, finding that much of Dr. Parisian's punitive damages testimony should not have been admitted and that the remaining evidence did not support the verdict.

II. Analysis

Wyeth and Upjohn raise a number of issues regarding the liability phase of the trial, which we examine in turn. Scroggin appeals the district court's post-judgment order striking her expert's testimony and related exhibits on punitive damages phase and granting Wyeth's and Upjohn's motion for judgment as a matter of law on punitive damages.

A. Preemption

Wyeth and Upjohn contend that Scroggin's state law claim for failure to warn is preempted by federal law. Because the FDA regulates pharmaceutical products and oversees labeling requirements, they argue that there can be no heightened duty under Arkansas law and that they could not comply with state law without violating FDA requirements.

The Supreme Court's recent decision in Wyeth v. Levine, 129 S. Ct. 1187 (2009), has foreclosed this preemption argument. In Levine, a Vermont jury found that Wyeth had inadequately warned about the risk of irreversible gangrene arising from the intravenous push administration of its drug, Phenergan. Id. at 1193. The Court rejected Wyeth's preemption arguments, noting that federal regulations do not prohibit drug manufacturers from strengthening their warnings prior to FDA approval to reflect new developments and comply with state laws. Id. at 1196-97.

[I]t has remained a central premise of federal drug regulation that the manufacturer bears responsibility for the content of its label at all times. It is charged both with crafting an adequate label and with ensuring that its warnings remain adequate as long as the drug is on the market.

Id. at 1197-98. As in Levine, there is no evidence that the FDA would not have permitted the strengthening of the labels of Premarin, Prempro, and Provera in a manner consistent with Arkansas law.

Likewise, Wyeth and Upjohn have not shown that state requirements obstruct the purposes of federal drug labeling regulation. Given the limited resources of the FDA and the extensive assortment of pharmaceutical products on the market, "the FDA [has] traditionally regarded state law as a complementary form of drug regulation." Id. at 1202. Congress is aware of the potential for conflict and has

enacted an express preemption provision for medical devices, but there is no such enactment for prescription drugs, id. at 1200, and none will be implied.

B. Statute of Limitations

Wyeth and Upjohn appeal from the district court's denial of their motion for judgment as a matter of law on their statute of limitations defense, arguing that Scroggin was aware of the risk of breast cancer while taking hormone replacement therapy and that her claim thus began to accrue when she was diagnosed with breast cancer. We review *de novo* a district court's determination on a motion for judgment as a matter of law. Carter v. Kan. City S. Ry. Co., 456 F.3d 841, 846 (8th Cir. 2006). "We apply the same standards as the district court, giving the nonmoving party all reasonable inferences and viewing the facts in the light most favorable to the nonmoving party. If conflicting inferences reasonably can be drawn from evidence, the jury is in the best position to determine which inference is correct." Christensen v. Titan Distrib., Inc., 481 F.3d 1085, 1092 (8th Cir. 2007) (citations and internal quotations omitted).

Arkansas law provides a three year statute of limitations on product liability actions. Ark. Code Ann. § 16-116-103.

A cause of action accrues when the plaintiff first becomes aware of her condition, including both the fact of the injury and the probable causal connection between the injury and the product's use, or when the plaintiff by the exercise of reasonable diligence, should have discovered the causal connection between the product and the injuries suffered.

Uhiren v. Bristol-Myers Squibb Co., 346 F.3d 824, 828 (8th Cir. 2003) (relying on Arkansas law) (citations and internal quotations omitted). Scroggin contends that discovery of a probable causal connection was not possible until the WHI findings were released.

Wyeth and Upjohn argue that the WHI findings revealed nothing significant to Scroggin; therefore, whatever Scroggin knew in 2002, she knew in 2000 when she was diagnosed with breast cancer. We conclude that a jury could find that Scroggin's cause of action accrued at some point after the publication of the WHI study's results. Wyeth and Upjohn changed their products' labeling significantly following the publication of the WHI findings, devoting substantial label space to the results of the study. Moreover, the WHI results were widely covered in mainstream media,¹⁰ and Prempro sales have dropped by fifty percent since 2001, suggesting that the WHI study did more than affirm that which was already known.

Wyeth and Upjohn also contend that Scroggin should have known of the breast cancer risk because she received the product warnings, she read the warnings, and Dr. Kuperman discussed these warnings with her. Two doctors testified that the labels Scroggin would have read did not convey a significant risk of breast cancer, and Dr. Kuperman thought the labels indicated that the evidence was inconclusive. Thus, Scroggin presented sufficient evidence for the jury to find that the warnings were inadequate, contradictory, and confusing.

Wyeth and Upjohn also assume knowledge on Scroggin's part because Dr. Hagans instructed her to stop taking hormone replacement therapy when he diagnosed her with breast cancer. This argument fails, for the Premarin and Prempro labels stated that women already known to have breast cancer should not use Premarin or Prempro. The label included that instruction because estrogen is contraindicated for

¹⁰The WHI study was the subject of Time Magazine's July 22, 2002 cover story, "The Truth About Hormones: A large, federally funded study provides definitive proof that estrogen and progestin are not age-defying wonder drugs. What's a woman to do?" The New York Times recently reported that the "[u]se of treatment plunged after [the WHI] findings were reported." Study Cites Hormones As Cancer Risk, N.Y. Times, July 15, 2009, at A13.

women with breast cancer, meaning that it can exacerbate their existing breast cancer and, as Justin Victoria testified, not because it suggests a causal connection. Cf. Roth v. G.D. Searle & Co., 27 F.3d 1303, 1308 (8th Cir. 1994) (noting that the doctor’s statement that the plaintiff never should have had the second intrauterine device inserted, coupled with unchallenged, plainly stated product warnings, put the plaintiff on inquiry notice).

The assertion that Scroggin would have been aware of the risk through her own due diligence is also without merit, for it ascribes to Scroggin the duty of being aware of not simply the possibility that her hormone replacement therapy caused her breast cancer, but that a causal connection was probable. The jury could reasonably conclude that if medical doctors were unsure of the risk, it is highly unlikely that a layperson would be more aware of that risk. See Deutsch v. Wyeth, Inc., No. MID-L-998-06 MT (N.J. Super. Ct. June 14, 2007) (order denying Wyeth’s motion for summary judgment based on statute of limitations) (“It is . . . entirely unreasonable to require a patient without medical training to make the logical connection between her ingestion of HRT drugs and her breast cancer and possess a reasonable belief that she could sue Wyeth for her injuries before the WHI findings were released to the public.”).

C. Causation

Wyeth and Upjohn assert that Scroggin failed to prove that their drugs were the cause of her injury. As part of her failure to warn claim, Scroggin was required to show both specific causation—that the hormone replacement therapy caused her injury—and proximate causation—that she would not have taken the combination therapy had Wyeth and Upjohn provided adequate warnings. See Ashley County v. Pfizer, Inc., 552 F.3d 659, 667 (8th Cir. 2009). Wyeth and Upjohn argue that the district court erred in admitting the testimony of Scroggin’s specific causation expert, in instructing the jury on proximate cause, and in denying their motion for judgment

as a matter of law because the evidence showed that Scroggin would not have done anything differently if an adequate warning had been provided.

1. Admission of Dr. Naftalis's Expert Testimony

Wyeth and Upjohn argue that the district court erred in admitting the testimony of Dr. Elizabeth Naftalis, Scroggin's expert witness on specific causation. "[A]bsent a clear and prejudicial abuse of discretion," we will not reverse a district court's determination on the admissibility of expert testimony. Bland v. Verizon Wireless, L.L.C., 538 F.3d 893, 896 (8th Cir. 2008).

Federal Rule of Evidence 702 provides for the admission of an expert opinion if it "will assist the trier of fact to understand the evidence or to determine a fact in issue," provided the expert is qualified to render the opinion and offers sufficient factual basis for her opinion, forms her opinion on reliable principles and methods, and applies these principles or methods to the facts of the case. Rule 702 reflects a "relax[ation of] the traditional barriers to opinion testimony," and the court's inquiry is intended to be flexible. Daubert v. Merrell Dow Pharms., Inc., 509 U.S. 579, 588, 594 (1993) (internal quotations omitted). The district court must assess whether the methodology used by the proposed expert is valid and whether it was properly applied.¹¹ Id. at 592-93. "There is no single requirement for admissibility as long as the proffer indicates that the expert evidence is reliable and relevant." Unrein v. Timesavers, Inc., 394 F.3d 1008, 1011 (8th Cir. 2005).

¹¹Daubert sets forth the following four factors for consideration, which do not constitute a definitive checklist or test: (1) whether the theory or technique applied can be tested, (2) whether the theory or technique has been subject to peer review or publication, (3) the known or potential rate of error, and (4) general acceptance. Daubert, 509 U.S. at 593-95.

Wyeth and Upjohn did not challenge Dr. Naftalis's qualifications as an expert witness before the district court, and they do not argue that the method she used, differential diagnosis, is not a sound and accepted methodology. Instead, they argue that differential diagnosis cannot be used to prove the cause of breast cancer because no one knows the cause of breast cancer. They note that Dr. Naftalis was not familiar with the details of Scroggin's family history of breast cancer until trial, and they argue that she did not properly account for Scroggin's various risk factors for breast cancer, such as breast density, her age, weight, and her smoking history.

Scroggin suffered from hormone-dependent breast cancer. Dr. Mariann Harrington, Scroggin's oncologist, tested the tumors in Scroggin's breasts for hormone receptors to inform her treatment. Both the left and right tumors were one hundred percent positive for estrogen and progesterone receptors. There was no dispute at trial that hormone-receptor-positive tumors are dependent upon hormones for their growth. Moreover, published research had concluded that hormone-receptor-positive tumors need hormones to grow, that menopausal symptoms result from hormone deficiency, and that there is a link between breast cancer and hormone replacement therapy. See Lauzon v. Senco Prods., Inc., 270 F.3d 681, 693 (8th Cir. 2001) (noting that "scientific reliability can also be shown by proof that the research and analysis supporting the proffered conclusions have been subjected to normal scientific scrutiny through peer review and publication").

Knowing that Scroggin's breast cancer was hormone dependent, Dr. Naftalis's differential diagnosis sought to determine the cause of Scroggin's breast cancer by ruling out the two possible sources of these hormones: (1) Scroggin produced the hormones herself, or (2) they came from the hormone replacement therapy she had taken for the past eleven years. Scroggin presented evidence that her menopausal symptoms were relieved by hormone replacement therapy, confirming that her own body was unable to produce sufficient hormones and therefore could not be the

cause.¹² The remaining source was the combination of Premarin, Provera, and Prempro. Accordingly, Scroggin presented evidence establishing a causal link between breast cancer and estrogen plus progestin use, particularly for the length of time Scroggin was taking the drugs.

We find unpersuasive the contention that Dr. Naftalis's testimony should not have been admitted because Scroggin has some breast cancer risk factors and a family history of breast cancer. Dr. Naftalis sufficiently established that hormones were necessary to the development of Scroggin's tumors and conducted her differential diagnosis from this starting point. Although not necessary to the formation of her opinion, Dr. Naftalis addressed the known causes of breast cancer and possible risk factors. Wyeth and Upjohn argue that this review was insufficient, but Dr. Naftalis's "explanations as to conclusions not ruled out went to weight and not admissibility." Id. at 694. Additionally, Scroggin submitted to every available genetic test for breast cancer, all of which came back negative for the most common breast cancer genes. Wyeth's genetics expert testified that he continues to believe that genetics caused Scroggin's breast cancer, but the jury concluded otherwise.

Wyeth's and Upjohn's reliance on Bland v. Verizon Wireless, L.L.C. is misplaced. 538 F.3d 893 (8th Cir. 2008). In that case, expert testimony was offered to show that the plaintiff's recent exposure to freon caused her exercise-induced asthma. Id. at 897. The exact cause of exercise-induced asthma is not known, and the plaintiff's expert could not provide a reliable opinion as to what caused the plaintiff's asthma. Id. at 898. The proximity in time between the plaintiff's exposure to freon

¹²Although Wyeth presented evidence disputing this association, the factual basis of an expert opinion is assessed by the jury, Larson v. Kempker, 414 F.3d 936, 941 (8th Cir. 2005), and the jury may have been persuaded by Wyeth's own documents asserting a link between hormone deficiency and uncomfortable menopausal symptoms. Further, Wyeth has not disputed that vaginal atrophy is caused by estrogen deficiency.

and her resulting asthma was the only basis for her doctor's opinion; the doctor failed to investigate other possible causes, including Bland's home or other environments. Id. Conversely, Dr. Naftalis was able to testify that Scroggin's breast cancer would not have developed without hormone replacement therapy because Scroggin's body was not producing sufficient amounts of hormones to allow hormone-receptor-positive tumors to develop. Thus, Dr. Naftalis ruled out the other possible cause of Scroggin's breast cancer, and her expert testimony was properly admitted.¹³ Wyeth and Upjohn had the opportunity to expose the testimony's weaknesses through vigorous cross-examination and the presentation of contrary evidence. See Daubert, 509 U.S. at 596.

2. Jury Instruction on Aggravation of Preexisting Condition and Promotion

Wyeth and Upjohn argue that the district court erred in modifying the Arkansas Model Instruction on proximate cause to reflect Scroggin's theory that estrogen plus progestin use promotes preexisting abnormal cells into malignancies. "We review a district court's decision on jury instructions for abuse of discretion, looking to the instructions as a whole to determine whether they fairly submitted the issues to the jury." Boerner v. Brown & Williamson Tobacco Co., 394 F.3d 594, 603 (8th Cir. 2005). "We afford the district court broad discretion in choosing the form and language of the instructions and will reverse a jury verdict only if the erroneous instruction affected a party's substantial rights." In re Prempro Prods. Liab. Litig.,

¹³The Minnesota Court of Appeals's recent unpublished opinion, Zandi v. Wyeth, Inc., No. 27-CV-06-6744, 2009 WL 2151141 (Minn. Ct. App. July 21, 2009) (unpublished), is distinguishable. Although Zandi involves similar facts, Minnesota law requires a more conservative review of expert testimony than the liberal thrust of the Federal Rules of Evidence and relies on a variant of the standard abandoned in Daubert. To the extent that Zandi excludes an expert opinion that relies on differential diagnosis to determine the cause of hormone-receptor-positive breast cancer in an individual with hormone-dependent breast cancer, we respectfully disagree.

514 F.3d 825, 829 (8th Cir. 2008) (internal quotations omitted) (quoting Slidell v. Millenium Inorganic Chems., Inc., 460 F.3d 1047, 1054 (8th Cir. 2006)).

“Model jury instructions are just that, models. They are not mandatory.” United States v. Wilson, 565 F.3d 1059, 1067 (8th Cir. 2009). The district court was not required to precisely follow Arkansas’s Model Instruction, but only to “fully and properly instruct upon all the elements of the case in light of controlling Arkansas law.” Wright v. Farmers Co-op of Ark. & Okla., 620 F.2d 694, 698 (8th Cir. 1980) (internal quotations omitted) (citing Stafford v. S. Farm Bureau Cas. Ins. Co., 457 F.2d 366, 367 (8th Cir. 1972) (per curiam)).

Under Arkansas law, “proximate cause is that cause which, in a natural and continuous sequence, produces damage.” Sluder v. Steak & Ale of Little Rock, Inc., 206 S.W.3d 213, 218 (Ark. 2005) (internal quotations omitted) (citing AMI Civ. 3d 501; Bull v. Manning, 433 S.W.2d 145 (Ark. 1968); Ben M. Hogan & Co. v. Krug, 351 S.W.2d 451 (Ark. 1961)). The district court’s instruction included this precise language, as well as the following definitions:

A ‘producing’ cause is one that in natural and continuous sequence causes or initiates injury and without which the injury would not have occurred. A ‘promoting’ cause is one that in natural and continuous sequence aggravates a pre-existing condition or disease and without which the full extent of the injury would not have occurred.

The court then clarified that the jury was to view the evidence in light of these definitions rather than how they may have been used during the trial.

Wyeth's argument¹⁴ acknowledges only two possible theories of Scroggin's case: either Scroggin already had breast cancer and the hormone replacement therapy aggravated it, or the therapy initiated the transformation of normal cells into cancerous cells. Given these alternatives, Wyeth asserts that including "promoting" in the instruction unfairly elevated Scroggin's presentation of the evidence and that the instruction was not supported by the evidence. Wyeth has refused to recognize Scroggin's theory of causation. Scroggin presented evidence that she had abnormal or susceptible cells, which were a pre-existing condition. In other words, she had these cells prior to her regimen of estrogen plus progestin. She also presented evidence that estrogen and progestin caused these cells to become cancerous. Dr. Colditz has described estrogen plus progestin's effect on these abnormal cells as "acting like a fertilizer to get them to grow rapidly and progress on to cancer." Dr. Naftalis testified that combination hormone therapy has a "promotion effect" on the "susceptible cell and turns it into cancer." Dr. Colditz stated that the epidemiologic field accepts promotion as the mechanism by which hormone replacement therapy causes breast cancer. Thus, the instruction was appropriately tailored to the facts. See Pershern v. Fiatallis N. Am., Inc., 834 F.2d 136, 139 (8th Cir. 1987).

The court showed no bias in its instruction. The producing-cause definition reflects Wyeth's theory of the case—that hormone replacement therapy does not initiate the first abnormal cells or turn normal cells into cancerous cells—and is appropriately supported by the evidence Wyeth presented. Scroggin argued promotion, Wyeth argued initiation, and the court instructed the jury on both theories. The court also instructed the jury that it could not award damages for any injury that did not occur as a result of Scroggin's taking Prempro or Premarin and Provera. The instruction contains the substantive requirements of proximate cause; what remains

¹⁴Upjohn adopted by reference Wyeth's argument regarding the proximate cause instruction. See Fed. R. App. P. 28(i).

is form and language, which we leave to the court's broad discretion. In re Prempro Prods. Liab. Litig., 514 F.3d at 829.

3. Denial of Wyeth's and Upjohn's Motions for Judgment as a Matter of Law on Proximate Causation

The district court denied Wyeth's and Upjohn's motion for judgment as a matter of law based on their claim that Scroggin did not prove that their failure to warn of the risk of breast cancer proximately caused her breast cancer. We review the denial of their motions *de novo*, "viewing the evidence in the light most favorable to the prevailing party and making all reasonable inferences in favor of the jury's verdict." Boerner, 394 F.3d at 598. "Judgment as a matter of law is only appropriate when no reasonable jury could have found for the nonmoving party." Mattis v. Carlon Elec. Prods., 295 F.3d 856, 860 (8th Cir. 2002). Ordinarily proximate cause is a question of fact, except where the evidence is such that reasonable minds cannot differ. Ashley County, 552 F.3d at 667 (citing Wilson v. Evans, 679 S.W.2d 205, 206 (Ark. 1984)).

Wyeth and Upjohn argue that the evidence was not sufficient to show that an adequate warning would have prevented Scroggin's breast cancer. The parties disagree about who had the burden to show what effect an adequate warning would have had. Specifically, they argue about the application of the heeding presumption—the presumption that a person would have heeded an adequate warning if given—and whether it applies to pharmaceutical cases. Notably, neither party asked Dr. Kuperman if he would have prescribed the medication to Scroggin if there had been an adequate warning.

Scroggin argues that the heeding presumption is a rebuttable presumption, shifting the burden to Wyeth and Upjohn to show that an adequate warning would not have prevented Scroggin's injuries. Although Arkansas law generally applies the

heeding presumption in this manner, see Smith v. Rogers Group, Inc., 72 S.W.3d 450, 458 (Ark. 2002), Arkansas has yet to consider the presumption in a pharmaceutical case. Wyeth argues that the presumption should only imply that the physician would have considered it, but that the burden remains on the plaintiff to show that an adequate warning would have altered the physician's decision to prescribe the product and the plaintiff's decision to take it.¹⁵

The Tenth Circuit noted in a pharmaceutical case that “[t]he vast majority of jurisdictions hold that where a warning is inadequate, the plaintiff is entitled to a rebuttable presumption that an adequate warning would have been heeded if one had been given.” Thom v. Bristol-Myers Squibb Co., 353 F.3d 848, 855 (10th Cir. 2003). Given the current application of the heeding presumption in Arkansas and the majority view, we conclude that Arkansas likely would require Wyeth and Upjohn to rebut the presumption even in a case involving pharmaceutical products. Moreover, Wyeth and Upjohn rely on Eck v. Parke, Davis & Co., 256 F.3d 1013, 1019 (10th Cir. 2001) (relying on Oklahoma law), which required the drug manufacturer defendants to rebut the presumption by showing that the additional information “would not have changed the prescribing physician’s course of treatment.” Wyeth and Upjohn failed to establish that Dr. Kuperman would have prescribed the hormone replacement therapy despite an adequate warning.

Although conflicting, the evidence on proximate causation was sufficient to allow the jury to find that a failure to warn was the proximate cause of Scroggin’s

¹⁵Wyeth and Upjohn rely primarily on Thomas v. Hoffman-LaRoche, Inc., 949 F.2d 806 (5th Cir. 1992). In Thomas, the Fifth Circuit acknowledged that no Mississippi Court applied the heeding presumption to a medical drug case, noting that state case law “strongly suggests that a presumption does not exist under Mississippi law.” Id. at 813. In Ackermann v. Wyeth Pharm., 526 F.3d 203 (5th Cir. 2008), the Fifth Circuit stated that Texas had “explicitly rejected the . . . read-and-heeded presumption.” Id. at 212-13 (citations and internal quotations omitted).

injuries. Dr. Kuperman testified that he still prescribes estrogen plus progestin to menopausal women and that the initially reported results of the WHI study indicated a slight relationship. On the other hand, his prescription practices for these drugs have changed since the WHI study. Since 2002, Dr. Kuperman has written fewer prescriptions for hormone replacement therapy drugs. Moreover, he tries to keep the prescription duration to below five years, as the breast cancer risk increases with use. Dr. Naftalis testified that Scroggin would not have developed breast cancer if she had taken the therapy for five years rather than eleven. Accordingly, the jury could reasonably conclude that had Wyeth and Upjohn adequately warned of the breast cancer risk, Scroggin would have been among Dr. Kuperman's patients who do not take hormone replacement therapy drugs or among those who take them for a shorter period of time.

Dr. Kuperman also testified that he would respect a patient's wishes and not prescribe hormone replacement therapy if she was concerned about the risk of breast cancer. Thus, the jury could have concluded that Scroggin would have chosen not to take the drugs if the warnings had been adequate. Although Wyeth and Upjohn focus on Scroggin's acknowledgment that she would have accepted a "small" risk and that she did not know that estrogen plus progestin use "causes" breast cancer, the jury was not so limited. The jury heard Scroggin explain her understanding of risk as anything that could possibly happen, even if highly unlikely, and how the equivocal language in the pre-WHI labels reassured her that the risk was small. The current labels do not simply identify the 1.24 relative risk reported from the WHI study, but also include a boxed warning, with straightforward language, and devote substantial attention to the risk of breast cancer. Scroggin testified that she would not have taken hormone replacement therapy if she had known of the risk as it was currently understood.

D. Punitive Damages

Scroggin's argument during the punitive damages phase of the trial was two fold: (1) Wyeth and Upjohn were aware that estrogen plus progestin could cause breast cancer but had consciously disregarded the risk, and (2) Wyeth downplayed the risk, campaigning against its acceptance within the scientific community, the FDA, and the general population. In support of her argument, Scroggin presented Dr. Parisian as an expert witness on FDA regulations and Wyeth's and Upjohn's lack of compliance therewith.

The district court ordered Dr. Parisian to base her opinion "on her observations over the years and her understanding of the regulations referenced in her expert report, her deposition, and the supplemental briefs." During Dr. Parisian's testimony, the district court expressed frustration that she was not linking her testimony to FDA regulations. Because Dr. Parisian's testimony consisted mostly of her reading documents, and not expert analysis, the district court concluded that "most of Dr. Parisian's punitive damages testimony should have been excluded." Thus, although it had denied Wyeth's and Upjohn's motions to strike during the trial, the district court granted their post-trial motions and struck much of Dr. Parisian's testimony and related exhibits.

Without that evidence, the district court determined that Scroggin "failed to present clear and convincing evidence warranting punitive damages" and granted Wyeth's and Upjohn's motions for judgment as a matter of law. The district court ruled that if it had not granted those motions, it would have granted a new trial on punitive damages.

1. Post-Judgment Exclusion of Dr. Parisian's Punitive Damages Testimony and Accompanying Exhibits

Scroggin argues that the district court erred in striking Dr. Parisian's testimony. We review a district court's decision to exclude expert testimony for an abuse of discretion. Larson, 414 F.3d at 940. Federal Rule of Evidence 702 permits expert testimony to assist the jury in understanding technical or scientific evidence.

As an initial matter, we disagree with Scroggin's contention that Wyeth and Upjohn did not preserve their objection to Dr. Parisian's testimony. The district court stated that the defendants "submitted motions to exclude, lodged numerous objections during the punitive damages stage, and requested, both orally and in writing, that Dr. Parisian's punitive damages testimony be stricken or excluded." That Wyeth and Upjohn did not object during Dr. Parisian's testimony until the court expressed its own concerns did not waive their objection, for as the court noted, "their specific points had been made and were well-known to [the court] and [Scroggin's] counsel."

Dr. Parisian's testimony began with a brief overview of some federal regulations, followed by discussion of specific exhibits, largely devoid of regulatory analysis. The record reflects that often Dr. Parisian simply read the contents of exhibits, thus undermining the asserted basis for expert testimony. At a sidebar conference during the testimony, the district court instructed Scroggin's counsel to relate the testimony to FDA guidelines; nevertheless, the testimony continued in the same manner. Accordingly, we cannot say that the district court abused its discretion in striking Dr. Parisian's testimony.

2. Grant of Judgment as a Matter of Law Dismissing Jury's Punitive Damages Award

Scroggin asserts that even without the excluded testimony and related exhibits, the evidence was sufficient to support the jury's award of punitive damages. We review *de novo* a court's grant of judgment as a matter of law. Carter, 456 F.3d at 846. "Judgment as a matter of law is only warranted where the evidence at trial is wholly insufficient to support a jury finding." Id.

Arkansas law allows for punitive damages when a defendant "knew or ought to have known . . . that his or her conduct would naturally and probably result in injury or damage and that he or she continued the conduct with malice or in reckless disregard of the consequences from which malice may be inferred." Ark. Code. Ann. § 16-55-206. "[M]alice is not necessarily personal hate; it is, rather, an intent and disposition to do a wrongful act greatly injurious to another." Yeakley v. Doss, 257 S.W.3d 895, 899 (Ark. 2007) (citing Fegans v. Norris, 89 S.W.3d 919 (Ark. 2002)). "A claim for punitive damages is properly submitted to the jury under Arkansas law where the claim is supported by substantial evidence." Morris v. Union Pac. R.R., 373 F.3d 896, 903 (8th Cir. 2004) (internal quotations omitted) (citing D'Arbonne Constr. Co. v. Foster, 123 S.W.3d 894, 898 (Ark. 2003)).

a. Upjohn

We affirm the district court's grant of judgment as a matter of law to Upjohn. Most of the evidence presented during the punitive damages phase concerned Wyeth, and the evidence related to Upjohn focused on its efforts to market Provera as "the other half of estrogen replacement therapy." These advertisements violated federal regulations, but there is no dispute that prescribing progestin along with estrogen had become the standard of care in hormone replacement therapy. Scroggin also contends that a jury could infer malice because Upjohn failed to conduct an in-house study of

the breast cancer risk after the Degge Group found that further study was needed. Upjohn, however, did not conceal or restrict the dissemination of the information. It allowed the Degge Group to publish its findings, thus informing the scientific community of the current state of the science. On this record, then, there was not substantial evidence showing that Upjohn acted with “such a conscious indifference to the consequences that malice may be inferred.” D’Arbonne Constr. Co., 123 S.W.3d at 898.

b. Wyeth

We adopt the district court’s alternative holding as to Wyeth and remand for a new trial on punitive damages. Scroggin presented sufficient evidence to submit the question of punitive damages to the jury, even without Dr. Parisian’s testimony. Moreover, many of the stricken exhibits had been admitted prior to Dr. Parisian’s testimony and without any requirement that they be presented in relation to Dr. Parisian’s knowledge of FDA regulations. Accordingly, the jury could have considered those exhibits and drawn its own conclusions.

In ruling on the post-verdict motions, the district court set forth a detailed analysis of the evidence, explaining that each piece failed to present clear and convincing evidence of reckless indifference. We conclude that this individualized treatment of the evidence may inadvertently have obscured the full scope of Wyeth’s conduct that the evidence collectively portrayed. Although Wyeth’s failure to organize one study to allow for adequate evaluation of the breast cancer risk, or its attempts to undermine the results of one adverse publication, may not reflect reckless disregard, a consistent pattern of such conduct might do so. A jury could find that although each study added to the evidence suggesting a risk of breast cancer, Wyeth nevertheless continued to engage in a practice of both inaction and mitigation.

The district court noted that the evidence showed that Wyeth attempted to convey that there was no definitive link between estrogen plus progestin hormone replacement therapy and breast cancer. But Scroggin's claim also rested on the theory that Wyeth deliberately avoided studying hormone replacement therapy's effect on breast cancer. Moreover, a jury could reasonably construe Wyeth's documents as repeated efforts over many years to undermine information and studies that attempted to show a breast cancer link. A jury reasonably could find that these efforts allowed Wyeth to promote the false understanding that hormone replacement therapy was not linked to breast cancer and then to promote reliance on this understanding. Viewed as a whole, then, the evidence presented could allow a jury to find or infer that Wyeth was guilty of malicious conduct within the meaning of Arkansas law.

There is also merit to Scroggin's assertion that the district court characterized certain evidence in Wyeth's favor. In entertaining a motion for judgment as a matter of law, the court "must draw all reasonable inferences in favor of the nonmoving party, and it may not make credibility determinations or weigh the evidence." Reeves v. Sanderson Plumbing Prods., Inc., 530 U.S. 133, 150 (2000). The law requires the district court to "disregard all evidence favorable to the moving party that the jury is not required to believe." Id. at 151. The court, however, credited Justin Victoria's characterization of Wyeth's response to the 1976 Hoover study, thus ignoring Wyeth's efforts to refute and mitigate the results of the study. Likewise, the documents suggesting that Wyeth had a policy of refusing drug samples for breast cancer studies are not as clear as Wyeth would have the jury believe. These documents, and many of the stricken documents, were Wyeth's internal documents and thus not capable of being rebutted or characterized by Scroggin's witnesses. The jury could have concluded that the documents spoke for themselves and rejected Wyeth's self-interested explanation. Cf. Wilcox v. State Farm Mut. Auto Ins. Co., 253 F.3d 1069, 1070-71 (8th Cir. 2001) (noting that it would not be obvious error to credit employer's affidavit detailing employee's performance deficiencies when employee was given a clear opportunity to contradict the affidavit).

For these reasons, we conclude that there was sufficient evidence upon which a jury could conclude that Wyeth acted with reckless disregard to the risk of injury, even without Dr. Parisian's testimony. The admission and the jury's consideration of Dr. Parisian's testimony, however, amounted to prejudicial error, and thus the appropriate remedy is a new trial. Because a new trial may be had on punitive damages alone without injustice to the parties, we adopt the district court's alternative judgment granting a new trial to Wyeth on the punitive damages claim. See Eng. v. Gulf & W. Mfg. Co., 728 F.2d 1026, 1029 (8th Cir. 1984) (citing Gasoline Prods. Co. v. Champlin Ref. Co., 283 U.S. 494, 500 (1931)).

We have considered Wyeth's and Upjohn's assertion that a new trial on the liability phase is required due to district court errors and conclude that none of the alleged errors affected Wyeth's or Upjohn's substantial rights.

III. Conclusion

The judgment against Wyeth and Upjohn on Scroggin's claim for compensatory damages is affirmed. The order granting judgment as a matter of law to Upjohn on Scroggin's claim for punitive damages is affirmed. We vacate the order granting judgment to Wyeth on Scroggin's claim for punitive damages, adopt the alternative judgment, and remand the case to the district court for a new trial on punitive damages.
