IN THE UNITED STATES DISTRICT COURT
WESTERN DISTRICT OF ARKANSAS
HOT SPRINGS DIVISION

In re:	:	**MDL Docket No. 4:03CV1507-WRW**
	:	**6:05CV06074**
PREMPRO PRODUCTS LIABILITY LITIGATION	:	
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	:	
SHIRLEY DAVIDSON	:	**PLAINTIFF**
	:	
v.	:	
	:	
WYETH, INC., et al.	:	**DEFENDANTS**

ORDER

Pending is Defendants' Motion to Preclude Any Expert Testimony that Prempro Use Increases Breast Cancer Risk When Taken for Only Three Years or Less (Doc. Nos. 36, 38, 40). Plaintiffs have responded[1] and Defendants have replied.[2] Hearings were held on Monday, November 29, 2010, and Wednesday, January 12, 2011. Plaintiffs' expert, Donald F. Austin, M.D., and Defendants' expert, Kurt T. Barnhart, M.D., M.S.C.E., both testified during the January 12, 2011 hearing.

I. BACKGROUND

The issue before the Court is whether Dr. Austin, an epidemiologist and Plaintiffs' general causation expert, can testify reliably that short-term use of Prempro[3] increases the risk of breast cancer. Plaintiffs, through Dr. Austin's expert opinion, propose that there is a statistically significant increased risk of breast cancer from short-term use of hormone replacement therapy ("HRT") --

[1]Doc. No. 40.

[2]Doc. No. 45.

[3]Prempro is a combination of conjugated equine estrogen and medroxyprogesterone. It is also referred to as CEE + MPA.

Prempro or its generic equivalents, in this particular instance. Defendants counter that Dr. Austin's opinion fails to rebut the highly reliable Women's Health Initiative ("WHI"), which showed a reduced risk of breast cancer with short-term use (around three years) of Prempro.

This Order is limited to only Prempro (and its generic equivalents) and ductal cancer. It appears there may be causation differences between lobular and ductal cancer as there are a few studies finding a causal connection between lobular cancer and short-term HRT use. Since this issue was not fully fleshed out at the hearing or in the papers, and the two short-term use cases set for trial on February 1, 2011, involve only ductal cancer, this Order will not address lobular cancer.

II. STANDARD

A. Burden of Proof

The admissions of expert testimony is governed by Rule 702 of the Federal Rules of Evidence, which reads:

> If scientific, technical, or other specialized knowledge will assist the trier of fact to understand the evidence or determine a fact in issue, a witness qualified as an expert by knowledge, skill, experience, or education, may testify thereto in the form of an opinion or otherwise, if (1) the testimony is based on sufficient facts or data, (2) the testimony is the product of reliable principles and methods, and (3) the witness has applied the principles and methods reliably to the facts of the case.[4]

When a party proffers an expert witness, deciding whether Rule 702 is satisfied is a preliminary issue governed by Federal Rule of Evidence 104(a).[5] Rule 104(a) requires the proponent of evidence to establish its admissibility by a preponderance of the evidence.[6] In determining admissibility, the trial court is not bound by any of the rules of evidence, except with regard to privilege.[7]

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[4]Fed. R. Evid. 702.

[5]*U.S. v. Martinez*, 3 F.3d 1191, 1196 n.10 (8th Cir. 1993).

[6]*Bourtjaily v. U.S.*, 483 U.S. 171 (1987).

[7]Fed. R. Evid. 104(a).

B. Legal Standard for Admissibility

The central inquiry under Rule 702 is whether the proffered expert's testimony is sufficiently reliable.[8] The trial court serves a gatekeeping function, ensuring that any expert testimony is reliable and relevant.[9]

To be admissible, expert testimony must satisfy the two prongs of Rule 702.[10] First, it must be based on scientific, technical, or other specialized knowledge.[11] If the testimony is scientific, it must be grounded in the methods and procedures of science.[12] Likewise, "knowledge" requires more than a subjective belief or an unsupported speculation, requiring instead an appropriate level of validation.[13] Second, the testimony must be relevant, in that it must help the trier of fact either understand the evidence or determine a fact in issue.[14] The burden of establishing relevancy and reliability rests on the proponent of the expert testimony.[15]

Courts have used a variety of factors to determine the reliability of proffered expert testimony. The most frequently discussed factors are those derived from the Supreme Court's opinion in *Daubert*, where the Court established that the trial court may consider:

> (1) whether the theory or technique can be or has been tested; (2) whether the theory or technique has been subjected to peer review and publication; (3) whether the theory or technique has a known or potential error rate and standards controlling the

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[8] *First Nat'l Bank v. Benham*, 423 F.3d 855, 861 (8th Cir. 2005).

[9] *Id.*

[10] *U.S. v. Cawthorn*, 429 F.3d 793, 799 (8th Cir. 2005).

[11] *Id.*

[12] *Id.*

[13] *Id.* at 799-800 (quoting *Daubert v. Merrell Dow Pharms.*, 509 U.S. 579, 590 (1993)).

[14] *Id.* at 799.

[15] *Moore v. Ashland Chem., Inc.*, 151 F.3d 269, 278-78 (5th Cir. 1998).

technique's operation; and (4) whether the theory or technique is generally accepted in the scientific community.[16]

Because the inquiry is "flexible and fact-specific, a court should use, adapt, or reject *Daubert* factors" as needed based on the facts of a particular case.[17]

The most recent amendments to Rule 702 added three general standards for courts to use in determining the reliability and relevance of proffered expert testimony. First, the proffered testimony must be based on sufficient facts or data.[18] Second, it must be the product of reliable principles and methods.[19] Third, the expert must have applied those principles and methods reliably to the facts of the case.[20]

The focus is not on the expert's conclusion, but on the methodology.[21] The proponent of the testimony "need not prove . . . that the expert's testimony is correct, but . . . must prove by a preponderance of the evidence that the testimony is reliable."[22] Determining the validity of an expert's conclusions is the duty of the finder of fact. The proponent of expert testimony has the burden to show both reliability and relevancy.[23]

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[16]*Benham*, 423 F.3d at 861 (citing *Daubert*, 509 U.S. at 593-94).

[17]*Unrein v. Timesavers, Inc.*, 394 F.3d 1008, 1011 (8th Cir. 2005).

[18]Fed. R. Evid. 702(1).

[19]Fed. R. Evid. 702(2).

[20]Fed. R. Evid. 702(3).

[21]*Moore*, 151 F.3d at 275-76.

[22]*Id*. at 276.

[23]*Barrett v. Rhodia, Inc.*, 606 F.3d 975, 980 (8th Cir. 2010) (quoting *Marmo v. Tyson Fresh Meats, Inc*., 457 F.3d 748, 757 (8th Cir. 2006)).

III. DISCUSSION

A. WHI

Since the inception of this litigation, Plaintiffs have relied heavily on the WHI results to support their allegations that Prempro causes breast cancer; it is Plaintiffs' evidentiary keystone in this litigation. Plaintiffs' experts and counsel alike repeatedly have praised the WHI study as the "gold standard,"[24] "mother of all clinical trials,"[25] "one of the most definitive, far reaching clinical trials of women's health ever undertaken,"[26] and "trump[ing] any observational studies."[27] Dr. Austin, specifically, agreed that the clinical trials like WHI are the "[t]op of the heap in terms of the hierarchy of evidence or reliability"[28] and no other randomized trial, to date, has greater power when assessing HRT and women's health.

The WHI was a "randomized controlled primary prevention trial" designed to "assess the major health benefits and risks of the most commonly used hormone preparation in the United States."[29] A "randomized trial, clinical trial, or true experiment, is considered the gold standard for determining the relationship of an agent to a disease or health outcome."[30] Studies like the WHI are

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[24]*Scroggin v. Wyeth*, 4:04-CV-01169-WRW (E.D. Ark.), Doc. No. 487 (Plaintiff's opening statement).

[25]*In re Prempro*, 4:03-CV-01507-WRW (E.D. Ark.), Doc. No. 2462-1 (Deposition of Plaintiffs' expert, Graham Colditz, M.D., December 18, 2006, at 276:21-277:17).

[26]*Id.* at Doc. No. 81 (Plaintiffs' MDL Master Complaint).

[27]*Id*. at Doc. No. 2462-42 (Testimony of Plaintiffs' expert, David Sackett, M.D., in *Reeves v. Wyeth, Inc.*, 4:05-CV-00163-WRW).

[28]*Id.* at Doc. No. 2444-14.

[29]*Id.* at Doc. No. 2505-2.

[30]Federal Judicial Center, *Reference Manual on Scientific Evidence*, 338 (2d ed. 2000).

the "best way to ensure that any observed difference between the two groups in an outcome is likely to be the result of exposure to the drug or medical treatment."[31]

Rowan T. Chlebowski, M.D., a primary WHI investigator, in describing the significance of the methodology employed, stated:

> The strengths of the WHI study of estrogen plus progestin include the randomized double-blind study design, the large ethnically diverse study population, comprehensive and detailed assessment of a range of breast cancer risk factors at baseline, use of placebo controls, the requirement for baseline and ongoing yearly mammography and clinical breast examination in both study groups, and the central adjudication of the breast cancer end point via pathology report review. The rates of discontinuation of study medications in both study groups are limitations. However, these discontinuation rates are comparable with those observed in other trials of menopausal hormones and are less than observed in current clinical practice.[32]

Accordingly, this Court has consistently found that the WHI study is the most significant and reliable study for considering the risk of breast cancer from Prempro.[33]

Unfavorably to Plaintiffs in this litigation, WHI found that, for women with no HRT use before the study, invasive breast cancer rates were lower in the Prempro group than in the placebo group; but "[i]n the fourth year and thereafter, invasive breast cancer rates were higher" for the Prempro group.[34] For women with previous HRT use, "the rate of invasive breast cancer incidence was greater in the third year and beyond" for the Prempro group, as compared to the placebo group.[35]

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[31] *Id*.

[32] *In re Prempro*, 4:03-CV-01507-WRW, Doc. No. 2462-37 -- Rowan T. Chlebowski, M.D., et al., *Influence of Estrogen Plus Progestin on Breast Cancer and Mammography in Healthy Postmenopausal Women*, 289 J. Am. Med. Assoc. 24, 3252 (2003).

[33] *Id*. at Doc. No. 2388.

[34] *Id.* at Doc. No. 2462-37.

[35] *Id*.

During the January 12, 2011 hearing, Dr. Austin agreed that, in WHI, women taking Prempro had lower rates of breast cancer than women taking placebo for "about three years," and that the "primary analysis of breast cancer showed no evidence of an increased breast cancer risk during the first three or four years . . . ."[36]

Although Plaintiffs have relied on WHI as the definitive study for establishing a causal connection between HRT use and breast cancer, they make great strides in this short-term use litigation to criticize the WHI study as unreliable. Plaintiffs' newfound criticism is not persuasive.

Dr. Austin agreed that WHI is an "ideal study," but qualified his position by claiming it is an ideal study "for what it was designed for," which is "for heart disease."[37] This claim is a bit misleading because, as Dr. Austin admitted under questioning, medical ethics preclude designing a clinical trial to specifically test for breast cancer. Furthermore, Dr. Austin has been inconsistent on this point. During the instant *Daubert* hearing he testified WHI is not good for evaluating risk as it relates to duration of use; but, earlier in this litigation he indicated that it "would be a good study to look at" when considering the relationship between duration and risk.[38]

Another criticism Dr. Austin advanced is that the WHI study was "not powered enough to detect a risk in various subtypes of breast cancer."[39] Yet, previously, Dr. Austin agreed that WHI, as a clinical trial, had the greatest power when assessing HRT and women's health.

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[36]*Id.* at January 12, 2011, *Daubert* Hearing Transcript.

[37]*Id.*

[38]*In re Prempro*, 4:03-CV-01507-WRW, January 12, 2011, *Daubert* Hearing Transcript.

[39]*Id.*

Plaintiffs' counsel (not Dr. Austin) propose a 2006 WHI assessment by Garnet L. Anderson, *et al*., in an effort to rebut the WHI findings.[40] They contend that the assessment found that once the WHI data was recalculated accounting for the "high dropout rate," the results "substantially underestimated the risk."[41] In considering this point, the Court notes that according to the authors "[s]ubsetting prior HT users by formulation, duration and recency created subgroups with sparse data, limiting statistical power," and "the sparseness of the data and resulting power limitations for some of these analyses prevent a precise estimate of the length of exposure needed to introduce excess risk."[42] Based on the criteria set out in Dr. Austin's report, the Anderson assessment would be "under powered" and, therefore, inappropriate for assessing short-term use risk. Notwithstanding, the Anderson article's graph titled, "Sensitivity Analysis of Invasive Breast Cancer in Adherent Participants with No Prior Hormone Use," showed that the E+P group does not pass the placebo group for incidences of breast cancer until after three years. Even the Calle Study, which was relied on by Plaintiffs, noted that in a "sensitivity analysis" the risk between Prempro users and placebo did not "beg[i]n to diverge" until year three.[43]

Additionally, it appears that the Food and Drug Administration has accepted the WHI results regarding short-term use, since the current label reads: "studies have also reported an increased risk of breast cancer for estrogen plus progestin therapy . . . after several years of use."[44]

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[40]*Id.* at Doc. No. 2480-59 -- Garnet L. Anderson, et al, *Prior Hormone Therapy and Breast Cancer Risk in the Women's Health Initiative Randomized Trial of Estrogen plus Progestin*¸ 55 Mautritas, at 9.

[41]*Id.* at Doc. No. 2480.

[42]*Id.* at Doc. No. 2480-59.

[43]*Id.* at Doc. No. 2480-85 -- Eugenia Calle, Ph.D., et al, *Postmenopausal Hormone Use and Breast Cancer Associations Differ by Hormone Regiment and Histological Subtype*, 115 Cancer at 936 (2009).

[44]*In re Prempro*, 4:03-CV-01507-WRW, Doc. No. 2485-1.

Finally, according to Dr. Austin, his short-term use report was written in about five hours at the behest and assistance of Plaintiffs' counsel. Dr. Austin testified that he had never really thought about the short-term use issue before Plaintiffs' counsel presented it to him shortly before the recent *Daubert* challenge in Puerto Rico. He testified, "[i]t had never been raised as an issue to me, is there an important, a biologically important and clinically important risk within three years. It was just not an issue that I had thought about."[45]

Dr. Austin's testimony also revealed that the process was driven largely by the lawyers. He stated he relied on the lawyers "for help with some of the citations."[46] When the Court asked what he meant by "citations," since his report contained none, Dr. Austin explained:

> And then when I got them, I tried to go through and verify every one of the -- every one of the things, and I didn't get all the way through the verification process by the time it had to go in, but I thought that I had relied on my memory well enough for the few that hadn't to be able to rely on them.[47]

Dr. Austin's testimony on these points leads the Court to find his opinions were hastily formed in an attempt to overcome overwhelmingly reliable evidence to the contrary. Given Plaintiffs' enormous reliance on the WHI study in this litigation, the Court concludes that this criticism that developed over the course of hours is not only inconsistent, but illogical.

Dr. Austin had the burden, under *Daubert*, to present reliable science to support his conclusions regarding the unreliability of the WHI. He has not met his burden. The Court finds the Plaintiffs' current criticism of the WHI unsupported.

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[45] *Id.* at January 12, 2011, *Daubert* Hearing Transcript.

[46] *Id.*

[47] *Id.*

B. Dr. Austin's Other Opinions

Dr. Austin relies on several observational epidemiological studies to support his opinion that short-term use of Prempro increases the risk of breast cancer. The observational trials that Dr. Austin relies upon are indisputably more susceptible to bias and other confounding factors, and are less reliable than clinical studies, like WHI.[48]

It is important to note that, at the *Daubert* hearing, Dr. Austin admitted that two (Li and Saxena) of the six studies he relied upon were flawed and should not have been included in his report. Dr. Austin's inclusion of flawed reports compounded by the hasty methodology in which the report was prepared, by themselves, significantly calls into question the reliability of his expert opinions.

Nevertheless, before explaining his reliance on the observational studies, he discredited the other clinical trials which showed no increased breast cancer risk associated with short-term use of Prempro. Dr. Austin asserted that he cannot rely on studies (1) that "mix together in the analysis some women currently using E+P with those who had stopped using E+P for a variable period of time"; (2) that "mix[] women of higher risk . . . with those whose risk has returned to their baseline risk . . . ."; and (3) "in which the risk from [estrogen alone and E+P] are analyzed conjointly and not independently analyzed . . . ."[49] He also pointed out that "under powered" studies "are usually not suitable for addressing" the question of the causal effect of breast cancer and E+P when the drug is used for three years or fewer.[50]

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[48]*Reference Manual on Scientific Evidence*, 338-39 (2d ed. 2000).

[49]*In re Prempro*, 4:03-CV-01507-WRW, Doc. No. 2485-1. Accordingly, he summarily rejected the following studies: Schairer (1994), Stanford (1995), Newcomb (1995), Chen (2002), and Rosenberg (2006).

[50]Dr. Austin lists the following studies as underpowered: Schairer (1994), Stanford (1995), Newcomb (1995), Schairer (2000), Chen (2002), Weiss (2002), Norman (2003), Rosenberg (2006), and Li (2008).

After applying his restrictions, Dr. Austin found that "some observational studies are useful in addressing" the short-term use question; in his report he cites the Million Women Study, the French Teachers Study, Li (2000), Saxena (2010), and Calle (2010). These are the only studies relied on by Dr. Austin to support his position that there is a statistically significant relationship between the short-term use of Prempro and breast cancer incidences. There are no "gold standard" clinical trials to support Dr. Austin's opinions.

1. Li (2000)

This "population-based case-control study" involves "537 female residents of King County, Washington."[51] The focus of the study was to determine whether E+P[52] was more likely to cause one type of cancer than another.

Interestingly, the Li (2000) results contradict Dr. Austin's opinions on short-term use, rather than support them. The study concluded that there was no "elevation in the risk of ductal carcinoma associated with CHRT use" for the users whose median use was only 3 years.[53] The study also noted that its findings were consistent with Schairer, *et al.* (a study criticized by Dr. Austin), where there was no increase "for CHRT use of < 4 years' duration."[54] The study also noted that one of its "primary limitations . . . was its small sample size" -- a criticism that Dr. Austin used to disregard

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[51]*In re Prempro*, 4:03-CV-01507-WRW, Doc. No. 2480-87 -- Christopher Li, *Hormone Replacement Therapy in Relation to Risk of Lobular and Ductal Breast Carcinoma in Middle-Aged Women*, 88 Cancer. Vol. 2570 (2000).

[52]E+P is referred to in the study as Combined Hormone Replacement Therapy or CHRT.

[53]*In re Prempro*, 4:03-CV-01507-WRW, Doc. No. 2480-87.

[54]This is the same study that Dr. Austin refers to a Schairer (2000) and dismisses as underpowered -- Catherine Schairer, et al., *Menopausal Estrogen and Estrogen-Progestin Replacement Therapy and Breast Cancer Risk*, 283 J. Am. Med. Assoc. 485 (2000).

other studies. Finally, the stdy specifically sets out that "the relation between duration of CHRT use and lobular and ductal breast carcinoma could not be assessed."[55]

When confronted by Li (2000)'s problems (as they relate to short-term use causation) during his January 11, 2011 deposition and, again, during the January 12, 2011 hearing, Dr. Austin admitted that it was "an error" to include Li (2000) in his expert report.[56]

2. Saxena (2010) (The California Teachers Study)

The Saxena (2010) study is a "prospective cohort of women . . . in the California State Teachers Retirement System."[57] Dr. Austin noted that the study "established a statistically significant increase risk [of breast cancer] at less that 2 years of use."[58]

But, the study recognized that "[a]n important limitation of our analysis includes the characterization of HT use at cohort entry only . . ." and that "some of the women contributing to the hazard estimate for current short-duration EPT . . . may in fact be longer-duration current users."[59] Since Saxena (2010) considered duration of use only at the time the study commenced, the duration assessments are not reliable. Dr. Austin even noted that the "most correct assessment" required follow-up regarding use during the study. Moreover, Dr. Austin conceded that the study should not have been included in his report, since it could not reliably be used to analyze short-term use.

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[55] *In re Prempro*, 4:03-CV-01507-WRW, Doc. No. 2480-87.

[56] *Id.* at January 12, 2011, *Daubert* Hearing Transcript.

[57] *Id.* at Doc. No. 2480-88 -- Tanmai Saxena, et al., *Menopausal Hormone Therapy and Subsequent Risk of Specific Invasive Breast Cancer Subtypes in the California Teachers Study*, 9 Am. Assoc. Cancer Research 1 (2010).

[58] *Id.*

[59] *Id.*

3. The French Teachers Study (E3N Cohort; Fournier)

The French Teachers Study was a "prospective cohort of 98,995 French women, which was designed to find out if breast cancer risk varied according to the delay between menopause onset and starting HRT treatment."[60] Dr. Austin noted that this study showed an increased risk of breast cancer at less than two years, and that the "E+P combinations studied included estrogen plus MPA."[61]

In their briefing, Plaintiffs reference the French Teachers Study and also cite Dr. Leslie Bernstein's editorial (mentioned in passing in Dr. Austin's report), which comments on the French Teachers Study. Plaintiffs point to Dr. Bernstein's comments that, "An immediate 50% increase in breast cancer risk observed within the first 2 years of use is alarming."[62] However, the next paragraph, mentioned by neither Dr. Austin nor Plaintiffs, qualified this statement:

> But, the results are not completely generalizable to other populations as the estrogen plus progestagen regimens used in France as studied in the E3N cohort differ from the most commonly used regiments in the United States, such as the E+P regimen studied in the WHI clinical trial. Women in the E3N study cohort used mainly transdermal or percutaneous estradiol combined with synthetic progestagens including dydrogesterone, nomegestrol acetate, promegestone, chlormadinone acetate, medrogestone, and cyproterone acetate. Few women took oral estrogens combined with medroxyprogesterone acetate. Thus, it will be important for other cohorts that focus on use of HT in United States populations to evaluate breast cancer risk associated use immediately after menopause.[63]

In fact, the French Teachers Study explicitly points out the limitations of its findings: "Because breast cancer risk may vary according to the characteristics of EP-MHT, we must specify

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[60]*Id.* at Doc. No. 2480-86 -- Agnes Fournier, et al., *Estrogen-Progestagen Menopausal Homrone Therapy and Breast Cancer: Does Delay From Menopause Onset to Treatment Initiation Influence Risk*, 27 J. of Clinical Oncology 5138, 5142 (2009).

[61]*In re Prempro*, 4:03-CV-01507-WRW, Doc. No. 2485-1.

[62]*Id.* at Doc. No. 2480-89 and Doc. No. 2480.

[63]*Id.* at Doc. No. 2480-89.

that, in our cohort, the estrogenic component consisted almost exclusively of estradiol compounds, with progesterone and dydrogesterone as the most frequently associated progestagen . . . ."[64] Furthermore, the Bernstein editorial relied on by Plaintiffs confirms that the French Teachers Study results cannot be applied reliably to women in the United States.

Bolstering the idea that the study could not be applied to American women, Dr. Austin admitted that the "vast majority" of French women ingest HRT with formulations different than Prempro, and that the "vast majority" of the women in the study did not ingest Prempro or its generic equivalent. Recognizing the importance of drug formulations, Dr. Austin in earlier causation opinions disregarded studies where the specific drug formulation could not be identified.[65] Previously, he also recognized the difference between HRT in the United States and in Europe, and refused to rely on European studies when making a finding regarding general causation. He has not (and cannot) explain why his previous practices would not apply in this instance.

Furthermore, Dr. Austin conceded that estradiol and conjugated equine estrogen ("CEE") -- the estrogen in Prempro -- should be considered separately when attempting to determine whether the two have "statistically significant different . . . effects,"[66] and this study did not separate the two.

Because the French Teachers study involved HRT medications where the "vast majority" were different from Prempro; did not separate estradiol from CEE; and provided no separate analysis for Prempro at the three year mark, Dr. Austin cannot reliably use it to support his opinions on short-term use of Prempro.

4. The Million Women Study ("MWS")

The MWS is a "a cohort of a quarter of British women aged 50-64 years . . . set up

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[64] *Id.* at Doc. No. 2480-86.

[65] *Id.* at January 12, 2011, *Daubert* Hearing Transcript.

[66] *Id.*

chiefly to investigate the relation between various patterns of use of HRT and breast cancer incidence and mortality."[67]

In his report, Dr. Austin relied most on the MWS to support his opinion regarding a causal relationship between Prempro and short-term use. The MWS conducted a separate assessment of Prempro at the five year mark,[68] and showed an increased risk of breast cancer for Prempro users, but the issue before the Court involves usages of around three years or fewer; the MWS did not separately assess Prempro for around three years or fewer. The MWS showed an increased risk of breast cancer users at the one year (actually 2.2 years) mark, but this assessment lumped together all estrogens, and included "almost exclusively" estradiol compounds,[69] the "most potent" form of estrogen.[70] This same issue -- not separating Prempro from other drugs -- was present in the French Teachers Study and also renders this study unreliable when assessing short-term use in the cases before the Court. Again, Dr. Austin agreed that it is ideal to look at only the data involving a specific chemical formulation when trying to determine whether that formulation is causing harm.[71]

Another drawback to the MWS's reliability is that it considered "years of use" only from the time of enrollment. In other words, if a participant had taken HRT two years before enrolling in the study, took it two more years during the study, and was then diagnosed with breast cancer, the MWS would consider her a two year user. This type of analysis appears to conflict with the restrictions

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[67]*In re Prempro*, 4:03-CV-01507-WRW, Doc. No. 2480-72 -- Million Women Study Collaborators, *Breast Cancer and Hormone-Replacement Therapy in the Million Women Study*, 362 The Lances Volume 419 (2003).

[68]This would actually be 6.2 years, since the MWS indicated that on average women were diagnosed with cancer 1.2 years after entering the study.

[69]*Id.* at January 12, 2011, *Daubert* Hearing Transcript.

[70]*In re Prempro*, 4:03-CV-01507-WRW, Doc. No. 2388.

[71]*Id.* at January 12, 2011, *Daubert* Hearing Transcript.

Dr. Austin used to disregard other studies, as well as his position that when looking at short-term use, one must be quite precise in the analysis. In an effort to overcome this problem, Dr. Austin points to the fact that there was an "average underestimate of 1.2 years" use -- in other words, one should add 1.2 years to every person on the chart, *e.g.*, the less than one year breakdown would actually be 2.2. years.

While the MWS was a significant study with regard to the risk of breast cancer from HRT, the study appears very unreliable with regard to short-term use of Prempro. Exposure during the study was neither measured nor recorded; thus, there is no way of knowing how many years the study participants actually took the medication (other than what they put on their enrollment forms, which can also be unreliable). Even Dr. Austin agreed that the investigators in the MWS failed to indicate the measured exposure that occurred between enrollment and diagnosis. There is no indication regarding what the degree of exposure of a "current user" was at the time of diagnosis in the MWS. According to Dr. Austin, the ideal approach would be to know exposure both before enrollment and during the study, up to the time of diagnosis; the MWS did not do this. Additionally, the MWS did not control for potential cofounders, which, according to Dr. Austin, would affect the accuracy of the results.

Accordingly, Dr. Austin's reliance on the MWS to make his conclusions is based on many "assumptions" -- assumptions that overlook an exact figure on years of use and what drug formulation was consumed by the participants. Dr. Austin cannot reliably use this study to support his opinion on the short-term use issue.

5. Calle Study

The Calle study was "a prospective cohort of 67,754 postmenopausal women in the U.S.," which looked at "the impacts of exogenous hormones on breast cancer incidences by type of

hormone preparation and histology of the cancer."[72] According to the study, "[n]o increase in risk was observed with E+P use of < 2 years for ductal . . . or lobular . . . breast cancer."[73] In fact, the rates of breast cancer were lower for Prempro users than nonusers. However, there was "significant increase in risk for both types of breast cancer at 2 to 3 years of use . . . and all years thereafter."[74]

Yet, the study proves unreliable for analyzing short-term Prempro use. Participants completed a questionnaire at the beginning of the study, but a follow-up questionnaire was not completed until five years later. In the interim, no data was collected regarding the participants' HRT use. Additionally, the study failed to set out how it accounted for years of use. Dr. Austin admitted that the Calle study did not accurately track years of use during the study, and this would result in underestimated exposure. When Dr. Austin was asked whether the Calle study's finding regarding two-years Prempro use was reliable, he noted that he could not "rule out the misclassification of exposure." The same would hold true for the Calle study findings that Dr. Austin claims support his opinions.

According to Dr. Austin, to detect the relationship between short-term Prempro use and breast cancer a study would "have to have characterized the exposure very carefully and accurately." The Calle study does not meet this criteria, because there was no way to measure how it accounted for previous use, and that he "could not rule out the misclassification of exposure." Accordingly, Dr. Austin cannot reliably cite the study to support his short-term use opinions.

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[72] *Id.* at Doc. No. 2480-85.

[73] *Id.*

[74] *Id.*

C. Other Reliability Issues

1. Power

Dr. Austin placed much emphasis on the power of different studies. According to him, "power is the probability that you will find an association if one exists." As was mentioned earlier, Dr. Austin dismissed nine observational studies that showed no increased between short-term use and breast cancer, "because of inadequate power."[75] Yet, earlier in this litigation, Dr. Austin relied on five of the studies to support his opinions -- Schairer (1994), Chen (2002), Chen (2004), Rosenberg (2006), and Weiss (2002). Since a study is either underpowered to establish a causal connection or it is not, there seems to be no justification for now dismissing these studies (that, or they never should have been relied on in earlier reports).

Additionally, Dr. Austin agreed that previously in this litigation he relied on studies, to support his opinion on a different issue, that had less power than the studies he criticized in his report. Dr. Austin's response to this issue is revealing:

> Look at what we're trying to conclude. And I say [regarding the earlier issue] you can't say there's an increased risk if you can't demonstrate it. That's not the same as proving there's no increased risk.

Dr. Austin has overlooked the fact that it is his burden to prove there is an increased risk; it is not Wyeth's burden to establish the opposite. Dr. Austin is the proponent of the expert testimony, and he is obliged to present reliable studies and a consistent methodology to support his opinions. Furthermore, it is Dr. Austin's responsibility is to reliably establish his position while adhering to the rules he sets out; that is, using only studies that have enough power; are precise, involve the same drugs, and closely track HRT use.

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[75] *Id.* at Doc. No. 2485-1.

2. Specific Drug Being Tested

Dr. Austin supports his findings by relying primarily (I believe the only exception is the Calle study) on studies that involve drugs other than the drugs at issue here -- specifically CEE + MPA (Prempro). However, many of the experts in the field recognize that their findings have limitations based on the specific drugs that were studied. For example, the WHI report noted that the study "evaluated single drug regimen, conjugated equine estrogens (0.625 mg/d) plus medroxyprogesterone acetate (2.5 mg/d), and cannot inform questions regarding risk associated with other oral or topical menopausal hormone therapies." The French Teachers Study sets out that "[b]ecause breast cancer risk may vary according to the characteristics of EP-MHT, we must specify that, in our cohort, the estrogenic component consisted almost exclusively of estradiol compounds, with progesterone and dydrogesterone as the most frequently associated progestagen . . . ."

A similar issue was before Judge Wilson and Judge Montgomery when they considered the parties submissions regarding estrogen-only use and breast cancer. The judges noted that "[t]o the extent [the studies relied on by the expert] involve other substances, the inquiry becomes whether they reliably predict the effects of Premarin."[76] The expert's testimony was found unreliable when it was noted that "she did not distinguish between CEE and estradiol, nor explain how the substances are equivalent."[77] Dr. Austin's opinions suffer the same flaw. In fact, Dr. Austin agreed that estradiol and CEE are different compounds, and should be considered separately when considering whether the two have statistically significant different effects.

The Eighth Circuit has noted, "Even minor deviations in molecular structure can radically change a particular substance's properties and propensities."[78] Accordingly, courts have concluded

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[76] *In re Prempro*, 4:03-CV-01507-WRW, Doc. No. 2388.

[77] *Id.*

[78] *Glastetter v. Novartis Pharms. Corp.*, 252 F.3d 986, 990 (8th Cir. 2001).

that when an expert summarily attributes the effects of one substance to another similarly classified substance, the expert's methodology is not reliable.[79]

3. Biological Plausibility

Dr. Austin heavily relies upon "biological plausibility" as a methodology to ultimately conclude that short-term use of Prempro causes breast cancer.[80] However, during the *Daubert* hearing, he conceded this methodology is not the most reliable. During cross examination of Dr. Austin, the following exchange took place:

> Q. In evaluating the relationship between exposure to a medication and the occurrence of a particular disease, isn't it true that you put limited weight on the criteria known as biological plausibility?
> A. I do.
> Q. And isn't it also true that you put limited weight on it because you believe that biological plausibility can be an unreliable measure of causality, correct?
> A. It's not a measure of causality, it is a criterion for determining how much evidence, how much to weigh the evidence in favor of or not.
> Q. Let's go to slide 286, please. So you gave a deposition in the *Avandia* litigation recently; is that right?
> A. Yes.
> Q. And at that time fact, you were asked the following question and you gave the following answer: You said that you put limited weight on the criteria of biological plausibility since it can be an unreliable measure of causality, true?
> Answer: True. That was your testimony, right?
> A. That's correct.
> Q. And you personally consider biological plausibility to be one of the weakest factors for causality, correct?
> A. Weakest criteria, yes.[81]

Again, the reliability of Dr. Austin's opinions are seriously called into question. For this reason, the Court must strike his causation opinions on short-term use of Prempro and the increased risk of breast cancer.

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[79]See, e.g., *McClain v. Metabolife Int'l, Inc.*, 401 F.3d 1233, 1244-45 (11th Cir. 2005); *Hollander v. Sandoz Pharms. Corp.*, 289 F.3d 1193, 1207 (10th Cir. 2002).

[80]*In re Prempro*, 4:03-CV-01507-WRW, Doc. No. 2485-1.

[81]*In re Prempro*, 4:03-CV-01507-WRW, January 12, 2011, *Daubert* Hearing Transcript.

CONCLUSION

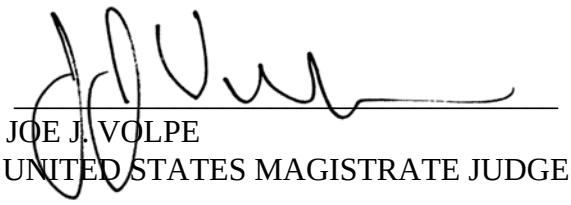
Dr. Austin contends that short-term use of Prempro causes breast cancer, and cites five studies to support his conclusions. However, he conceded the following: two of the studies he admitted should not have been included in his report (Li (2000) and Saxena (2010)); two of the studies primarily involved drug combinations that were not Prempro (MWS, French Teachers Study); and one of the studies did not reliably track duration of use, which is essential when making a short-term use causation finding (Calle (2009)). With no studies to reliably support his position, along with a failed effort to discredit WHI results, Dr. Austin's opinion on short-term use causation are not sufficiently reliable to be admissible under *Daubert*.

Based on the findings of fact and conclusions of law above, Defendants' Motions to Preclude Any Expert Testimony that Prempro Use Increases Breast Cancer Risk When Taken for Only Three Years or Less (Doc. Nos. 36, 38, 40) are GRANTED.

Under 28 U.S.C. § 636(b)(1)(A) and Local Rule 72.1, the parties have a right of appeal to United States District Judge Billy Roy Wilson through filing a motion by 4 p.m., Friday, January 21, 2011. The specific requirements for appeal are set out in 28 U.S.C. § 636(b)(1)(A) and Local Rule 72.1. The appeal should relate directly to the findings of the Court in this Order and be limited to seven (7) pages. Any other motions in response to this Order must be filed by the same date.

All other deadlines for the *Kuhn v. Wyeth*, No. 6:04CV06042-WRW and *Davidson v. Wyeth*, No. 6:05CV06074-WRW cases are STAYED.

IT IS SO ORDERED this 19th day of January, 2011.



JOE J. VOLPE
UNITED STATES MAGISTRATE JUDGE