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DORA BAILEY and CAROL BAILEY, w/h: Plaintiffs, v. WYETH, INC., WYETH PHARMA-CEUTICALS, INC., PFIZER, INC., and PHARMACIA & UPJOHN CO., Defendants.	SUPERIOR COURT OF NEW JERSEY MIDDLESEX COUNTY LAW DIVISION DOCKET NO. L-0999-06 MT
LORETTA DEBOARD, Plaintiffs, v. WYETH, INC., WYETH PHARMA-CEUTICALS, INC., PFIZER, INC., and PHARMACIA & UPJOHN CO., Defendants.	DOCKET NO. L-1147-06 MT
BETTE KOSITSKY and MARK KOSITSKY, w/h Plaintiffs, v. WYETH, INC., WYETH PHARMA-CEUTICALS, INC., PFIZER, INC., and PHARMACIA & UPJOHN CO., Defendants.	DOCKET NO. L-1019-06 MT OPINION

APPROVED FOR PUBLICATION

SEPTEMBER 29, 2011

COMMITTEE ON OPINIONS

Argued: June 17, 2008
Decided: July 11, 2008

Esther E. Berezofsky and Kevin Haverty (Williams, Cuker & Berezofsky, attorneys) and Richard S. Lewis (Cohen, Milstein, Hausfeld & Toll, PLLC) of the Washington, D.C. bar, admitted pro hac vice, for plaintiffs.

Lauren E. Handler (Porzio Bromberg & Newman, P.C.), George E. McDavid, Michael T. Scott, and Daniel K. Winters (Reed Smith LLP), and William R. Murray (Williams & Connolly LLP) of the Washington, D.C. bar, admitted pro hac vice, attorney for defendant Wyeth, Inc. and Wyeth Pharmaceuticals, Inc.

David J. Cooner and Gita F. Rothschild, (McCarter & English LLP, attorneys) and Jay P. Mayesh (Kaye Scholer LLP) of the New York bar, admitted pro hac vice, for defendant Pfizer and Pharmacia & Upjohn Co.

HAPPAS, J.S.C.

I. Introduction

This opinion addresses the motions for summary judgment by defendants Wyeth, Inc., Wyeth Pharmaceuticals, Inc. (collectively "Wyeth"), Pfizer Inc.,[1] and Pharmacia & Upjohn Co. ("Upjohn"), as to plaintiffs Dora and Carol Bailey's claims for (1) violations of the New Jersey Products Liability Act ("PLA"), N.J.S.A. 2A:58C-1 to -11, including (a) failure to warn, (b) design defect,[2] (2) fraud and misrepresentation, (3) negligent misrepresentation and (4) violations of the New Jersey Consumer Fraud Act ("CFA"), N.J.S.A. 56:8-1 to -156. Plaintiffs' claims arise out of breast cancer injuries allegedly

[1] Pfizer is the parent of and successor to Pharmacia & Upjohn Co., which manufactured and distributed Provera during the time relevant to this case. All claims against Pfizer were dismissed by stipulation and consent order dated May 7, 2008.

[2] Two days after oral argument, on June 19, 2008, the court received correspondence from plaintiffs withdrawing their design defect claim.

suffered by Dora as a result of her ingestion of Provera®, Premarin®, and Prempro™, the three hormone replacement therapy ("HRT") products involved in this litigation.[3]

II. Factual Background

Premarin, Prempro, and Provera are FDA-approved prescription drugs. Studies in the 1970s and 1980s suggested that long term use of estrogen alone could increase the risk of endometrial hyperplasia. Scientists then studied and published articles indicating progestin to be effective in reducing the risk of endometrial hyperplasia associated with taking estrogen alone. Thereafter, medical associations began recommending the addition of a progestin when a physician prescribed estrogen to a nonhysterectomized woman.[4]

a) Premarin and Prempro

Premarin and Prempro are the brand names for specific FDA-approved estrogen and combination estrogen plus progestin prescription drugs produced and marketed by Wyeth. Premarin consists of conjugated equine estrogen ("CEE") and was first approved by the FDA in 1942. Prempro consists of CEE and medroxyprogesterone acetate ("MPA"), a synthetic progestin, and was approved by the FDA on December 30, 1994. Premarin and Prempro remain on the market today and are approved by the FDA to treat menopausal symptoms and for prevention of osteoporosis.

b) Provera

[3] Defendants filed similar motions in DeBoard v. Wyeth, L-1147-06 MT. Oral argument in Bailey and DeBoard were consolidated; James A. Morris, Esq., of Brent Coon & Associates, represents DeBoard. A separate letter opinion in DeBoard has been issued on this date.

[4] See American College of Obstetricians & Gynecologists, Estrogen Replacement Therapy, ACOG Technical Bulletin 70, 2-4 (June 1983); American College of Obstetricians & Gynecologists, Estrogen Replacement Therapy, ACOG Technical Bulletin 93, 3-4 (Apr. 1986).

Provera is the brand name for an FDA-approved progestin, specifically MPA, produced and marketed by Upjohn. The FDA approved Provera for marketing in 1959 to treat secondary amenorrhea, functional uterine bleeding, infertility, and related conditions due to hormone imbalance in the absence of organic pathology. The pregnancy-related indications were withdrawn in 1972. In 1998, after Dora stopped using Provera, the FDA approved the following indication: "to reduce the incidence of endometrial hyperplasia in nonhysterectomized postmenopausal women receiving 0.625 mg conjugated estrogen." Letter from FDA to Pharmacia & Upjohn (Aug. 4, 1998). Provera continues to be approved by the FDA and on the market today.

c) Dora's Use of Provera, Premarin, and Prempro

Dora first complained to her physician in 1989 of experiencing menopausal symptoms. She was prescribed Premarin and Provera. However, she did not fill the prescription. She first filled a prescription for Premarin and Provera in February 1991.[5] She continued taking HRT for the next several years. On April 15, 1996, her physician switched her prescription to Prempro. She was diagnosed with breast cancer on May 28, 2002. On or about May 28, 2002, she stopped taking Prempro. She continued to suffer menopausal symptoms including vaginal atrophy, which her physician treated by prescribing a topical HRT medication.[6]

III. Authority of the FDA

[5] Plaintiffs' fact sheet and prescription records show Dora's first use of HRT to be in 1991. However, plaintiffs contend that Dora was taking HRT from January 1989 to May 2002. Nonetheless, she deferred to the prescription records as to the term of her use of the products at issue in this case.

[6] The topical HRT medication is not involved in this litigation.

The United States Food and Drug Administration ("FDA") is responsible for "promot[ing] the public health by promptly and efficiently reviewing [drug manufacturers'] clinical research and taking appropriate action on the marketing of regulated products in a timely manner." 21 U.S.C.A. § 393(b)(1).[7] The FDA controls the introduction of new drugs to the American public. 21 U.S.C.A. § 355(a). The Federal Food, Drug and Cosmetics Act ("FDCA") enacted in 1938, required all new drugs to be tested for safety before marketing. 21 U.S.C.A. §§ 301-399. The results of testing are submitted to the FDA as part of a New Drug Application ("NDA"). Amendments to the FDCA in 1962 strengthened the law. The FDA must ensure that the new drug is both safe[8] and effective prior to marketing. See 21 U.S.C.A. § 393 (b)(2)(B) (The FDA shall "protect the public health by ensuring . . . drugs are safe and effective"). The FDA will not grant approval of a NDA unless the drug is shown to be safe and effective. 21 U.S.C.A. § 355. Drugs approved between 1938 and 1962 were reevaluated to ensure compliance with the efficacy standard.[9] The 1962 amendments also granted authority to the FDA over prescription drug advertising.

a) NDA

All drugs must be FDA-approved before marketing in the United States. The sponsoring pharmaceutical company must submit a NDA to the FDA. The NDA

[7] Many of the relevant regulations have been revised or relocated since the approval of the drugs at issue and Dora's ingestion of said drugs; thus, the court will set forth the regulations presently in effect and note the former regulation only where the substance of the regulation has changed.

[8] The FDA explains on its website that "no drug is absolutely safe; all drugs have side effects. 'Safe' [] means that the benefits of the drug appear to outweigh the risks." http://www.fda.gov/Fdac/features/2002/402_drug.html (last visited July 3, 2008).

[9] The National Academy of Sciences/National Research Council on behalf of the FDA conducted the Drug Efficacy Study Implementation ("DESI") to ensure that all previously approved drugs were safe and effective. Indications on the Provera labeling for use in pregnant women were removed in 1972 based on the DESI review finding a significant teratogenic risk to the fetus.

requires, among other things, reports of investigation into the safety and effectiveness of the drug, the components and production methods used in the drug's manufacturing, and copies of draft labeling proposed for the drug. See 21 C.F.R. § 314.50. Once the drug is approved, the pharmaceutical company remains obligated to report to the FDA adverse drug experiences and any "significant new information . . . that might affect the safety, effectiveness, or labeling of the drug product." 21 C.F.R. § 314.81(b)(2)(i).

A pharmaceutical company seeking approval of additional indications for a drug must submit a supplemental new drug application ("sNDA"). The FDA reviews the sNDA, including the data from clinical studies supporting the change, with the same degree of scrutiny as the original NDA. The FDA will reject the sNDA or NDA if it finds that:

> (1) the investigations [of the drug's safety and effectiveness] do not include adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof;
>
> (2) the results of such tests show that such drug is unsafe for use under such conditions or do not show that such drug is safe for use under such conditions;
>
> . . . . or
>
> (7) based on a fair evaluation of all material facts, such labeling is false or misleading in any particular.
>
> [21 U.S.C. § 355(d).]

If after reviewing an application and all information it has about the product, the FDA determines that the available scientific evidence is inadequate to show that the product is safe or that it is not effective for its proposed use, the FDA will reject the sNDA. 21 C.F.R. § 314.125(b). Indeed, if the FDA concludes that there has not been sufficient

study of the product to assure that it is safe for its proposed use, the FDA will reject the sNDA. C.F.R. at § 314.125(b)(4).

b) Labeling

In the context of prescription drugs, "[t]he term 'labeling' means all labels and other written, printed or graphic matters (1) upon any article or any of its containers or wrappers, or (2) accompanying such article." 21 U.S.C.A. § 321(m). In 2006, the FDA codified the longstanding policy that labeling must "adequately inform[] users of the risks and benefits of the product and [be] truthful and not misleading." 71 Fed. Reg. 3922 (Jan. 24, 2006).

Proposed labeling is submitted as part of the NDA and reviewed by the FDA. Prescription drug "labeling must contain a summary of the essential scientific information needed for the safe and effective use of the drug," including, among other things, potential safety hazards associated with use of the drug. 21 C.F.R. § 201.56(a).[10] Drug companies are precluded from listing conflicting opinions regarding studies showing a potential risk. 21 C.F.R. § 1.21(c)(1). In addition, the NDA must include a "summary of the benefits and risks of the drug, including a discussion of why the benefits exceed the risks under the conditions stated in the labeling." 21 C.F.R. § 314.50(d)(5)(viii). The FDA will advise the applicant of necessary revisions to the labeling. Often several versions of the labeling are exchanged between the FDA and the pharmaceutical company before reaching the final approved labeling.

In addition to warning about risks from approved uses, the FDA has authority to impose warnings about off-label or unapproved uses when there is evidence of a

[10] Prior to the amendments in 2006, 21 C.F.R. § 201.56 used the term "shall" instead of "must," and did not have an enumerated list defining essential scientific information.

clinically significant risk.[11] See 21 C.F.R. § 201.57 (1988) (prior to 2006 amendments) (**"**A specific warning relating to a use not provided for under the 'Indications and Usage' section may be required by the Food and Drug Administration if the drug is commonly prescribed for a disease or condition, and there is a lack of substantial evidence of effectiveness for that disease or condition, and such usage is associated with serious risk or hazard").[12] Furthermore, "the labeling shall be revised to include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug; a causal relationship need not have been proved." 21 C.F.R. § 201.80(e) (after 2006 amendments); see also 21 C.F.R. § 201.57(e) (prior to 2006 amendments). Prior to the Food and Drug Administration Modernization Act of 1997, the only uses a drug could be marketed, promoted or advertised for were the indications listed in the NDA and approved by the FDA. The law changed in 1997 to allow pharmaceutical companies to

[11] At oral argument on June 17, 2008, the court requested that counsel submit a five page or less analysis of the FDA's authority, pursuant to 21 C.F.R. § 201.57, to require warnings for off-label uses and to compel additional studies. This analysis was due by noon on June 23, 2008. The court stressed to keep the supplement simple, just the law and no facts. On June 23, 2008, the court received a five page brief setting forth the law from each defendant. Plaintiffs filed a seventeen page brief, with approximately 800 pages of exhibits which restated and further developed their position presented during oral argument and earlier pleadings. Plaintiffs introduced a new expert opinion from attorney William B. Schultz, whose affidavit is dated June 23, 2008. Defendants objected to plaintiffs' untimely and improper submission. All general and case-specific expert reports were to be served by the plaintiffs on or before September 27, 2007, as directed by court order dated June 19, 2007. The court is cognizant of its obligation to consider all facts presented prior to ruling on a motion for summary judgment. Thus, plaintiffs' submission has been considered. However, Schultz's opinion is inadmissible. In addition to not being timely served, it is an impermissible opinion on an issue of law. See Steele v. Deputy Orthopedics, Inc., 295 F. Supp. 2d 439, 446 (D.N.J. 2003) (expert opinion regarding nature and scope of FDA's regulations would not assist trier of fact to understand evidence, nor help jury to determine fact in issue); Troxclair v. Aventis Pasteur, Inc., 374 N.J. Super. 374, 383-85 (App. Div. 2005) (expert testimony on whether vaccine component was an "adulterant" within meaning of Vaccine Act did not create issue of fact because we "need not accept a plaintiff's experts' opinions when they bear upon construction of a statute or a matter of law").

[12] In 2006, this section was amended to apply to drugs approved after 2001. The FDA's authority to include warnings about off-label use for drugs approved prior to 2001 was re-designated as 21 C.F.R. §201.80.

distribute information regarding off-label use provided the company complies with the enumerated requirements. 21 U.S.C. § 401 (1997).[13]

c) Changes Being Effected ("CBE")

Generally, proposed changes in labeling are first submitted to the FDA for approval. 21 C.F.R. § 314.70(a)-(d). A limited exception is with the use of a changes being effected ("CBE") supplement. 21 C.F.R. § 314.70(c). When a new safety issue emerges with a product, the pharmaceutical company may temporarily add to the product's labeling under subsection (c), which describes "changes that may be made before FDA approval." 21 C.F.R. § 314.70(c).[14] Nonetheless, the FDA must be notified

[13] Although § 401 expired on Sept. 30, 2006, the FDA remains tolerant of drug companies distributing materials to physicians concerning off-label uses. See FDA Proposes Guidance for Dissemination of Information on Unapproved Uses of Medical Products, http://www.fda.gov/bbs/topics/NEWS/2008/NEW01798.html (last visited July 3, 2008). Issued on Feb. 15, 2008, the good reprint practices instructs that "the article or reference be published by an organization that has an editorial board . . . fully disclose any conflicts of interest . . . should be peer-reviewed . . . recommends against distribution of special supplements or publications that have been funded by one or more of the manufacturers of the product in the article . . . supported by credible medical evidence." Ibid.

[14] This regulation was amended in 2006. The court in Colacicco, supra, 521 F. 3d at 259 n.4, vacated on other grounds, Wyeth v. Levine, 555 U.S. 555, 129 S. Ct. 1187, 173 L. Ed. 2d 51 (2009), summarized the changes:

> The regulation now refers to changes under subsections (b), (c), and (d) as "major," "moderate," and "minor" changes, respectively. 21 C.F.R. § 314.70(b), (c), (d) (2007). For the purposes of this litigation, subsections (b) and (d) are not materially different. Subsection (c), however, is now titled "Changes requiring supplement submission at least 30 days prior to distribution of the drug product made using the change (moderate changes)." Id. § 314.70(c). Nonetheless, that subsection also states that the FDA "may designate a category of changes for the purpose of providing that, in the case of a change in such category, the holder of an approved application may commence distribution of the drug product involved upon receipt by the agency of a supplement for the change." Id. § 314.70(c)(6). The listed categories include changes in labeling "[t]o add or strengthen a contraindication, warning, precaution, or adverse reaction." Id. § 314.70(c)(6)(iii)(A). Thus, for all practical purposes, subsection (c)(2)(i) has simply been relocated to subsection (c)(6)(iii)(A), but the FDA may determine that products incorporating such labeling changes may not be distributed until the agency has received the CBE supplement or thirty days thereafter. Finally, the FDA now provides express notice that if it "disapproves the supplemental application, it may order the manufacturer to cease distribution of the drug product(s) made with the manufacturing change." Id. § 314.70(c)(7).

and will subsequently review the modified labeling to ensure compliance with FDA regulations.

In 1982, when the CBE procedure was proposed, the FDA stated, "'[t]hese supplements would describe changes placed into effect to correct concerns about newly discovered risks from the use of the drug.'" 73 Fed. Reg. 2849 (Jan. 16, 2008) (quoting 47 Fed. Reg. 46622, 46623 (Oct. 19, 1982)). Recently, the FDA reaffirmed its longstanding position. "[A CBE supplement] is appropriate to amend the labeling for an approved product only to reflect newly acquired information . . . to add or strengthen a contraindication, warning, precaution, or adverse reaction only if there is sufficient evidence of a causal association." 73 Fed. Reg. 2848 (Jan. 16, 2008). The FDA explicitly defines "newly acquired" as "data, analyses, or other information not previously submitted to the agency." Id. at 2850.

d) Misbranded

A pharmaceutical company that independently institutes a change in labeling may be subject to penalty or seizure if the drug is deemed misbranded by the FDA. See 21 U.S.C.A. § 333 (authorizing penalties); 21 U.S.C.A. § 334 (authorizing seizure); 21 U.S.C.A. § 355(e) (providing withdrawal authority); 21 C.F.R. § 7.45(a) (providing authority to request recall). A drug is misbranded "[i]f its labeling is false or misleading in any particular." 21 U.S.C.A. § 352(a). "If [the drug's] labeling lacks adequate warnings against use . . . where its use may be dangerous to health, or if it is dangerous to health when used in the . . . manner . . . prescribed, recommended, or suggested in the labeling therof" the drug is misbranded. 21 U.S.C.A. § 352(f)-(j). Distribution of misbranded drugs is prohibited by the FDCA. 21 U.S.C.A. § 331.

e) Off-Label Use

The FDA policy of regulating drugs and not the practice of medicine has been consistent since the creation of the agency in 1983, by the enactment of the FDCA. This policy was noted by the FDA at the 1991 advisory committee. "The FDA's job and legal mandate is not to regulate the practice of medicine but simply to regulate the availability of medications to the practicing population at large." Transcript of Fertility and Maternal Health Drugs Advisory Committee meeting 46:17-20 (June 20, 1991). Allowing physicians to prescribe for off-label use "is an accepted and necessary corollary of the FDA's mission to regulate in this area without directly interfering with the practice of medicine." Buckman Co. v. Plaintiffs' Legal Comm., 531 U.S. 341, 350, 121 S. Ct. 1012, 1018, 148 L. Ed. 2d. 854, 862 (2001) (discussing FDA regulation of medical devices).

Off-label activity has been defined by the FDA as a "use for indication, dosage form, dose regimen, population or other use parameter not mentioned in the approved labeling." Janet Woodcock, M.D., A Shift In The Regulatory Approach, PowerPoint, at slide 3 (June 23, 1997), http://www.fda.gov/cder/present/diamontreal/regappr/sld003.htm) (last visited July 3, 2008). Off-label prescribing of drugs is both legal and ethical. The New Jersey Legislature declared "'off-label' use of an FDA-approved drug [to be] legal when prescribed in a medically appropriate way." N.J.S.A. 26:1A-36.9(e).

The FDA has long acknowledged that undue restrictions on off-label use could have adverse health consequences. In 1982, the FDA Drug Bulletin informed the medical community that "[o]nce a [drug] product has been approved for marketing, a

physician may prescribe it for uses or in treatment regimens or patient populations that are not included in approved labeling." 12 FDA Drug Bulletin 4, 5 (1982). The agency went on to state that

> "unapproved" or more precisely "unlabeled" uses may be appropriate and rational in certain circumstances, and may, in fact reflect approaches to drug therapy that have been extensively reported in medical literature . . . Valid new uses for drugs already on the market are often first discovered through serendipitous observations and therapeutic innovations.
>
> [Id. at 5.]

Following the accepted medical standard of care, physicians frequently prescribe drugs for off-label or unapproved uses.[15] In the 1980s, 1990s and even today the medical standard of care is to prescribe progestin when estrogen is prescribed to treat menopausal symptoms in a woman who has an intact uterus.[16] This standard of care was endorsed by the American College of Obstetricians and Gynecologists as early as 1983.[17]

The medical community's understanding of the benefit of prescribing progestin to reduce the risk of endometrial hyperplasia in women with a uterus taking estrogen is reflected in the prescription data presented at the 1990 advisory committee meeting. Transcript of Fertility and Maternal Health Drugs Advisory Committee meeting 207:12-17, 227:6-10 (Feb. 1, 1990). Comparing the medical reason for prescribing Provera, from

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[15] "One study estimated that 21 percent of drugs prescribed by office-based physicians were for off-label uses." See U.S. Gov't Accountability Office, Medicare Part D: Plan Sponsors' Processing and CMS Monitoring of Drug Coverage Requests Could be Improved, GAO 08-47, 15 n.26 (2008) (citing D. Radley, et. al., Off-Label Prescribing Among Office-Based Physicians, 166 Archives of Internal Med. (May 8, 2006)) available at http://www.gao.gov/new.items/d0847.pdf.

[16] Dora's prescribing physicians acknowledge this was and remains the medical standard of care.

[17] See American College of Obstetricians & Gynecologists, Estrogen Replacement Therapy, ACOG Technical Bulletin 70, 2-4 (June 1983); American College of Obstetricians & Gynecologists, Estrogen Replacement Therapy, ACOG Technical Bulletin 93, 3-4 (Apr. 1986); American College of Obstetricians & Gynecologists, Hormone Replacement Therapy, ACOG Technical Bulletin 166, 3-4 (Apr. 1992); American College of Obstetricians & Gynecologists, Hormone Replacement Therapy, ACOG Educational Bulletin 247, 4 (May 1998).

1977 to 1987, "[t]here is an increasing trend toward the use of estrogens and progestins in the treatment of menopause, and it looks like both are continuing to increase." Transcript of Fertility and Maternal Health Drugs Advisory Committee meeting 61:20-22 (Feb. 1, 1990). "The most common diagnosis in 1977 was amenorrhea . . . and in 1987 we see that the major diagnosis is now menopausal symptoms." Id. at 57:18-21.

f) Advisory Committees

The FDA draws on its own expertise and enforcement powers as well as the expertise of outside medical authorities. The FDA may "establish such technical and scientific review groups as are needed to carry out the functions of the Administration." 21 U.S.C.A. § 393(e). Technical and scientific review groups are commonly referred to as advisory committees. The FDA can seek the opinion of an advisory committee at any time. "Advisory committees provide independent advice and recommendations to the FDA on scientific and technical matters related to the development and evaluation of products regulated by the Agency." New Drug Application (NDA) Process at Advisory Committee, http://www.fda.gov/cder/regulatory/applications/NDA.htm (last visited July 3, 2008). Advisory committee meetings are open to the public. The advice from an advisory committee is not binding on the FDA. The advisory committee is composed of "scientific experts such as physician-researchers and statisticians, as well as representatives of the public, including patients." Ibid. The scientists must be "qualified by training and experience to evaluate the safety and effectiveness of the drugs . . . and . . . to the extent feasible, possess skill and experience in the development, manufacture, or utilization of such drugs." 21 U.S.C.A. § 355(n)(3)(A). At least two of the panelists

must be "specialists or have other expertise in the particular disease or condition for which the drug under review is proposed to be indicated." 21 U.S.C.A. § 355(n)(3)(D).

In 1984, the FDA convened the Fertility and Maternal Health Drugs Advisory Committee to assess the safety and efficacy of estrogen taken alone and in combination with progestin.[18] The committee reviewed published reports and concluded that "the use of these two hormones does not result in harmful effects." Minutes of FDA Fertility and Maternal Health Drugs Advisory Committee 8 (Apr. 26-27, 1984). The Fertility and Maternal Health Drugs Advisory Committee consisted of outside experts from medical academia and other public health agencies, including the National Cancer Institute and the National Institutes of Health.

The committee met again in 1990 and 1991. The presentations and discussion at the 1990 meeting focused on the risk of cancer in the breast and endometrium (uterine lining) and proper labeling.[19] Dr. Linda Golden, of the FDA, reminded committee members that, "the Food and Drug Administration has approved short-acting estrogens for hormone replacement therapy. They have not explicitly approved progestins for this purpose, although the wide use of progestins [in combination with estrogen] for this indication clinically makes the topic highly timely and important." Transcript of Fertility and Maternal Health Drugs Advisory Committee meeting 39:15-19 (Feb. 1, 1990). In 1991, the advisory committee met again for a workshop on the current status of combined

[18] "The committee should also consider the concomitant use of progestins with estrogen replacement therapy and review the reported incidence of breast cancer with estrogen use." Minutes of FDA Fertility and Maternal Health Drugs Advisory Committee 2 (Apr. 26-27, 1984).

[19] The purpose of the 1990 meeting was to discuss the risk of breast cancer and endometrial cancer for those who chose to use HRT, not to balance the risks and benefits of HRT. See Transcript of Fertility and Maternal Health Drugs Advisory Committee meeting 7:1-13 (Feb. 1, 1990).

HRT. The experts discussed the risk of breast cancer, safety data and labeling for estrogen and progestin products.

The committee concluded in 1984, 1990, and again in 1991, that there was insufficient evidence to determine the effects of progestin with estrogen therapy on the risk of breast cancer. In 1984, the committee reported "[t]here is a dearth of data on the safety of long-term estrogen therapy or the addition of progestins. The bulk of evidence indicates that estrogens are not associated with an increased risk of breast cancer." Minutes of FDA Fertility and Maternal Health Drugs Advisory Committee 10 (Apr. 26-27, 1984).

In 1990, "the committee felt that the addition of progestins to estrogen replacement therapy decreases the risk of endometrial cancer. They do not believe that there is sufficient data about the effects of progestins added to estrogen replacement therapy on the risk of breast cancer." Transcript of Fertility and Maternal Health Drugs Advisory Committee meeting 227:6-10 (Feb. 1, 1990). To the question "[d]oes the addition of progestins to estrogen therapy alter the risk of breast cancer in post-menopausal women? The committee unanimously responds that there are insufficient data to make a statement at this time." Transcript of Fertility and Maternal Health Drugs Advisory Committee meeting 207:12-17 (Feb. 1, 1990).

In her opening remarks to the 1991 advisory committee, Golden stated:

> The FDA has been dealing with the question of how to balance these risks and benefits in terms of our legal mandate to approve or not approve either a new indication or a new combination. In addition, breast cancer questions with long-term use of estrogens and/or progestins have been raised, as you all know.
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> [Transcript of Fertility and Maternal Health Drugs Advisory Committee meeting 50:1-6 (June 20, 1991).]

After a lengthy discussion the committee did not recommend any change to the labeling of estrogen or progestin or the clinical use of HRT. As one member of the committee commented, concerning the risk of "breast cancer, there are no data about the added progestins, we are all concerned that there might be a higher rate over a long period of time, but that is true of estrogen alone or estrogen plus progestin." Transcript of Fertility and Maternal Health Drugs Advisory Committee meeting 244:21-24 (June 21, 1991). At the close of the 1991 meeting, the consensus was that "the committee does not feel that the data are adequate to answer the question of whether or not progestins alter any breast cancer risk that might be induced by ERT [estrogen replacement therapy]. This is certainly one area where more data are needed and will be forthcoming." Id. at 225:2-6.

In addition to having advisory committees composed of outside experts, the FDA formed a working group of seven FDA scientists to assess the use of estrogens and progestins together and review the information submitted with the Prempro NDA. See Center for Drug Evaluation and Research, Guidance for Clinical Evaluation of Combination Estrogen/Progestin-Containing Drug Products Used for Hormone Replacement Therapy of Postmenopausal Women 1 (Mar. 20, 1995) (publication "[p]repared by the FDA HRT Working Group").

g) Class Labeling

The FDA has promulgated class labeling guidelines for a limited number of drugs. Estrogen and progestin products, including Premarin, Prempro and Provera, have been among the pharmaceuticals subject to FDA class labeling guidelines and guidance. Class labeling guidelines for progestin and estrogen drug products were first issued in the

1970s. 42 Fed. Reg. 37646 (July 22, 1977) (progestin drug products); 41 Fed. Reg. 47573 (Oct. 29, 1976) (estrogen drug products).

A labeling guideline is a mandatory requirement. Warning language in the labeling produced by the pharmaceutical company must be consistent with the labeling guideline. A class labeling guidance is an informal document that does not bind or otherwise obligate the agency or a person referring to them and are not formal agency opinions. 55 Fed. Reg. 18762 (May 4, 1990) (revoking estrogen class labeling guidelines and instituting class labeling guidance). The FDA sparingly issues class labeling guidelines and guidance. Class labeling guidelines and guidance ensure consistency in labeling of all products in the same chemical or pharmacologic family.

The estrogen product class labeling guidelines promulgated in 1976 were revised by the FDA in October 1987 and February 1990. On May 4, 1990, the FDA revoked estrogen "guideline texts" and stated its intent to issue "informal labeling guidances." 55 Fed. Reg. 18761-62 (May 4, 1990). Labeling of estrogen products continue to be subject to FDA labeling guidance and must include a patient package insert containing information concerning the drug's benefits and risks. 21 C.F.R. § 310.515.

In 1989, the FDA revised the progestin product class labeling guidelines to reflect new scientific information about the risk of congenital abnormalities. 54 Fed. Reg. 1243 (Jan. 12, 1989). In the announcement outlining the changes in progestin products class labeling, the FDA advised that before deviating from the guidelines, "the applicant should first discuss the matter further with the [FDA] agency to prevent expenditures of money and effort for labeling that the agency may later determine to be unacceptable."

Id. at 1244. Effective November 16, 2000, the FDA revoked the labeling guidance of progestin drug products.[20] 64 Fed. Reg. 62209 (Nov. 16, 1999).

In 1992, the FDA reviewed the medical literature and scientific data concerning HRT and issued revised class labeling guidance for both progestin and estrogen products. In January 1992, the FDA issued new guidance for progestin drug products, adding language to address the use of progestins in combination with estrogens.[21] The FDA did not add language to address a possible association with breast cancer in the revised progestin product class labeling guidance. Instead, the FDA found the evidence supported inclusion of a breast cancer warning in the labeling of estrogen products. In August 1992, class labeling guidance for estrogen products was revised to include a warning about breast cancer and a discussion of the possible benefits and risks of using estrogen in combination with progestin.[22] Plaintiffs' expert, Dr. Suzanne Parisian,

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[20] The FDA did not formally switch, by publication in the Federal Register, from issuing guidelines to guidance for labeling of progestin products as was done with estrogen products. The FDA continued to use the term guidelines until 2000, when the agency used the term guidance in revoking progestin product class labeling. See 64 Fed. Reg. 62209 (Nov. 16, 2000). Thus, this court will refer to the 1992 class labeling for progestin drug products as guidance and not guidelines.

[21] Under precautions in the progestin product labeling the following language was added:

> Studies of the addition of a progestin product to an estrogen replacement regimen for seven or more days of a cycle of estrogen administration have reported a lowered incidence of endometrial hyperplasia. Morphological and biochemical studies of endometria suggest that 10-13 days of a progestin are needed to provide maximal maturation of the endometrium and to eliminate any hyperplastic changes. Whether this will provide protection from endometrial carcinoma has not been clearly established. There are possible risks which may be associated with the inclusion of progestin in estrogen replacement regimen, including adverse effects on carbohydrate and lipid profiles. The dosage used may be important in minimizing these adverse effects.
>
> [Letter from FDA to Upjohn Company (Jan. 28, 1992).]

In addition, the boxed warning about limb reduction birth defects was removed from the labeling "since the content is no longer deemed sufficiently serious to warrant the use of the box." Ibid.

[22] Under "Warnings" in the estrogen product labeling guidance the following language was added:

concedes that the progestin class labeling guidance, which did not contain a specific breast cancer warning, represented the FDA's "best thinking" on the issue.

h) Division of Drug Marketing, Advertising and Communications ("DDMAC")

DDMAC is the branch of the FDA responsible for reviewing prescription drug advertising and promotional labeling to ensure that the information contained is not false or misleading. DDMAC issues three types of letters to pharmaceutical companies: advisory, untitled, and warning.

Advisory letters address promotional materials submitted to the FDA before publication. Pharmaceutical companies may voluntarily submit proposed promotional materials to the FDA for review and comment. The FDA provides this service to ensure marketing materials are in compliance with the regulations before they are publicly disseminated. See Center for Drug Evaluation and Research, 2005 Report to the Nation: Improving Public Health Through Human Drugs 45 (2005), http://www.fda.gov/cder/reports/rtn/2005/rtn2005.pdf.

> Breast Cancer. While the majority of studies have not shown an increased risk of breast cancer in women who have ever used estrogen replacement therapy, some have reported a moderately increased risk (relative risks of 1.3-2.0) in those taking higher doses or those taking lower doses for prolonged periods of time, especially in excess of 10 years. Other studies have not shown this relationship.
>
> [Labeling Guidance for Estrogen Class Products Physician Labeling 5 (Rev. Aug. 1992)]

In the "Precautions" the following language was added:

> Studies of the addition of progestin for 10 or more days of a cycle of estrogen administration have reported a lowered incidence of endometrial hyperplasia than would be induced by estrogen treatment alone . . . there are, however, possible risks which may be associated with the use of progestins in estrogen replacement regimens . . . While the effects of added progestins on the risk of breast cancer are also unknown, available epidemiological evidence suggests that progestins do not reduce, and may enhance, the moderately increased breast cancer incidence that has been reported with prolonged estrogen replacement therapy.
>
> [Id. at 7.]

An untitled letter "addresses promotion violations that are less serious than those addressed in warning letters." CDER Handbook, Untitled Letter, http://www.fda.gov/cder/handbook/ (last visited July 3, 2008). "In such letters, DDMAC usually requests that a company take specific action to bring the company into compliance within a certain amount of time, usually 10 working days. There is no requirement that the agency take enforcement action." Ibid.

Warning letters "are issued only for violations of regulatory significance. Significant violations are those that may lead to enforcement action if not promptly and adequately corrected." FDA Regulatory Procedures Manual § 4-1-1 (2008), http://www.fda.gov/ora/compliance_ref/rpm/pdf/ch4.pdf. FDA centers are instructed to "issue warning letters, not untitled letters, for promotional activities if the nature of the activity is such that the center would support further regulatory action." Id. at § 4-1-5. Unlike untitled letters, which can be issued by any FDA compliance official, "warning letters are issued by the DDMAC Division Director and receive concurrence from appropriate officials in the Center for Drug Evaluation and Research. Companies have 15 working days to respond to the warning letter. Warning letters are put on display at the time of issuance in FDA's Freedom of Information Office." CDER Handbook, Warning Letter, http://www.fda.gov/cder/handbook/ (last visited July 3, 2008).

IV. Women's Health Initiative ("WHI")

The WHI study filled a void in the medical community's research and understanding of the risks and benefits of HRT. As noted by the FDA medical officer reviewing the Prempro NDA, there are challenges in understanding what relationship, if any, HRT had with the development of breast cancer. These challenges include "the long

latency between exposure to promotional agents and detection of clinical tumors . . . [in addition] prospective studies take many years to conduct and require extremely large sample sizes to ensure statistically meaningful treatment group comparisons." Medical Officer's Review of Original and Resubmitted NDA Submissions 6-7 (Dec. 30, 1994).

In 1991, Dr. Bernadine Healy, the director of the National Institutes of Health ("NIH"), obtained funding from Congress to conduct the WHI. The prestige of the NIH helped secure funding from Congress, FDA support, recruitment of study centers and investigators to provide for the thousands of patients needed to participate in the study. The WHI study consisted of a set of clinical trials and an observational study, which together involved 161,808 generally healthy postmenopausal women. Jacques E. Rossouw, et al., Risks and Benefits of Estrogen Plus Progestin in Healthy Postmenopausal Women: Principal Results from the Women's Health Initiative Randomized Controlled Trial, 288 J. Am. Med. Ass'n 321, 330 (2002). This was the first U.S. study of its size and duration to examine the causes, prevention and treatment of diseases that affect women. Jacques E. Rossouw, et al., The Evolution of the Women's Health Initiative: Perspectives from the NIH, 50 J. Am. Med. Women's Ass'n 50 (Mar./Apr. 1995). One of the clinical studies was to examine the risks and benefits of HRT. The clinical trials were envisioned to last fifteen years and designed using the accumulated evidence at the time. Over 27,000 women enrolled in the HRT trials, with 16,608 taking estrogen plus progestin and 10,739 taking estrogen alone.

The Post-menopausal Estrogen and Progestin Intervention ("PEPI") study was a feasibility precursor to the WHI. PEPI was designed to test the effects of various dosage regimens of estrogen and estrogen plus progestin on lipids, clotting factors, glucose

homeostasis, and bone mineral density over a three-year period. Rossouw, supra, 50 J. Am. Med. Women's Ass'n at 51. The results of PEPI, published in 1994, helped establish the appropriate dosage of progestin necessary to protect women from endometrial hyperplasia, which was then used in the WHI study of HRT. Ibid.

Wyeth agreed to provide Premarin and combination estrogen plus progestin (later approved by the FDA as Prempro) and corresponding placebos for the study. Since the FDA had yet to approve a combination estrogen plus progestin, the NIH was required to submit an investigational NDA before conducting the WHI study. See 21 C.F.R. §§ 312.1 to 312.160 (requiring submission of an investigational NDA for use of non-FDA-approved drugs in medical studies). Wyeth had previously filed, in 1983, an investigational NDA in order to proceed with studies using combination estrogen and progestin. Wyeth agreed to allow the NIH to reference the confidential research information contained in Wyeth's investigational NDA concerning Prempro.

The WHI clinical trials on the long-term use of estrogen and progestin in post-menopausal women ended after approximately 5.2 years. Rossouw, supra, 288 J. Am. Med. Ass'n at 330. In July 2002, the WHI study was stopped due to an increased risk of invasive breast cancer. The WHI reported an overall relative risk of 1.26 for breast cancer associated with long-term (more than five years) hormone therapy use and subsequent analysis of this data reported an adjusted relative risk of 1.24. When the WHI study results were released, the Premarin and Prempro labeling listed a relative risk of 1.3 to 2.0. The labeling was subsequently modified to include the results of the WHI, including the lower relative risk of invasive breast cancer.

V. History of the Provera, Premarin, and Prempro Labels

a) Provera

The Provera labeling has been significantly revised on multiple occasions since the initial approval of the drug in 1959. In the late 1960s, a contraindication for use of the product in women with "known or suspected malignancy of the breast" was added to the labeling. See, e.g., Physicians' Desk Reference 2577 (1995); Physicians' Desk Reference 2180 (1989). In 1971, with further modifications in 1972, a warning about the development of malignant nodules in the mammary glands of beagle dogs was added.[23] The Provera labeling was further revised in accordance with the FDA promulgated class labeling guidelines and guidance of progestin drug products issued in 1977, 1989, and 1992. See Labeling Guidance for Estrogen Class Products Physician Labeling, supra n. 22, 5.

In December 1991, the FDA approved changes to the Provera labeling. These changes included additional language in the "Precautions" section addressing the use of progestins in combination with estrogens:

> Studies of the addition of a progestin product to an estrogen replacement regimen for seven or more days of a cycle of estrogen administration have reported a lowered incidence of endometrial hyperplasia. Morphological and biochemical studies of endometria suggest that 10-13 days of a progestin are needed to provide maximal maturation of the endometrium and to eliminate any hyperplastic changes. Whether this will provide protection from endometrial carcinoma has not been clearly established.

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[23] This warning remained in the labeling during the time period Dora ingested Provera. The following language was under "Warnings":

> Beagle dogs treated with medroxyprogesterone acetate developed mammary nodules some of which were malignant. Although nodules occasionally appeared in control animals, they were intermittent in nature, whereas the nodules in the drug-treated animals were larger, more numerous, persistent, and there were some breast malignancies with metastases. Their significance with respect to humans has not been established.
>
> [See Physicians' Desk Reference 2180 (1989).]
>
> See also Physicians' Desk Reference 2577 (1995).

[Letter from FDA to Upjohn Company (Dec. 18, 1991).]

See also Physicians' Desk Reference 2472 (1993).

The "Precautions" section also included a discussion of the risks of adding a progestin to estrogen therapy:

> There are possible risks which may be associated with the inclusion of progestin in estrogen replacement regimen, including adverse effects on carbohydrate and lipid profiles. The dosage used may be important in minimizing these adverse effects.
>
> [Ibid.]

The FDA did not add language to the Provera label concerning the risk of breast cancer associated with the combination use of estrogen and progestin. Subsequently, in January 1992, the FDA issued revised guidance for all progestin drug products, which included the precautionary language listed above. Although the progestin product labeling guidance was silent concerning the risk of breast cancer associated with HRT, the FDA added such warning language to the revised estrogen product labeling guidance issued in August 1992. See Labeling Guidance for Estrogen Class Products Physician Labeling, supra n. 22, 5.

Throughout the time Dora ingested Provera, 1991 to 1996, the label listed "known or suspected malignancy of breast" as a contraindication. In July 1997, Upjohn submitted a sNDA seeking approval of an indication that would authorize the marketing of Provera for use in combination with estrogen. The FDA approved the additional indication in 1998, after Dora stopped using Provera. The FDA found Provera to be safe and effective "to reduce the incidence of endometrial hyperplasia in nonhysterectomized postmenopausal women receiving 0.625 mg conjugated estrogen." Letter from FDA to Pharmacia & Upjohn (Aug. 4, 1998). The labeling was revised to include the newly

approved indication along with additional minor modifications. The FDA commented in detail on numerous sections of the labeling, often dictating its exact content.[24] The approved labeling did not contain a breast cancer warning.

b) Premarin

When Premarin was approved in 1942, the label was silent regarding any risk to the breast or endometrium. See Transcript of Fertility and Maternal Health Drugs Advisory Committee meeting 43:14-16 (Feb. 1, 1990). By 1950, a contraindication had been added warning physicians not to prescribe "where there is a familial or personal history of mammary or general malignancy." Id. at 43:16-18. In 1962, the contraindication was changed to a caution, recommending cyclic use. Golden explained the history of the Premarin labeling at the 1990 advisory committee meeting:

> By 1974, . . . the caution was replaced by a contraindication again, and contraindications included known or suspected cancer of the breast and known or suspected estrogen-dependent neoplasia, such as cancer of the endometrium. In addition, a warning was placed, a warning not to give estrogen to women with recurrent chronic mastitis or abnormal mammograms because of the possibility of stimulation of undiagnosed estrogen-dependent neoplasia.
>
> [Id. at 44:2-11.]

A boxed warning was added in 1977, after epidemiologic studies provided conclusive evidence of the risk of endometrial cancer. A warning about the breast was also included. Id. at 44:12-25.

In 1986, Wyeth submitted a sNDA seeking approval of another indication for Premarin. Upon reviewing this sNDA, the FDA approved Premarin for use to prevent osteoporosis. In 1991, when Dora filled her first prescription for Premarin, the drug was

[24] See Faxes from FDA to Pharmacia & Upjohn (July 13, 1998, July 17, 1998, July 24, 1998); Letter from FDA to Pharmacia & Upjohn (Aug. 4, 1998).

approved for treatment of moderate to severe vasomotor symptoms associated with menopause, atrophic vaginitis, atrophic urethritis and osteoporosis prevention. See Physicians' Desk Reference 2434 (1991).[25] During the relevant time period, the "Contraindications" included the following language: "[e]strogens should not be used in women (or men) with any of the following conditions. . . [k]nown or suspected cancer of the breast." Physicians' Desk Reference 2790 (1996); Physicians' Desk Reference 2727 (1995); Physicians' Desk Reference 2434 (1991).

Under "Warnings" the Premarin labeling included the following language:

> *Induction of malignant neoplasms.* 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. Women on this therapy should have regular breast examinations and should be instructed in breast self-examination.
>
> [Physicians' Desk Reference 2434 (1991).]
>
> See also Physicians' Desk Reference 2790 (1996).

The Premarin labeling also included the following under "Precautions:"

> *Addition of a progestin.* Studies of the addition of a progestin for seven or more days of a cycle of estrogen administration have reported a lowered incidence of endometrial hyperplasia. Morphological and biochemical studies of endometrium suggest that 10 to 13 days of progestin are needed to provide maximal maturation of the endometrium and to eliminate any hyperplastic changes. Whether this will provide protection from endometrial carcinoma has not been clearly established. There are possible additional risks which may be associated with the inclusion of progestin in estrogen replacement regimens. The potential risks include adverse effects on carbohydrate and lipid metabolism. The choice of progestin and dosage may be important in minimizing these adverse effects.
>
> [Ibid.]

[25] By 1994, the indication for "atrophic urethritis" had been removed. See Physicians' Desk Reference 2594 (1994).

Wyeth acted quickly to revise the Prempro and Premarin labeling to incorporate the results from the WHI study of HRT released in July 2002. On or about August 28, 2002, Wyeth sent 550,000 letters including revised labeling to physicians. In bold type the letter cautioned, "because of the potential increased risks of cardiovascular events, breast cancer and venous thromboembolic events, use of PREMPRO, PREMPHASE, and PREMARIN should be limited to the shortest duration consistent with treatment goals and risks for the individual woman, and should be periodically reevaluated."

c) Prempro

Before approving the Prempro NDA in 1994, the FDA required multiple changes to the labeling. The final FDA-approved labeling warned about the potential risk of breast cancer.

Under "Warnings" the Prempro labeling included the following language:

> 1. *Induction of malignant neoplasms*
>
> *Breast cancer.* Some studies have reported a moderately increased risk of breast cancer (relative risk of 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. The majority of studies, however, have not shown an association in women who have ever used estrogen replacement therapy.
>
> The 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. Other studies have not shown this relationship. In a one year clinical trial of PREMPRO, PREMPHASE™ and Premarin alone, 5 new cases of breast cancer were detected among 1377 women who received the combination treatments, while no new cases were detected among 347 women who received Premarin alone. The overall incidence of breast cancer in this clinical trial does not exceed that expected in the general population.
>
> Women on hormone replacement therapy should have regular breast examinations and should be instructed in breast self-examination, and women over the age of 50 should have regular mammograms.

[Physicians' Desk Reference 2803 (1996).]

Under "Precautions" the labeling stated, "[w]hile the effects of added progestins on the risk of breast cancer are also unknown, available epidemiologic evidence suggests that progestins do not reduce, and may enhance, the moderately increased breast cancer risk that has been reported with prolonged estrogen replacement therapy (see Warnings)." Id. at 2804 (emphasis omitted).

In 1995, the one-pill version of Prempro was approved and the labeling was modified to include a section discussing cases of breast cancer reported in a recently published study. These changes were reflected in the 1997 Physicians' Desk Reference.[26] The warning language remained the same from 1996 to 2002, the time period during which Dora ingested Prempro.[27] When the data from the WHI study was released Wyeth promptly incorporated it into the labeling. The revised labeling of Prempro warns of a lower relative risk of breast cancer in the "Warnings" section (1.09-1.86) than was listed when Dora used Prempro (1.3-2.0). Compare Physicians' Desk Reference 3379 (2005) with Physicians' Desk Reference 2906 (1997).

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[26] The following language was added under "Warnings":

> In the three year clinical Postmenopausal Estrogen Progestin Intervention (PEPI) trial of 875 women to assess differences among placebo, unopposed Premarin, and three different combination hormone therapy regimens, one (1) new case of breast cancer was detected in the placebo group (n=174), one [1] in the Premarin alone group (n=175), none in the continuous Premarin plus continuous medroxyprogesterone acetate group (n=174), and two (2) in the continuous Premarin plus cyclic medroxyprogesterone acetate group (n=174).
>
> [Physicians' Desk Reference 2907 (1997).]

[27] During this time period the placement of the breast cancer warning changed. Compare Physicians' Desk Reference 2906-07 (1997) (listing breast cancer directly under induction of malignant neoplasms in the "Warnings" section) with Physicians' Desk Reference 3376 (1999) (listing endometrial cancer and then breast cancer under induction of malignant neoplasms in the "Warnings" section).

As part of the approval of Prempro, the FDA obtained a commitment from Wyeth to "conduct a comprehensive investigation of breast cancer risk in users and non-users of the [Prempro] NDA regimens at appropriate and reasonable cost." Letter from the FDA to Wyeth-Ayerst Lab. 2 (Dec. 30, 1994). The FDA wrote, "[t]he most feasible approach appears to be a case-control study in areas of the United States when and where the NDA regimens are used extensively." Ibid. In August 1995, Wyeth submitted a draft protocol synopsis for such a study. On November 8, 1995, FDA officials met with Wyeth representatives to discuss the phase IV commitment. Dr. Bruce Stadel, a FDA epidemiologist, noted that the initiation of the phase IV case-control study would be eight or nine years away. He expressed "second thoughts" about the wisdom of conducting the phase IV case-control study, as the WHI would likely provide the same type of data. He asked Wyeth to submit a report evaluating whether the phase IV case-control study would be superfluous. According to Wyeth, the WHI researchers were also concerned that a separate study would interfere with recruitment of participants for the WHI study and not provide any new data. In September 1997, Wyeth submitted a comprehensive evaluation of WHI, Women's International Study of Long-duration Oestrogen After Menopause ("WISDOM") and the proposed case-control study. Letter from Wyeth-Ayerst Research to FDA (Sept. 25, 1997). The FDA concluded that Wyeth's continuing support of WHI and WISDOM would fulfill its phase IV commitment to conduct an investigation of the breast cancer risk with Prempro. Letter from FDA to Wyeth-Ayerst Research (Nov. 12, 1997).

VI. Analysis of Plaintiffs' Failure to Warn Claim

a) Statutory Presumption of Adequacy

A pharmaceutical company "that communicates adequate information on the dangers and safe use of the [prescription drug] product, . . . taking into account the characteristics of, and the ordinary knowledge common to, the prescribing physician[]" will not be liable for a failure to warn under the PLA. N.J.S.A. 2A:58C-4. The New Jersey Legislature went further than those in other states and accorded deference to the FDA's determination of appropriate labeling of prescription drugs by including a rebuttable presumption in the PLA.[28] Defendants who comply with FDA regulations are granted a rebuttable presumption of adequate labeling. N.J.S.A. 2A:58C-4 specifically provides: "If the warning or instruction given in connection with a drug . . . has been approved or prescribed by the federal Food and Drug Administration under the 'Federal Food, Drug, and Cosmetic Act,' a rebuttable presumption shall arise that the warning or instruction is adequate." In the context of prescription drugs, the adequacy of a warning may be determined as a matter of law. Banner v. Hoffmann-La Roche Inc., 383 N.J. Super. 364, 378 (App. Div. 2006), certif. denied, 190 N.J. 393 (2007).

The parties agree that the PLA accords a rebuttable presumption of adequacy based on FDA approval. However, they dispute the effect and operation of the rebuttable presumption. Plaintiffs contend that the presumption follows N.J.R.E. 301, whereby a plaintiff can rebut the presumption by showing some evidence tending to disprove the adequacy. Plaintiffs argue that once such evidence is shown, the presumption will vanish, leaving them with the burden of proving the label's inadequacy. Defendants, thereafter, would be entitled to no probative benefit from the presumption. Defendants contend, however, that N.J.R.E. 301 does not purport to identify the substantive evidence

[28] HRT cases have been tried in other jurisdictions; however, none of these jurisdictions have adopted an FDA compliance defense similar to N.J.S.A. 2A:58C-4.

required to overcome the presumption of adequacy under the PLA. Therefore, plaintiffs' reliance on expert opinions that defendants' warnings should have said something different is misplaced because those opinions are not based on the evidentiary predicate required to overcome the presumption of adequacy.

New Jersey courts have recognized that before the FDA warning presumption will be deemed rebutted, the plaintiff must produce a specific type of evidence demonstrating intentional misconduct by the manufacturer. See William A. Dreier, John E. Keefe, Sr., & Eric D. Katz, New Jersey Products Liability & Toxic Torts Law § 15:4 at 443 (2008). The New Jersey Supreme Court first defined the specific type of evidence needed to overcome the presumption of adequacy granted by the PLA in Perez v. Wyeth Lab., Inc., 161 N.J. 1, 24 (1999). The exception to the presumption of adequacy crafted in Perez was reaffirmed by the Supreme Court in Rowe v. Hoffman-La Roche, Inc., 189 N.J. 615, 626 (2007). The Perez Court held "for all practical purposes, absent deliberate concealment or nondisclosure of after-acquired knowledge of harmful effects, compliance with FDA standards should be virtually dispositive" of a failure to warn claim. Perez, supra, 161 N.J. at 25 ("[a]ny duty to warn physicians about prescription drug dangers is presumptively met by compliance with federal labeling"); see also Rowe, supra, 189 N.J. at 626. The Appellate Division recently recognized an additional basis for overcoming the presumption of adequacy set forth in the PLA, namely, a pharmaceutical company's "economically-driven manipulation of the post-market regulatory process." McDarby v. Merck, 401 N.J. Super. 10, 63 (App. Div. 2008).

Presently, the presumption of an adequate warning based on compliance with FDA regulations will be deemed rebutted only if the following proof is presented: (i) deliberate concealment or nondisclosure of after-acquired knowledge of harmful effects ("Perez/Rowe exception") or (ii) manipulation of the post-market regulatory process ("McDarby exception") Rowe, supra, 189 N.J. at 626; Perez, supra, 161 N.J. at 25; McDarby, supra, 401 N.J. Super. at 63. The Court in Perez, explained that compliance with FDA regulations provides "compelling evidence that the manufacturer satisfied its duty to warn the physician." Perez, supra, 161 N.J. at 24 (emphasis added). In contrast, the McDarby exception requires substantial evidence of manipulation of the post-market regulatory process. McDarby, supra, 401 N.J. Super. at 71. In McDarby, the court focused on the intentional misconduct of the pharmaceutical manufacturer after market approval and found that the Perez/Rowe exception did not apply to the facts of the case. Id. at 71. Although plaintiffs may present expert testimony in an attempt to rebut the statutory presumption, Prince v. Garruto, Galex & Cantor, 346 N.J. Super. 180, 188-89 (App. Div. 2001), the presumption in favor of the adequacy of FDA-approved warnings will not be deemed rebutted unless plaintiffs produce the type of evidence identified in Perez, Rowe, or McDarby.

Plaintiffs argue that the Perez presumption deals only with direct-to-consumer ("DTC") prescription drug advertising cases and is not generally applicable to failure to warn claims. This court disagrees. Prior to Perez, the statutory presumption of adequacy was analyzed in Feldman v. Lederle Laboratories, 125 N.J. 117 (1991), cert. denied, 505 U.S. 1219, 112 S. Ct. 3027, 120 L. Ed. 2d 898 (1992) ("Feldman II"). The Court in Perez acknowledged its earlier analysis of the presumption in Feldman II. Perez, supra, 161

N.J. at 24. Given the Court's statement in Perez that "the same rebuttable presumption should apply," the presumption discussed in Perez and Feldman II must be appraised under the same standard. Ibid. Contrary to plaintiffs' argument, the presumption crafted in Perez was not confined to DTC advertising.[29]

Prior to Perez, Rowe, and McDarby, the presumption of adequacy was governed by N.J.R.E. 301. See Feldman II, supra, 125 N.J. at 157; Dreier, supra, 30 Seton Hall L. Rev. at 811 ("[p]rior to Perez, the common understanding of the statutory presumption of adequacy flowed from Feldman II and was to be governed by New Jersey Rule of Evidence 301"). The Court in Feldman II acknowledged the uncertainty as to the actual effect of the statutory presumption of adequacy. See Feldman II, supra, 125 N.J. at 157 ("The actual effect of the statute, however, is less clear"). It was not until the Court decided Perez that the effect of the statutory presumption was again revisited. The treatment of warnings was substantially changed in Perez, which established a liability standard based upon compliance with applicable federal statutes and administrative regulations. The Perez Court did not apply the traditional rule of presumption, N.J.R.E. 301. If it had, the statutory presumption of the PLA would have disappeared. Instead, the Court in Perez held that in a failure to warn case, the presumption of adequacy afforded to a manufacturer's compliance with FDA requirements is stronger and of greater evidentiary weight than the customary presumption referenced in N.J.R.E. 301. See Dreier, Keefe, & Katz, New Jersey Products Liability & Toxic Torts Law, supra, § 15:4 at 443 ("The Perez presumption is thus much stronger than the typical [N.J.R.E. 301]

[29] Perez, supra, 161 N.J. at 25; see also William A. Dreier, Direct-to-Consumer Advertising Liability: An Empty Gift to Plaintiffs, 30 Seton Hall L. Rev. 806, 813 (2000) (concluding that presumption analyzed in Perez was not confined to direct-to-consumer advertising in light of earlier analysis in Feldman II).

presumption, which 'disappears' from the case in the face of a sufficient quantum of contrary evidence"). The court in McDarby confirmed that the presumption in a PLA failure to warn action should be afforded greater evidentiary weight. McDarby, supra, 401 N.J. Super. at 71 ("The instruction at issue adequately informed the jury that the presumption of adequacy could only be overcome by 'substantial evidence,' thereby according the presumption a significance greater than would otherwise be the case, while not according it conclusive effect").

b) Overcoming the Presumption

The PLA grants a presumption that an FDA-approved prescription drug label is adequate. The ultimate decision of the FDA to provide or not provide certain information in a prescription drug label cannot be criticized unless a plaintiff has provided evidence of the pharmaceutical company's deliberate concealment or nondisclosure of after-acquired knowledge of harmful effects, or if the pharmaceutical company was found to have manipulated the post-market regulatory process. The court in McDarby specifically addressed the defendant pharmaceutical company's manipulation of the post-market regulatory process which caused the product's warning to be diluted and delayed the dissemination of information determined by the FDA to belong in the drug's labeling.

Plaintiffs have failed to present any evidence of deliberate concealment or nondisclosure of after-acquired knowledge by either Wyeth or Upjohn. In fact, plaintiffs' expert, Parisian, has testified that she has "not seen any evidence" that "Upjohn had information about the risk of breast cancer associated with Provera or Provera in conjunction with estrogens that it failed to disclose to the FDA." Parisian admitted that in 1994 the scientific studies examining whether progestin added to estrogen increased

the potential risk of breast cancer were "confusing." As to Wyeth, Parisian was asked the following:

> Q. Are you contending - - are you going to testify in this case that Wyeth withheld any information, either adverse event reports, published medical literature, any information on safety, regarding Premarin, Prempro or the combination of MP - - of Premarin and MPA before that was approved, from the FDA? Information the company actually had in its possession that it withheld from the FDA?
>
> A. No. And as you know, I never said that in my report.

There is no dispute that plaintiffs have failed to present any evidence that satisfies the Perez/Rowe exception to the presumption of adequacy.

Next, the court must consider whether plaintiffs have presented evidence of manipulation by defendants of the post-market approval regulatory process. The court disagrees with plaintiffs' argument that the McDarby requirement of substantial evidence of inadequacy is not limited to manipulation of the post-market approval regulatory process. The court will analyze separately plaintiffs' proofs as they relate to both Wyeth and Upjohn.

i. The McDarby exception and Wyeth

The first theory asserted by plaintiffs is that Wyeth should have done more to study the risks of combining estrogen and progestin. Plaintiffs contend that Wyeth should have studied the risk of breast cancer following the increased use of progestin in combination with estrogen to combat endometrial hyperplasia. If Wyeth conducted proper studies, plaintiffs assert, Wyeth would have been obliged to propose far stronger language warning of the breast cancer risk in the Prempro NDA. Plaintiffs argue that Wyeth did nothing despite the FDA expressing concerns about the risk of breast cancer from HRT. As to Prempro, Wyeth's alleged failure to test occurred during the pre-

approval period; thus, plaintiffs' failure to test claim does not fall within the McDarby exception. As for Premarin, the McDarby exception also does not apply. Unlike the facts in McDarby, the risk of breast cancer was not newly discovered, the FDA was knowledgeable of the risk, and neither the FDA nor any of its advisory committees requested Wyeth conduct specific testing. Nonetheless, the court will address plaintiffs' failure to test allegation.

The court in McDarby recognized that the FDA's "pre-market approvals of drugs are generally thorough in nature." McDarby, supra, 401 N.J. Super. at 64. The court quoted approvingly the view of a former FDA commissioner that "on the day of new drug approval . . . the FDA's determinations about labeling ought not to be subject to re-examination by courts or juries in failure-to-warn cases." Id. at 82 (citing David A. Kessler & David C. Vladeck, A Critical Examination of the FDA's Efforts to Preempt Failure-To-Warn Claims, 96 Geo. L.J. 461, 466 (Jan. 2008) (hereinafter "Kessler & Vladeck")). Plaintiffs argue that the FDA could not require Wyeth to do a study until Wyeth actually came within the FDA's authority and that did not occur until 1994 when Wyeth asked the FDA to approve Prempro. The facts show that Premarin and Prempro have been extensively regulated by the FDA since the approval of Premarin in 1942, as evidenced by the FDA labeling guidelines and guidance for estrogen products. The FDA has been continuously involved in the development, review, and approval of Premarin and Prempro, including ongoing review and approval of their labels.[30] If the FDA found

[30] Wyeth submitted the following list of major events in the FDA's ongoing review of Premarin and Prempro:

> 1942: FDA approval of Premarin. 1966: Wyeth submission of over 500 published articles in support of DESI review of Premarin. 1972: FDA adoption of DESI review of estrogens, finding Premarin effective for relief of vasomotor symptoms and vaginal atrophy and "probably" effective for prevention of osteoporosis. 1975: FDA Advisory

the studies concerning the risk of breast cancer from ingesting Premarin plus progestin were inadequate, the FDA had authority over Wyeth in 1986 when Wyeth sought approval of an additional indication, prevention of osteoporosis, for Premarin. At a minimum, in 1986, the FDA could have withheld approval of the new indication or required a post-approval study of Premarin plus progestin. Instead, the FDA exercised its power to require Wyeth to add a precaution regarding the combined use of such drugs. Similarly, in 1994, the FDA could have withheld approval of the Prempro NDA pending completion of the WHI and/or required different warnings. The FDA found at the time of approval that adequate testing had been done and the data supported the conclusion that Prempro was safe and effective.

Committee meeting on endometrial cancer issue. 1976: publication of first FDA Estrogen Labeling Guideline. 1978: Wyeth submission to FDA of literature review on effect of added progestin on endometrial hyperplasia/cancer. 1979: Wyeth submission of literature review of breast cancer studies to the FDA. 1982: Wyeth submission of initial protocol for Prempak study. 1983: Wyeth submission of IND for Prempak study. 1984: FDA Advisory Committee meeting on whether to add language on the effects of added progestin to labeling. 1986: FDA approval of adding language on the effect of added progestins to the Premarin label. 1986: Wyeth submission of "paper NDA" for Prempak. 1986: FDA approval of estrogens as fully effective for prevention of osteoporosis. 1987: FDA rejection of "paper NDA" submitted by Wyeth for approval of Prempak. 1987: FDA Estrogen Labeling Guideline. 1988: Wyeth submission of clinical development program for Prempro to FDA. 1989: Wyeth submission of final protocol for Prempro Pivotal Trial after extensive discussions with FDA. 1990: FDA Advisory Committee meeting on breast and endometrial cancer. 1990: FDA Advisory Committee meeting on potential cardiovascular indication for Premarin. 1991: FDA Advisory Committee meeting on combination hormone therapy products. 1992: Wyeth submission of Prempro NDA. 1993: FDA Refusal to File Prempro NDA. 1993: Wyeth resubmission of Prempro NDA. 1993: Initiation of HERS clinical trial. 1993: Initiation of WHI clinical trial. 1994: FDA's Medical Officer's Review and Approval of two-pill Prempro NDA. 1995: Initiation of HOPE study on lower doses of combination hormone therapy. 1995: FDA's Medical Officer's Review and Approval of single pill Prempro. 1997: FDA approval of Wyeth support of WHI and WISDOM as fulfilling Phase IV commitment to further investigate breast cancer risk. 1998: FDA's Medical Officer's Review and Approval of Prempro dose 0.625/5.0 mg. 2002: Preliminary results of HRT arm of WHI published. 2002: Wyeth Dear Doctor Letters and initial label changes regarding WHI. 2003: FDA Class labeling changes regarding WHI and Wyeth Dear Doctor Letter. 2003: FDA Approves lower doses of Premarin and Prempro.

If the court were to accept plaintiffs' theory that Wyeth failed to test before filing its NDA, then in any failure to warn case, the presumption of adequacy accorded an FDA-approved drug labeling could be nullified by a plaintiff contending that the FDA would have approved a different warning had the defendant manufacturer done additional tests before filing its NDA. Moreover, plaintiffs' argument that one need look no further than the differences between the Prempro labels pre- and post-WHI to show how inadequate the Prempro label was prior to the WHI study is flawed. The presumption will have no real effect if it is sufficient to rebut the presumption with evidence that the manufacturer subsequently strengthened the warning. Inherent in the drug approval process is the expectation that warnings will be revised and often strengthened over time. McDarby acknowledged that at the time of approval, the FDA's knowledge base may be close to perfect, but also highly limited because, at that point, the drug has been tested on a relatively small population of patients. McDarby, supra, 401 N.J. Super. at 64 (quoting Kessler & Vladeck, supra, at 466). There is no reason to believe that the New Jersey Legislature was not aware of this fact when it created the presumption of adequacy. Furthermore, the scientific studies and data considered in review of the Prempro NDA were not limited in the ways discussed by Kessler & Vladeck in McDarby. Estrogen and progestin had been available on the market and widely used in combination by women for many years.

If the FDA had any doubt about the warning it approved in 1994, the agency had the authority to revisit that warning and revise it as a condition for approval of the one-pill Prempro in 1995 or the 0.625 mg CEE/5.0 mg MPA dose of Prempro in 1998. In fact, when the FDA approved the one-pill Prempro in 1995, the agency directed Wyeth to

add the breast cancer results from the PEPI trial to the warning. Plaintiffs' contention that Wyeth failed to conduct safety studies leading to inadequate warnings on its drugs is without merit, given the FDA's extensive regulatory record of Premarin and Prempro.

According to plaintiffs, Wyeth also manipulated the regulatory process by putting specific representations in the Prempro label which it knew to be untrue, and minimized or discounted studies that showed an increased breast cancer risk. Upon reviewing the voluminous exhibits and documents submitted by both parties, the court finds these arguments to be unsupported by the evidence. Alternatively, plaintiffs attempt to overcome the presumption of adequacy by citing the letters from the FDA to Wyeth concerning marketing materials. Plaintiffs identify eight letters sent to Wyeth from the FDA. Six of the eight letters were advisory pre-review letters. These letters show interactions with the FDA about draft ads or promotional materials, which Wyeth had voluntarily submitted pre-public dissemination to obtain FDA comment. The remaining letters sent to Wyeth were untitled. Wyeth was never issued a warning letter. A full review of the relevant documents reveals that the FDA actively exercised its regulatory authority and took prompt and effective action. Furthermore, Wyeth promptly addressed all recommendations and concerns raised by the FDA. The letters referred to by plaintiffs fail to demonstrate any intentional misconduct by Wyeth, a necessary requirement before the adequate warning presumption will be deemed rebutted.

Lastly, plaintiffs argue that Wyeth manipulated the regulatory process by "ghost writing" articles. Wyeth is alleged to have conceived and drafted medical articles relating to HRT, which were then published in peer-reviewed journals by authors who did not acknowledge Wyeth's involvement. Plaintiffs do not dispute the medical accuracy of

the information contained in the relatively small number, approximately thirty-seven, published articles initiated by Wyeth.[31] Plaintiffs' expert, Parisian, admits the beneficial contribution of the information contained in at least one article initiated by Wyeth. This article reviewed and summarized 135 previously published articles. As noted in Scroggin v. Wyeth, trial, "[T]he information [in the article] that's provided to the doctor is essential, because physicians tend to be busy." There is no dispute that the articles were subject to a rigorous peer review process and were factually and medically sound. The identified articles were published after 1994 and would not have "polluted" the information regarding HRT already available to the FDA. There is no proof that these corporate-initiated articles in any way delayed the implementation of what the FDA requested be in the Premarin or Prempro labeling or diluted the warnings on these drugs.

ii. The McDarby exception and Upjohn

Plaintiffs assert that they have submitted substantial evidence of post-market manipulation of the regulatory process as to Upjohn. Plaintiffs first argue that the presumption of adequacy has been rebutted as to Upjohn because Provera was not approved by the FDA for treatment of menopausal symptoms nor use in combination with estrogen. When Dora ingested Provera, the labeling did not contain a risk of breast cancer warning. In 2007, a warning about the risk of breast cancer was added to the Provera labeling. As shown in the timeline below, plaintiffs' argument must be rejected.

In July 1977, the FDA promulgated regulations requiring the use of certain warning information in the labeling for progestin drug products. In 1989, the FDA revised the guidelines based on new scientific data, primarily to update information about

[31] The parties agreed at oral argument that approximately thirty-seven articles initiated by Wyeth were published without disclosing Wyeth's involvement. Plaintiffs' counsel expressed concern that there might be others yet to be identified.

the risk of congenital abnormalities. There is no dispute that the Provera labeling was consistent with these guidelines. In 1984, 1990, and then again in 1991, the FDA convened advisory committees to assess the safety and efficacy of estrogen, progestin and the use of both drugs together. The advisory committees addressed whether use of HRT was associated with an increased risk of breast cancer and discussed the proper labeling of these drugs.

In December 1991, the FDA approved changes to the Provera labeling that included precautionary language about the use of progestins and estrogens. Upjohn was instructed by the FDA to use the exact language reviewed and approved by the FDA. In January 1992, after the advisory committee meetings and the FDA's extensive assessment of HRT, the FDA issued revised labeling guidance for progestin products. The guidance included detailed language in the contraindications, warnings, precautions, and adverse reactions section. The revised FDA guidance included language addressing the use of progestins in combination with estrogens. Yet again, with respect to the specific question of what should be said in the labeling for Provera concerning the risk of breast cancer, the FDA found no justification for inclusion of any specific warning language and did not include such language in the guidance. The Provera labeling was consistent with the FDA guidance. In fact, plaintiffs' expert testified that the FDA's 1992 labeling guidance represented the best thinking of the FDA. In the same year, 1992, the FDA issued revised labeling guidance for all estrogen products that included a revised specific warning concerning the risk of breast cancer.

The FDA was well aware that physicians were prescribing progestin products off-label with estrogen products. Prior to reviewing the sNDA submitted by Upjohn in 1997,

for the approval of an indication that would authorize the marketing of Provera for use in combination with conjugated estrogen, the FDA was involved with reviewing and ultimately approving the NDA for Prempro in 1994. When the FDA ultimately approved the use of Provera with estrogen in 1998, it ratified the 1992 progestin product labeling guidance and again found no reason to include a breast cancer warning. The 1998 label was a reflection of the FDA's continuing judgment and "best thinking" that a warning about the risk of breast cancer should be in the estrogen labeling rather than the progestin labeling. Plaintiffs' expert, Parisian, testified that she did not disagree with this decision made by the FDA. The FDA found Provera safe and effective for use consistent with its approved labeling and instructed Upjohn to use the exact language the FDA reviewed and approved. The FDA did not require Upjohn to conduct more testing. The FDA recognized that the WHI study was underway and would provide more definitive information about the possible risk of breast cancer.

The FDA repeatedly reviewed and approved the Provera labeling. At the same time, the FDA was actively involved with gathering and assessing information regarding the safety of estrogen, progestin and combined hormone therapy. When Dora was taking Provera, the FDA had not approved it for use in combination hormone therapy. However, the FDA was well aware that Provera was being prescribed off-label with Premarin. Plaintiffs proffer no evidence that once Dora's physicians decided to prescribe estrogen to treat her menopausal symptoms, they would not have followed the accepted medical standard of care of prescribing a progestin to protect against the risk of endometrial hyperplasia associated with taking estrogen alone.

The decision of Dora's physicians to prescribe Provera off-label, and the fact that the FDA had not yet approved Provera for the particular indication for which it was prescribed to Dora, does not rebut the statutory presumption of adequacy to which the Provera labeling is entitled. During the time period when Dora was prescribed Provera, the drug was subject to both scientific and regulatory scrutiny. The FDA had the authority to require a specific risk of breast cancer warning in the labeling and was sufficiently knowledgeable on this issue to determine whether such a warning was necessary. The FDA's decision not to include a risk of breast cancer warning on the Provera label was deliberate and informed. Plaintiffs cannot use the fact that Provera was prescribed off-label to rebut the statutory presumption of adequacy. When the FDA approved such use in 1998, shortly after Dora stopped taking Provera, the risk of breast cancer was not included in the labeling. This approval confirmed the FDA's earlier decision that a risk of breast cancer warning was not necessary. Plaintiffs' argument that because Provera was prescribed off-label the "FDA could not possibly have concluded there was no need for Upjohn to warn about the safety of Provera and estrogen on the risk of breast cancer" is not supported by the submitted facts.

Even if the court were to accept plaintiffs' argument that the FDA is powerless to require specific warnings regarding drugs that are prescribed off-label unless there is a "pending application before the FDA," the Provera timeline reveals that Provera was before the FDA on pending applications in 1991 and 1998. On both occasions, the FDA found the inclusion of any specific warning language associating combination use with an increased risk of breast cancer to be unverified. The FDA did not include such language in the progestin guidelines, guidance, or Provera labeling. This was, in part, because in

1992, the FDA also issued revised class labeling guidance for estrogen products which included a warning about breast cancer.

In considering the specific examples of conduct presented by plaintiffs of Upjohn's alleged post-market manipulation of the regulatory process, and after reviewing the volumes of exhibits submitted by all parties, this court concludes that plaintiffs' proofs are insufficient to establish that Upjohn manipulated the post-market regulatory process. The proofs submitted by plaintiffs do not establish any intentional misconduct by Upjohn which caused the warnings on the Provera label to be diluted or the dissemination of information determined by the FDA to belong in the Provera labeling to be delayed. Plaintiffs rely upon documents concerning drugs other than Provera and instances of conduct by Upjohn that occurred long after Dora stopped ingesting Provera. As to the four promotional materials which prompted the FDA to send Upjohn untitled letters, two in the mid 1980's and two in 1990, these letters are unrelated to plaintiffs' claim of failure to warn about the risk of breast cancer. There is no dispute that Upjohn promptly addressed all recommendations and concerns raised by the FDA. Moreover, the letters referred to by plaintiffs fail to demonstrate any intentional misconduct by Upjohn, a necessary requirement before the FDA warning presumption will be deemed rebutted.

iii. Summary

The court recognizes that some of the conduct of Wyeth and Upjohn cited by plaintiffs may have been less than exemplary. However, the actions and/or inactions of defendants have to be viewed in light of plaintiffs' failure to warn claim and the presumption of adequacy established by our Legislature. Plaintiffs have not presented

compelling or substantial evidence of the type necessary to rebut the presumption of adequacy.

The FDA has been actively involved in the labeling and monitoring of Premarin, Provera, and Prempro for several decades. The FDA was well informed of the prevalent practice of prescribing Provera off-label in combination with Premarin for the treatment of menopausal symptoms for years prior to the approval of Prempro, the first FDA-approved combination HRT. The FDA had authority under 21 C.F.R. 201.57 (1988) (prior to 2006 amendments) to include language in the labeling to warn about health hazards associated with off-label use. During each of the three advisory committee meetings held by the FDA in 1984, 1990, and 1991, the FDA acknowledged the increasing practice of prescribing progestin with estrogen to treat menopausal symptoms. The FDA knew there was a risk of breast cancer in women who ingested estrogen alone or in combination with progestin. At the advisory committee meetings, experts, including FDA representatives and practitioners, discussed the breast cancer risk and what warnings were scientifically supported and appropriate to list in the labeling.

The risk of breast cancer was not newly discovered after the approval of Prempro. Plaintiffs concede that before Dora ingested HRT, the worldwide medical literature included published studies suggesting that the combination of synthetic progestin and estrogen could increase the risk of breast cancer. Plaintiffs' case-specific expert, Dr. Richard Hirschman, testified that the potential of breast cancer and HRT was commonly understood in the medical community long before Dora ever used it. All known data on the subject of HRT and the risk of breast cancer were reviewed by the FDA, the advisory

committees, and the FDA's HRT working group.[32] The FDA and its own experts were active participants in all decisions regarding Premarin, Provera, and Prempro, unlike the FDA's participation with Vioxx as discussed in McDarby.

The Prempro Summary Basis of Approval by the FDA clearly sets forth the FDA's knowledge about off-label prescription practices of physicians and the possible risk of breast cancer. In approving Prempro, the FDA specifically reviewed numerous epidemiologic studies conducted between 1976 and 1994. Medical Officer's Review of Original and Resubmitted NDA Submissions (Dec. 30, 1994). The medical officer's review reflects the careful consideration given by the FDA to all relevant information in deciding whether to approve Prempro. Golden specifically reviewed the scientific literature about breast cancer and recognized that "many more years are still needed before the relationship between HRT and breast cancer can be definitively determined." Id. at 7. She further stated that, "the true effect of HRT on breast cancer incidence and mortality must be considered the single most important safety issue concerning this class of drugs." Ibid. Nonetheless, the FDA approved Prempro in 1994 having found the testing adequate and the data supporting the conclusion that Prempro was safe and effective. The FDA noted that further data on the associated risks of HRT would be forthcoming from the WHI. Ibid. The approval of Prempro was conditioned upon Wyeth conducting a phase IV study.[33] Wyeth fulfilled this commitment to the satisfaction of the FDA by supporting the WHI and WISDOM studies. Plaintiffs take issue with how the

[32] The facts here are similar to those in Chambers v. G.D. Searle & Co., 441 F. Supp. 377, 384 (D. Md. 1977), where the defendants had no further information regarding their products and associated risks than what was already reviewed by the advisory committees and the FDA; therefore defendant's motion for a directed verdict was granted.

[33] Since the 1980s, the FDA often obtains a commitment for a post-approval study as a condition for the approval of a drug. See Nancy Mattison & Barbara W. Richard, Postapproval Research Requested by the FDA at the Time of NCE Approval, 1970-1984, 21 Drug Info. J. 309, 323 (1987) (noting that post approval studies are now standard FDA practice and are not an exceptional requirement).

commitment was satisfied and argue that Wyeth should have conducted specific studies earlier. If plaintiffs' allegation was true that in 1994 Prempro was unsafe due to insufficient scientific data, despite warnings in the labeling, then the FDA was obligated to reject the NDA. See 21 U.S.C.A. § 355(d)(1).

During the post-market regulatory process, the FDA remained actively involved in regulating, monitoring, and requesting changes in the labeling of Premarin, Provera and Prempro. The FDA specified language in the labeling by promulgating class labeling guidelines and guidance. This differs from other drugs, such as Vioxx, where the FDA "did not have the [statutory] authority to compel labeling changes, but instead had to negotiate [all] changes with the drug's sponsor." See McDarby, supra, 401 N.J. Super. at 65. The shortcomings of the FDA emphasized in McDarby are not implicated here. The FDA utilized a comprehensive and scientific process to decide whether to approve Prempro and/or change the labeling or approve additional indications for Premarin and Provera. The FDA was actively involved in the post-market surveillance of these drugs. During the period of time that Dora used defendants' drugs, neither Wyeth nor Upjohn resisted labeling changes proposed by the FDA due to emerging safety concerns, unlike the defendant in McDarby, which rejected many of the FDA-proposed labeling changes. Id. at 85-86. There is no evidence in this case that defendants actively sought to dilute the labeling recommendations of the FDA, nor is there evidence that defendants ever intentionally withheld any risk information from the FDA. Wyeth promptly took action in response to the results released from the WHI study, which included sending thousands of letters to inform physicians of the results and updating the labeling for Premarin and

Prempro.[34] Plaintiffs' expert, Dr. Blume, acknowledged that Wyeth moved with speed after receiving the adverse data from the WHI study.

As previously set forth, the FDA had the regulatory authority to require a specific breast cancer warning in the labeling of Provera, Premarin, or Prempro, and was sufficiently knowledgeable on this issue to determine whether such a warning was necessary. The FDA's decision not to include a more specific breast cancer warning in its labeling guidelines or guidance was both deliberate and informed. Any flaws in the FDA process are the responsibility of the United States Congress and the Executive Branch to correct, as they are in the best position to evaluate the pharmaceutical regulatory process. Alternatively, the New Jersey Legislature can elect to alter the rebuttable presumption afforded pharmaceutical manufacturers by the PLA, should they wish to do so. However, at the present time, the New Jersey Legislature and the New Jersey Supreme Court have acknowledged the FDA's authority and experience in determining appropriate warnings in the labeling of prescription drugs.

The proofs are sufficient to conclude that plaintiffs have failed to set forth either compelling or substantial evidence necessary to overcome the presumption of adequacy relating to the Premarin, Provera, and Prempro labels approved by the FDA.

VII. Plaintiffs' Non-PLA Causes of Action

In addition to claims under the PLA, plaintiffs' complaint contains causes of action for negligence, breach of implied warranty, breach of express warranty, fraud and misrepresentation, and negligent misrepresentation. Plaintiffs' complaint also asserts a claim under the New Jersey Consumer Fraud Act ("CFA"). Plaintiffs voluntarily

[34] The court's analysis does not focus on the actions of Upjohn after Dora stopped using Provera in 1996.

dismissed their claims for negligence, breach of implied warranty, and breach of express warranty. Defendants move for summary judgment on the basis that the PLA subsumes plaintiffs' non-PLA causes of action.[35]

a) CFA

In addition to other causes of action, plaintiffs' complaint asserts a claim under the CFA.[36] Plaintiffs argue that defendants misled physicians and the public about the safety of Provera, Premarin, and Prempro, and that defendants' fraudulent misrepresentation led directly to plaintiffs' purchase of those drugs and receipt of less than what they were promised. According to plaintiffs, this purely economic loss is separate and distinct from the damages plaintiffs incurred as a result of Dora's physical injuries, which plaintiffs allege were caused by her ingestion of these products. In this section, the court will address whether the CFA is subsumed by the PLA.

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[35] Despite the recent decisions in Sinclair and McDarby, plaintiffs advised the court by correspondence dated June 19, 2008 that plaintiffs were pursuing their CFA, fraud and misrepresentation and negligent misrepresentation claims. See Sinclair v. Merck, No. A-117-06, (App. Div., June 4, 2008); McDarby v. Merck, 401 N.J. Super. 10 (App. Div. 2008).

[36] Specifically, count VIII sets forth that:

> 113. Plaintiff(s) incorporate by reference all other paragraphs of this complaint as if fully set forth here and further allege as follows:
>
> 114. Defendant engaged in unconscionable commercial practices, deception, fraud, false promise, misrepresentation and/or the knowing concealment suppression or omission of material facts with the intent that others rely upon such concealment suppression or omission.
>
> 115. As a direct and proximate cause of one or more of these wrongful acts or omissions of the Defendant, Plaintiff(s) suffered profound injuries which required and will require medical treatment and hospitalization; has become and will become liable for medical and hospital expenses; lost and will lose financial gains; all of which damages will continue in the future.
>
> 116. Plaintiff(s) suffered an ascertainable loss of money or property as a result of defendant's use or employment of unconscionable commercial practices as set forth above and seeks treble damages, attorney's fees and costs of suit.

The PLA, N.J.S.A. 2A:58C-1 to -11, was enacted in 1987 to "re-balance the law 'in favor of manufacturers.'" Rowe, supra, 189 N.J. at 623 (quoting Dreier, Keefe, & Katz, New Jersey Products Liability & Toxic Torts Law, supra, § 15:4). The PLA provides the exclusive remedy for harm caused by a product. A products liability action is defined as "any claim or action brought by a claimant for harm caused by a product, irrespective of the theory underlying the claim, except actions for harm caused by breach of an express warranty." N.J.S.A. 2A:58C-1(b)(3).[37] Shortly after the PLA was enacted, the New Jersey Supreme Court acknowledged that the PLA reflects the Legislature's "intent to limit the expansion of products-liability law by creating absolute defenses and rebuttable presumptions of non-liability." Shackil v. Lederle Lab., Div. of Am. Cyanamid, Co., 116 N.J. 155, 187 (1989). The PLA "established the sole method to prosecute a product liability action." Tirrell v. Navistar Int'l., Inc, 248 N.J. Super. 390, 398 (App. Div.), certif. denied, 126 N.J. 390 (1991).

The Supreme Court decision in In re Lead Paint Litigation, 191 N.J. 405 (2007), which was recently relied upon by the Court in Sinclair v. Merck & Co., 195 N.J. 51 (2008) is determinative of whether plaintiffs' CFA claim is barred by the PLA. In Lead Paint, twenty-six municipalities and counties sought to recover, from manufacturers and distributors of lead paints, the costs of detecting and removing lead paint from homes and buildings, of providing medical care to residents affected with lead poisoning, and of developing programs to educate residents about the dangers of lead paint. 191 N.J. at 408-09. Although the complaints initially sought recovery through a wide variety of

[37] See N.J.S.A. 2A:58c-1(b)(2) (defining harm as: "(a) physical damage to property, other than to the product itself; (b) personal physical illness, injury or death; (c) pain and suffering, mental anguish or emotional harm; and (d) any loss of consortium or services or other loss deriving from any type of harm described in subparagraphs (a) through (c) of this paragraph").

legal theories, the Court was called upon to consider only whether the plaintiffs had stated a cognizable claim based on the common law tort of public nuisance. Ibid. The Supreme Court held that the PLA encompasses virtually all possible causes of action relating to harms caused by consumer products:

> We begin with the Product Liability Act itself. As one commentator has noted: "[w]ith the passage of the Product Liability Act, . . . there came to be one unified, statutorily defined theory of recovery for harm caused by a product, and that theory is, for the most part, identical to strict liability."
>
> The language chosen by the Legislature in enacting the PLA is both expansive and inclusive, encompassing virtually all possible causes of action relating to harms caused by consumer and other products. That language encompasses both the product at issue here and the harms plaintiffs attribute to that product. There can be no doubt that the paint products distributed or sold by defendants were intended to be used by consumers. Similarly, the harms plaintiffs seek to vindicate in this action are addressed in the context of a products liability claim. Those harms include 'physical damage to property[,] . . . personal physical illness [or] injury,' and the like.
>
> [Id. at 436-37 (citations omitted).]

The essential essence of the claims asserted by the plaintiffs in Lead Paint was that the defendants failed to warn of the dangers of lead paint; thus, plaintiffs' exclusive remedy was the PLA. Id. at 437. The Court noted that the harms plaintiffs sought to vindicate were addressed in the context of a products liability claim:

> Were there any doubt about the essential nature of the claims asserted by plaintiffs, a careful reading would demonstrate that they sound in products liability causes of action. The central focus of plaintiffs' complaints is that defendants were aware of dangers associated with lead--and by extension, with the dangers of including it in paint intended to be used in homes and businesses--and failed to warn of those dangers. This classic articulation of tort law duties, that is, to warn of or to make safe, is squarely within the theories included in the PLA. In light of the clear intention of our Legislature to include all such claims within the scope of the PLA, we find no ground on which to conclude that the claims being raised by plaintiffs, regarding an ordinary household product used by consumers, were excluded from the scope of that Act.
>
> [Ibid.]

In the case at bar, plaintiffs contend that the purchase of defendants' products and their receipt of less than what they were promised is an economic loss separate and distinct from the physical injury suffered by Dora as a result of her ingestion of defendants' products. Plaintiffs argue that the "PLA's codification of a separate remedial scheme for Dora's physical injuries does not preempt the CFA's creation of a damages action for plaintiffs' purely economic losses." However, the central focus of plaintiffs' lawsuit and the "essential nature of their claims" is that Wyeth and Upjohn failed to warn of the dangers of their drugs. See Lead Paint, supra, 191 N.J. at 437.[38] The Court in Lead Paint concluded that a plaintiff cannot avoid the exclusive remedy of the PLA by seeking economic damages on a theory not normally pled in a products liability action. In Lead Paint, the plaintiffs sought economic damages including the cost of remediation and developing programs to educate residents about the dangers of lead paint on the grounds that a product had exposed consumers to a risk of injury. Id. at 409. The Court, however, held that the plaintiffs' claims were subsumed by the PLA because they primarily alleged harm caused by a defective product. Ibid.

In McDarby, the Appellate Division applied the Lead Paint ruling to a pharmaceutical drug case and found that the plaintiffs' CFA claims were subsumed within the PLA. McDarby, supra, 401 N.J. Super. at 95. The court found the core of the plaintiffs' argument to be that the pharmaceutical company failed to warn of known

[38] Plaintiffs' reliance on the recent unpublished case Wendling v. Pfizer, Inc., No. A-1807-06, (App. Div. Mar. 31, 2008), is misplaced. Wendling was a veterinary pharmaceutical case where the court addressed the issue of whether the PLA bars plaintiffs' CFA and common law negligent misrepresentation claims. Id. at *17. Plaintiffs did not allege a product defect or that the drug was not reasonably fit for its intended use because of inadequate warnings. Thus, the court found that it was not the product itself that caused the harm, but its alleged misleading promotion. Id. at *22. Under such circumstances, the court concluded that plaintiffs' common law negligent misrepresentation claim was not subsumed by the PLA. Ibid. In contrast, Dora specifically asserts both a claim of failure to warn and a claim that the drugs at issue caused her to develop breast cancer. Unlike Wendling, the plaintiffs' claims are exactly the type of claims governed by the PLA.

dangers from its product, resulting in alleged economic harm to the plaintiffs. Id. at 97. The economic harm upon which the plaintiffs based their claims was found to be encompassed within the definition of harm set forth in the PLA. Ibid.

The New Jersey Supreme Court rendered its opinion as to whether the CFA is subsumed within the PLA less than one week after the McDarby decision. In Sinclair, the Court found that the plaintiffs sought to avoid the requirements of the PLA by asserting their claims as CFA claims. Sinclair, supra, 195 N.J. at 65. Sinclair was a products liability action wherein the plaintiffs sought to recover the costs of medical monitoring without alleging a physical injury.

> The language of the PLA represents a clear legislative intent that, despite the broad reach we give to the CFA, the PLA is paramount when the underlying claim is one for harm caused by a product. The heart of plaintiffs' case is the potential for harm caused by Merck's drug. It is obviously a product liability claim. Plaintiffs' CFA claim does not fall within an exception to the PLA, but rather clearly falls within its scope. Consequently, plaintiffs may not maintain a CFA claim.
>
> [Id. at 66.]

Plaintiffs in this case allege that they were victims of fraudulent conduct recoverable under the CFA because defendants misrepresented the safety of their products by failing to warn plaintiffs of their dangers. To allow plaintiffs to seek damages for loss of their co-payments as a result of purchasing defendants' drugs under a theory of consumer fraud will "create a cause of action entirely inconsistent with the PLA's comprehensive legislative scheme." See Lead Paint, supra, 191 N.J. at 439; see also Sinclair, supra, 195 N.J. at 65.

Plaintiffs' CFA claim merely charges that defendants misrepresented the safety risks of their products, thus causing Dora's injury. "This classic articulation of tort law

duties, that is, to warn of or to make safe, is squarely within the theories included in the PLA." Lead Paint, supra, 191 N.J. at 437. In New Jersey "the PLA is paramount when the underlying claim is one for harm caused by a product." Sinclair, supra, 195 N.J. at 66.

For the aforementioned reasons, plaintiffs' CFA claim is subsumed by the PLA.

b) Fraudulent Misrepresentation and Negligent Misrepresentation

Plaintiffs' fraudulent misrepresentation and negligent misrepresentation claims are also subsumed by the PLA for the same reasons cited above. The court will briefly discuss the evolution of these common law claims and their viability today when asserted in a products liability action. The PLA enacted on "July 22, 1987, applies to product liability actions filed on or after the date of enactment." Tirrell, supra, 248 N.J. Super. at 398. A "product liability action" is defined as "any claim or action brought by a claimant for harm caused by a product, irrespective of the theory underlying the claim, except actions for harm caused by breach of an express warranty." N.J.S.A. 2A:58C-1(b)(3). The PLA "established the sole method to prosecute a product liability action" and after its enactment, "only a single product liability action remains." Tirrell, supra, 248 N.J. Super. at 398-99. In Repola v. Morbark Industries, Inc., the Third Circuit held that the PLA "effectively creates an exclusive statutory cause of action for claims falling within its purview." 934 F.2d 483, 492 (3d Cir. 1991). The court in Repola also predicted that "the New Jersey Supreme Court would hold that the PLA generally subsumes common law product liability claims, thus establishing itself as the sole basis of relief under New Jersey law available to consumers injured by a defective product." Ibid. This prediction was accurate. The recent opinion in Sinclair supports the conclusion that claims for harm

caused by a product are governed by the PLA irrespective of the theory underlying the claim. 195 N.J. at 65.

New Jersey state and federal courts have consistently dismissed product liability claims based on common law theories, with the exception of express warranty, when those theories allege harm caused by a product. See Brown v. Philip Morris, 228 F. Supp. 2d 506, 516 (D.N.J. 2002).[39] Courts interpreting the PLA have determined that the PLA subsumes a plaintiff's common-law claim for strict liability negligence and implied breach of warranty. See Tirrell, supra, 248 N.J.Super. at 647-48.

Whether the PLA subsumes plaintiffs' fraud claims has also been an issue that has been addressed by our courts. In Brown, the court relied upon two earlier district court decisions that showed support for the PLA subsuming the plaintiffs' strict liability, negligence and fraud claims. 228 F. Supp 2d. at 517. The first case relied upon by the court in Brown was Walus v. Pfizer, 812 F. Supp. 41 (D.N.J. 1993). In Walus, the plaintiff asserted theories of negligence, strict liability, failure to warn, fraud, misrepresentation, and negligent and intentional infliction of emotional distress. Id. at 42. After analyzing the PLA and cases interpreting it, the court granted summary judgment to the defendants. Id. at 45. With regard to the fraud claim the court concluded

[39] See e.g., Port Auth. of N.Y. & N.J. v. Arcadian Corp., 189 F.3d 305, 313 (3d Cir. 1999) (dismissing negligence claim, stating that "under New Jersey law negligence is no longer viable as a separate claim for harm caused by a product"); Repola, supra, 934 F.2d at 489-94 (dismissing claims of negligence and negligent failure to warn); Thomas v. Ford Motor Co., 70 F. Supp. 2d 521, 528-29 (D.N.J. 1999) (dismissing common-law claim for negligent manufacture); Reiff v. Convergent Techs., 957 F. Supp. 573, 583 (D.N.J. 1997) (dismissing negligence and breach of warranty claims); McWilliams v. Yamaha Motor Corp., USA, 780 F. Supp. 251, 262 (D.N.J. 1991) (dismissing claims of negligence and breach of implied warranty), aff'd. in part, rev'd. in part on other grounds, 987 F.2d 200 (3d Cir. 1993); Tirrell, supra, 248 N.J. Super. at 399 (dismissing negligence claim); see also, e.g., Green v. Gen. Motors Corp., 310 N.J. Super. 507, 517 (App. Div. 1998) (stating that "causes of action for negligence, strict liability and implied warranty have been consolidated into a single product liability cause of action" under the PLA); Ramos v. Silent Hoist & Crane Co., 256 N.J. Super. 467, 473 (App. Div. 1992) (stating that the "Legislature has consolidated the negligence, breach of warranty and strict liability theories for product liability claims" into single product liability action under PLA).

that the PLA subsumed the claim and noted that "New Jersey treats all product liability actions the same, regardless of the theory asserted. Plaintiffs cannot . . . recast [] their product liability claims as fraud claims." Ibid. (citations omitted). The Brown court also relied upon Midili v. Phillip Morris, Inc., Civ. A. No. 99-3900 (D.N.J. June 29, 2000), wherein the defendants were accused of committing "fraud in the marketing of [] cigarettes for having concealed information about their addictive and carcinogenic qualities and for having manipulated the nicotine levels of these cigarettes while failing to disclose that such manipulation occurred." Brown, supra, 228 F. Supp 2d. at 517 (quoting Midili, supra, No. 99-3900 at *2). The court found that the plaintiff's fraud claim was frivolous and specifically held that "[a]t its core, [the plaintiff's] claim for fraud against [the defendant] concerns physical injuries allegedly suffered as a result of the use of [] cigarettes. An intricate analysis of state law is not required to discern that this claim is a product liability claim 'recast' as a common-law fraud claim." Ibid. (quoting Midili, supra, No. 99-3900 at *10).

After reviewing plaintiffs' complaint, there is no doubt plaintiffs' common-law causes of action, including their fraud and misrepresentation (count V) and negligent misrepresentation (count VII) claims involve harm caused by a product under the PLA.[40]

[40] Specifically, counts V and VII set forth that:

> 91. Defendants fraudulently, intentionally and/or negligently misrepresented the safety and effectiveness of their Hormone Therapy Products and fraudulently, intentionally and/or negligently concealed material adverse information regarding their safety and effectiveness.
> . . .
>
> 99. As a direct and proximate result of one or more of those wrongful acts or omissions of the Defendants, Plaintiff(s) suffered profound injuries; required medical treatment and hospitalization; and Plaintiff(s) became liable for medical and hospital expenses.
> . . .

Plaintiffs cannot recast a products liability claim as a fraudulent or negligent misrepresentation claim. The courts in New Jersey have consistently affirmed this position. In Lead Paint, the Court emphasized that "[w]ith passage of the Product Liability Act, . . . there came to be one unified, statutorily defined theory of recovery for harm caused by a product." Id. at 436 (quoting Dreier, Keefe, & Katz, New Jersey Products Liability & Toxic Torts Law, supra, § 1:2-1 at 6) (emphasis added). This proposition was recently affirmed in McDarby and Sinclair.

VIII. Conclusion

For the reasons set forth above, plaintiffs' CFA claim and causes of action for fraudulent misrepresentation and negligent misrepresentation are subsumed by the PLA; thus, such claims are dismissed. Plaintiffs have failed to provide the specific type of evidence necessary to overcome the rebuttable presumption of adequacy afforded the FDA-approved labeling on Provera, Premarin, and Prempro. Therefore, the warnings on the labels are deemed adequate as a matter of law. Accordingly, defendants' motions for summary judgment are granted.

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106. Defendant, having undertaken the manufacturing, marketing, distribution, and/or promotion of the Hormone Therapy Products described herein, owed a duty to provide accurate and complete information regarding its products.

. . .

112. As a direct and proximate result of one or more of these wrongful acts or omissions of the Defendant, Plaintiff(s) suffered profound injuries which are permanent and continuing in nature; required and will require medical treatment and hospitalization; has become and will become liable for medical and hospital expenses; lost and will lose financial gains; has been and will be kept from ordinary activities and duties and will continue to experience mental and physical suffering, all of which damages will continue in the future.