

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

IN RE:

FOSAMAX PRODUCTS LIABILITY LITIGATION

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MASTER FILE

1:06-MD-1789 (JFK)

OPINION & ORDER

APPEARANCES:

FOR THE PLAINTIFF'S STEERING COMMITTEE:

Timothy M. O'Brien, Esq.
Meghan Tans, Esq.
Ned McWilliams, Esq.
LEVAN PAPANATONIO THOMAS MITCHELL
ECHSNER & PROCTOR, P.A.

Michelle Parfitt, Esq.
James Green, Esq.
ASHCRAFT & GEREL

FOR DEFENDANT MERCK & CO, INC.:

Norman C. Kleinberg, Esq.
William J. Beausoleil, Esq.
HUGHES HUBBARD & REED LLP

Paul F. Strain, Esq.
David J. Heubeck, Esq.
Stephen Marshall, Esq.
VENABLE LLP

Christy D. Jones, Esq.
BUTLER SNOW O'MARA STEVENS & CANNADA PLLC

JOHN F. KEENAN, United States District Judge:

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Currently pending in this multi-district litigation ("MDL") are omnibus Daubert motions filed by the Plaintiffs Steering Committee ("PSC") and Defendant Merck & Co., Inc. ("Merck"). For the following reasons, the Court rules as follows.

I. Background¹

Merck makes and distributes Fosamax (alendronate), an FDA-approved drug widely prescribed for the treatment or prevention of osteoporosis. Fosamax belongs to a class of drugs called bisphosphonates. Bisphosphonate drugs have become standard treatment for various metabolic and oncologic diseases related to abnormalities in the bone remodeling cycle.

Also referred to as bone turnover, the bone remodeling cycle is a continuous process of renewal in which old or damaged bone is broken down (resorbed) and then replaced with new bone. The process starts by activation of the osteoclast, which is the cell responsible for resorption. The osteoclast breaks down a small amount of bone, leaving an excavated pit that becomes the bone remodeling unit. A bone-building cell called an osteoblast then fills the bone remodeling unit with organic bone matrix

¹ The facts set forth herein are the Court's findings based upon the record generated by these motions. Some of this information was submitted under seal. To the extent quoted or discussed below, such information is hereby unsealed in light of the strong presumption of public access to a decision affecting several hundred cases.

that, once mineralized, becomes new bone. The living bone cell itself is called the osteocyte. The rate of bone remodeling varies depending on the skeletal site.

Osteoporosis is a disease that afflicts more than 10 million Americans over the age of 50, 80% of whom are women. In healthy young adults, bone resorption and formation are balanced. With aging, bone turnover can become unbalanced due to relative decreases in osteoblast activity or increases in osteoclast activity. In addition, as women age, the decline in estrogen levels after menopause can stimulate osteoclast activity and resorption. The uneven remodeling cycle produces net bone loss. Over time, this leads to reduced bone density and quality and an increased risk of fracture.² An additional 34 million Americans have low bone mass and are considered at risk for osteoporosis, a state referred to as osteopenia. The high incidence of fracture in persons with osteoporosis is a major public health concern.

Several other diseases are related to abnormalities in bone turnover. Paget's disease of bone is characterized by accelerated turnover that results in the production of new bone that is structurally defective. In metastatic bone disease, tumors metastasize into the skeleton and stimulate osteoclast

² A person traditionally is diagnosed with osteoporosis when his or her bone mineral density ("BMD") is more than 2.5 standard deviations ("SD") below the mean for young adults of the same sex. This is referred to as a t-score of -2.5 SD.

activity, causing hypercalcemia and bone pain. One form of osteopetrosis, which is a group of disorders characterized by very dense bone, involves defective osteoclast function.

Bisphosphonates are synthetic analogues of inorganic pyrophosphate. At the tissue level, the primary effect of all bisphosphonates is to inhibit bone resorption. Because bone resorption and formation are linked, bisphosphonates also have a secondary effect of decreasing formation and remodeling. In addition, bisphosphonates are known to inhibit angiogenesis, which is the sprouting of new blood vessels from existing ones.

The first generation bisphosphonates, developed in the 1960s and 1970s, were relatively weak. The new generations have a nitrogen-containing amino side chain that greatly enhances their anti-resorptive potency.

At the cellular level, bisphosphonate binds to the surface of bone mineral, accumulating preferentially in areas with a high rate of bone turnover. At active sites of resorption, the bisphosphonate is released from bone and taken up into the osteoclast. There, it inhibits enzymes necessary for the osteoclast's function and survival. Nitrogen-containing bisphosphonate that is not released during resorption remains in the bone and has a half-life of ten or more years.

The FDA approved Fosamax in 1995 for the treatment of osteoporosis and Paget's disease and in 1997 for the prevention

of osteoporosis. Fosamax was the first of three nitrogen-containing bisphosphonates approved for oral administration to treat these conditions.³ Since their market introduction, oral bisphosphonates have been prescribed by doctors over 225 million times. The efficacy of these drugs in arresting bone loss and reducing the risk of fracture in osteoporotic persons is well-established.

Also on the market are two nitrogen-containing bisphosphonates which are intravenously administered for the treatment of metastatic bone disease and multiple myeloma.⁴ These intravenous ("IV") bisphosphonates are prescribed in higher doses and are more potent than the ones taken orally for osteoporosis. In addition, oral bisphosphonates are poorly absorbed into the bloodstream. Therefore, they have lower bioavailability for incorporation into bone than IV bisphosphonates.

Since October 2003, there have been published reports of bisphosphonate users developing a rare condition called osteonecrosis of the jaws ("ONJ"). ONJ is characterized clinically by an area of dead jaw bone that becomes exposed to the oral cavity. Symptoms can include pain, swelling, and

³ The two others are Actonel (risedronate), manufactured by Proctor & Gamble Pharmaceuticals and Sanofi-Aventis US, and Boniva (ibandronate), manufactured by Roche Laboratories, Inc.

⁴ These are Aredia (pamidronate) and Zometa (zoledronic acid), both manufactured by Novartis Pharmaceuticals Corp.

purulent secretion.

The vast majority of ONJ cases since 2003 have been reported in patients taking IV bisphosphonates. However, there have been reports of ONJ in patients taking oral bisphosphonates. The condition usually develops after an invasive dental procedure, such as a tooth extraction, but has presented spontaneously in some cases.

In August 2004, the FDA issued a Post-Marketing Safety Review concluding that ONJ may be a class effect of all bisphosphonates, rather than limited to IV bisphosphonates. In July 2005, at the FDA's request, Merck updated the Fosamax label to make reference to ONJ.

ONJ can occur in the absence of bisphosphonate use, but its background rate in the population is not known. It has been reported to occur with radiation therapy to the head and neck, osteomyelitis (inflammation/infection of bone marrow), osteopetrosis, herpes zoster virus infection, chemotherapy, and major trauma.⁵ The risk of developing ONJ is increased by factors such as periodontal disease, poor oral hygiene, and trauma.

As reports of ONJ in bisphosphonate users increased, many medical, dental, and oral maxillofacial organizations

⁵ The nomenclature used to describe the condition can take into account its etiology. For example, ONJ with radiation therapy is referred to as osteoradionecrosis or radiation necrosis.

commissioned expert panels to study the problem. They have issued guidelines and recommendations for diagnosing, preventing, and treating what is now commonly referred to as "bisphosphonate-associated ONJ ('BON')" or "bisphosphonate-related ONJ ('BRONJ')." For example, under a working definition promulgated by the American Academy of Oral & Maxillofacial Surgeons ("AAOMS"), a person can be diagnosed with BRONJ if the following three conditions are met: (1) current or previous treatment with a bisphosphonate, (2) exposed, necrotic bone in the maxillofacial region that has persisted for more than eight weeks, and (3) no history of radiation therapy to the jaws. The AAOMS also devised a staging system that categorizes patients with BRONJ into stage 0, stage 1, stage 2, or stage 3, depending on their clinical signs and symptoms. In severe cases, regions of necrotic bone must be surgically removed.

By all estimates, the risk of developing ONJ while taking an oral bisphosphonate for osteoporosis is very small. According to Merck, the worldwide reporting rate among Fosamax users is less than what Merck refers to as 1 in 100,000 patient-treatment years. This number is consistent with a study conducted in Germany that found the prevalence to be 3.8 in 100,000 patients (.00038%). Other studies have found the prevalence to be substantially higher. A survey conducted in Australia, published in 2007, calculated the rate to be between

0.01% to 0.04% for all oral bisphosphonate users and 0.09% to 0.34% for those who had dental extractions. A recent FDA-approved database study by Kaiser Permanente found it to be 0.09% for oral bisphosphonate users.

Since 2006, approximately 800 federal actions have been filed by plaintiffs who allege that Fosamax caused them to develop ONJ. Pursuant to 28 U.S.C. § 1407, these cases were consolidated in this Court for pretrial coordination.⁶ The parties recently completed generic fact and expert discovery, as well as case-specific discovery in a sample of cases. The first of three "bellwether" or test trials is scheduled to commence on August 11, 2009.

The strict products liability and negligence claims asserted by plaintiffs in this MDL are predicated primarily on a failure to warn theory. The substantive state law that governs these claims varies. In general, the plaintiffs will have to prove, among other things, that Fosamax is capable of causing ONJ (general causation) and that Merck should have known of this risk and provided a warning.

On behalf of all plaintiffs, the PSC has designated seven witnesses who have proffered expert testimony relevant to

⁶ Actions filed by persons who have taken IV bisphosphonates and allege ONJ-related injuries have been consolidated in the Middle District of Tennessee as In re Aredia and Zometa Prods. Liab. Litig., MDL No. 1760. Actions filed by users of Actonel or Boniva are proceeding in this Court alongside the Fosamax MDL.

these common issues. Merck has designated a number of witnesses who would offer opposing expert testimony. On May 8, 2009, each side filed a motion challenging the other's experts pursuant to Federal Rule of Evidence 702.⁷ The Court has considered the voluminous submissions presented on the motions, including the expert reports, curriculum vitae, and deposition testimonies of the challenged witnesses. Earlier this month, five witnesses were examined at a hearing pursuant to Federal Rule of Evidence 104, otherwise known as a Daubert hearing. See Daubert v. Merrell Dow Pharms., Inc., 509 U.S. 579 (1993).

The Court's role on these motions is not to decide whether Fosamax can cause ONJ or whether Merck acted as a reasonably prudent drug manufacturer. That task is assigned to the jury. As discussed below, the Court's duty is to ensure that the proffered expert testimony is reliable enough to be admitted at trial as evidence for the jury to consider.

⁷ In addition, each plaintiff in the three bellwether cases has designated an expert to testify on specific causation, i.e., that the Fosmax ingested by plaintiff caused her to develop ONJ. Merck has moved to exclude each of the specific causation experts and for summary judgment in all three cases. The Court will rule on Merck's challenges to the specific causation experts when it decides the summary judgment motions.

II. Applicable Law

Federal Rule of Evidence 702 governs the admissibility of expert testimony and provides:

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

Fed. Rule Evid. 702. Essentially, the witness must be qualified as an expert, the testimony must be reliable, and the testimony must assist the trier of fact.

Qualification as an expert is viewed liberally and may be based on "a broad range of knowledge, skills, and training." In re TMI Litig., 193 F.3d 613, 664 (3d Cir. 1999); In re Methyl Tertiary Butyl Ether ("MTBE") Prods. Liab. Litig., No 1-00-1898, 2008 WL 1971538, at *5 (S.D.N.Y. May 7, 2008) (stating that "[c]ourts within the Second Circuit have liberally construed expert qualification requirements" (internal quotation marks omitted)). A witness's qualifications "can only be determined by comparing the area in which the witness has superior knowledge, skill, experience, or education with the subject

matter of the witness's testimony." Carroll v. Otis Elevator Co. 896 F.2d 210, 212 (7th Cir. 1990) (quoting Gladhill v. General Motors Corp., 743 F.2d 1049, 1052 (4th Cir. 1984)).

Rule 702's three reliability-based requirements were added in 2000 to codify Daubert and its progeny, Kumho Tire Co. v. Carmichael, 526 U.S. 137 (1999), and General Elec. Co. v. Joiner, 522 U.S. 136, 146 (1997). See Fed. R. Evid. 702 advisory committee's note. In Daubert, the Supreme Court held that the traditional "general acceptance" test enunciated in Frye v. United States, which required that a scientific technique be generally accepted in the relevant scientific community to be admissible, was superseded by the Federal Rules of Evidence and inconsistent with their liberal standards of admissibility. Daubert, 509 U.S. at 585-89; see also Amorgianos v. National R.R. Passenger Corp., 303 F.3d 256, 266 (2d Cir. 2002). The Court interpreted Rule 702 to require district courts to act as gatekeepers by ensuring that expert scientific testimony "both rests on a reliable foundation and is relevant to the task at hand." Daubert, 509 U.S. at 597. This requires "a preliminary assessment of whether the reasoning or methodology underlying the testimony is scientifically valid and of whether that reasoning or methodology properly can be applied to the facts in issue." Id. at 592-93; see also Kumho Tire, 526 U.S. 137

(holding that this gate-keeping function applies to all expert testimony, whether based on scientific, technical or other specialized knowledge).

To be scientifically valid, the subject of expert testimony need not be "known to a certainty" because, "arguably, there are no certainties in science." Daubert, 509 U.S. at 590. Rather, the testimony must rest on "good grounds, based on what is known." Id. (internal quotation marks omitted). Daubert set forth a non-exclusive list of factors that courts might consider in gauging the reliability of scientific testimony. Id. at 593-95. These factors are: (1) whether the theory has been tested; (2) whether the theory has been subject to peer review and publication; (3) the known or potential rate of error and whether standards and controls exist and have been maintained with respect to the technique; and (4) the general acceptance of the methodology in the scientific community. Id. Whether some or all of these factors apply in a particular case depends on the facts, the expert's particular expertise, and the subject of his testimony. Kumho Tire, 526 U.S. at 138. A district court has broad discretion both in determining the relevant factors to be employed in assessing reliability and in determining whether that testimony is in fact reliable. Kumho Tire, 526 U.S. at 153; Zuchowicz v. United States, 140 F.3d 381, 386 (2d Cir. 1998).

The requirement that expert testimony "assist the trier of fact" goes primarily to relevance. Daubert, 509 U.S. at 591. Relevance can be expressed as a question of "fit"—"whether expert testimony proffered in the case is sufficiently tied to the facts of the case that it will aid the jury in resolving a factual dispute." Id. (quoting United States v. Downing, 753 F.2d 1224, 1242 (3d Cir. 1985)). In addition, expert testimony is not helpful if it simply addresses "lay matters which the jury is capable of understanding and deciding without the expert's help." United States v. Lumpkin, 192 F.3d 280, 289 (2d Cir. 1999). Finally, the testimony is not helpful if it "usurp[s] either the role of the trial judge in instructing the jury as to the applicable law or the role of the jury in applying that law to the facts before it." United States v. Duncan, 42 F.3d 97, 101 (2d Cir. 1994) (quoting United States v. Bilzerian, 926 F.2d 1285, 1294 (2d Cir. 1991)).

To fulfill its gate-keeping function, the district court must "undertake a rigorous examination of the facts on which the expert relies, the method by which the expert draws an opinion from those facts, and how the expert applies the facts and methods to the case at hand," in order to ensure that each step in the expert's analysis is reliable. Amorgianos, 303 F.3d at 267. However, in accordance with the liberal admissibility

standards of the Federal Rules of Evidence, only serious flaws in reasoning or methodology will warrant exclusion. Id. "As long as an expert's scientific testimony rests upon 'good grounds, based on what is known,' it should be tested by the adversary process—competing expert testimony and active cross-examination—rather than excluded from jurors' scrutiny for fear that they will not grasp its complexities or satisfactorily weigh its inadequacies." Ruiz-Troche v. Pepsi Cola of Puerto Rico Bottling Co., 161 F.3d 77, 85 (1st Cir. 1998) (quoting Daubert, 509 U.S. at 596); see also Amorgianos, 303 F.3d at 267. If an expert's testimony lies within "the range where experts might reasonably differ," the jury, and not the trial court, should "decide among the conflicting views of different experts." Kumho Tire, 526 U.S. at 153.

The Daubert analysis focuses on the principles and methodology underlying an expert's testimony, not on the expert's conclusions. 509 U.S. at 595. However, the Supreme Court in Joiner recognized that "conclusions and methodology are not entirely distinct from one another." 522 U.S. at 146. Therefore, "[a] court may conclude that there is simply too great an analytical gap between the data and the opinion proffered." Id. (stating that "nothing in either Daubert or the Federal Rules of Evidence requir[es] the admission of opinion

evidence connected to existing data only by the ipse dixit of the expert.")

The ultimate object of the court's gate-keeping role under Rule 702 is to "make certain that an expert, whether basing testimony upon professional studies or personal experience, employs in the courtroom the same level of intellectual rigor that characterizes the practice of an expert in the relevant field." Kumho Tire, 526 U.S. at 152. "The flexible Daubert inquiry gives the district court the discretion needed to ensure that the courtroom door remains closed to junk science while admitting reliable expert testimony that will assist the trier of fact." Amorgianos, 303 F.3d at 267.

Finally, like all evidence, expert testimony may be excluded under Rule 403 if its "probative value is substantially outweighed by the danger of unfair prejudice, confusion of the issues or misleading the jury, or by considerations of undue delay, waste of time, or needless presentation of cumulative evidence." Fed. R. Evid. 403.

With these general principles in mind, the Court now turns to the various challenges the parties have raised to each other's experts.

III. The Present Motions

Merck brings the following motions: (1) Motion to Exclude General Causation Witnesses Dr. Robert E. Marx, Dr. John W. Hellstein, Dr. Alastair N. Goss, and Dr. Mahyar Etminan; (2) Motion to Exclude Dr. Suzanne Parisian; (3) Motion to Exclude Dr. Curt D. Furberg; and (4) Motion to Exclude Dr. Gordon Guyatt. In addition, Merck raises several Daubert challenges on specific issues or parts of the witnesses' proposed testimony.

The PSC moves for an order (1) precluding eight of Merck's designated experts from offering an opinion on general causation and/or medical issues relating to bisphosphonates; and (2) placing certain restrictions on testimony by any Merck witness about the anti-fracture efficacy of Fosamax.

A. Merck's Motions

1. Motion to Exclude Expert Testimony about General Causation

Plaintiffs have designated three oral maxillofacial experts and one epidemiologist to opine on general causation.

Dr. Robert E. Marx is the Chief of Oral and Maxillofacial Surgery and the Director of Research at the University of Miami School of Medicine. He proposes to testify that all bisphosphonates, including Fosamax, cause what he refers to as bisphosphonate-induced ONJ by over-suppressing bone remodeling in the jaws. He further would testify that

bisphosphonate-induced ONJ is clinically distinct from other forms of ONJ and does not respond to typical ONJ treatments. Furthermore, he finds the clinical presentation of bisphosphonate-induced ONJ to be nearly identical to ONJ seen with osteopetrosis, a disease involving impaired osteoclastic function. In addition, Dr. Marx would testify that there is no durational threshold before a Fosamax user is at risk for BRONJ, altering his prior, oft-repeated opinion that there is minimal or no risk until there has been three years of continuous use.

Dr. John W. Hellstein is a Clinical Professor at the University of Iowa, College of Dentistry, where he is also the Director of the Surgical Oral Pathology Laboratory. Similar to Dr. Marx, Dr. Hellstein offers an opinion that bisphosphonate-associated ONJ is a clinically distinct pathology caused by bisphosphonates, primarily through the over-suppression of bone turnover. He also opines that the condition is similar to other diseases characterized by reduced osteoclastic function. In addition, he likens bisphosphonate-associated ONJ to "phossy jaw," an exposed jaw necrosis observed in the 19th and early 20th century in factory workers exposed to white phosphorus.

Dr. Alastair N. Goss is a Professor of Oral and Maxillofacial Surgery at the University of Adelaide, Australia, and also serves as the Director of Oral and Maxillofacial Surgery at two Adelaide hospitals. The PSC has retained him to

opine that there is a causal relationship between bisphosphonate drugs, including Fosamax, and ONJ. He further would testify that there is no time-to-onset threshold that allows the conclusion that a person is not at risk of developing ONJ before three years of use. At a de benne esse deposition taken in Adelaide, Dr. Goss also presented photographs of patients with bisphosphonate-associated ONJ and opined that the mechanism underlying the disease is the over-suppression of bone turnover.

Dr. Mahyar Etminan is an Assistant Professor of Medicine at the University of British Columbia and a research scientist at the Center for Clinical Epidemiology and Evaluation in Vancouver. He holds a Doctor of Pharmacy and a Masters Degree in Clinical Epidemiology. He would offer the opinion that epidemiological studies are not always necessary to establish causation, especially when the adverse event in question is very rare. Based upon his application of the Bradford Hill criteria, he would testify that there is reliable scientific data establishing a causal relationship between bisphosphonates, including Fosamax, and ONJ.

a. Merck's Position

Merck moves to exclude testimony on general causation by all four of plaintiff's proposed experts on the subject. Merck argues that the scientific consensus, reflected in several position papers issued by reputable scientific bodies, is that

the current level of evidence is insufficient to support the conclusion that oral bisphosphonates can cause ONJ. Merck notes that no randomized controlled trials or epidemiological studies demonstrate that Fosamax users suffer an increased risk of ONJ over nonusers. According to Merck, the opinions of plaintiff's experts lack a reliable foundation because they are based upon mere case reports and case series, prevalence studies, adverse event reports, inapplicable animal studies, and unproven hypotheses about the mechanism or mechanisms through which Fosamax supposedly causes ONJ.

Merck also identifies additional factors that it believes undermine the reliability of the proffered general causation opinions. Merck contends that plaintiffs' oral maxillofacial experts are unable to clinically distinguish ONJ allegedly caused by bisphosphonates from other conditions involving exposed necrotic bone and delayed healing.⁸ Merck also argues that Dr. Etminan cannot utilize the Bradford Hill factors to assess causality because those factors may be applied only after a controlled epidemiological study demonstrates a statistically significant association between an exposure and a disease. Merck further claims that Dr. Etminan is not qualified

⁸ In addition, Merck claims that Dr. Marx's reversal of his prior opinion that there is minimal or no risk of ONJ until three years of continuous Fosamax treatment undermines his opinion on general causation and should be excluded. This issue is discussed below.

to apply the Bradford Hill criteria and that, in any event, applying them does not support the view that Fosamax causes ONJ.

b. PSC's Position

The PSC responds that its experts have applied proper methodology in forming their general causation opinions because they relied on the totality of the available scientific evidence. According to the PSC, multiple lines of reliable evidence provide a sufficient foundation for its experts' opinions. That evidence consists of biologic plausibility, three prevalence studies, hundreds of peer-reviewed and published case reports and case series, adverse event reports, several animal studies, evidence showing that other bisphosphonates cause ONJ, and, for certain experts, their own published studies and/or clinical experience. The PSC claims that its experts are eminently qualified to appreciate the causation significance of this evidence.

Furthermore, according to the PSC, experts are entitled to reach general causation opinions in the absence of evidence from epidemiological studies. The PSC argues that the clinical trials for Fosamax were not designed or large enough to detect rare and unexpected adverse events like ONJ and that Merck's own scientists concluded that epidemiologic studies were not feasible. Finally, the PSC argues that the association between Fosamax and ONJ is well-established and admitted by two

of Merck's experts, that several position papers and medical treatises reflect a general consensus on causality, and that the position papers cited by Merck are not authoritative.

c. Court's Ruling

The arguments presented by both sides overlook the different methodologies employed on the one hand by the PSC's three oral maxillofacial experts, Drs. Marx, Hellstein, and Goss, and on the other hand by its epidemiology expert, Dr. Etminan. These differences are important because admissibility under Rule 702 turns on whether the "expert employs in the courtroom the same level of intellectual rigor that characterizes the practice of an expert in the relevant field." Kumho Tire, 526 U.S. at 152.

i. The Oral Maxillofacial Experts

The testimony of Drs. Marx, Hellstein, and Goss on general causation is admissible under Rule 702. Each is a leading expert in the field of oral maxillofacial pathology and on the topic of ONJ. In forming their opinions on general causation, they rely upon their clinical experience in treating ONJ, understanding of the physiology of the jaws and the pharmacology of bisphosphonates, and review of the available scientific literature and evidence. Their theory on the mechanism of causation is generally accepted as biologically plausible. In addition, they formed their opinions

independently of litigation, have published them in leading peer-reviewed journals, and frequently are cited by others in the field.

The Court first addresses Merck's argument about the absence of evidence from controlled studies. It is well-settled that an expert on medical causation need not always base his opinion on epidemiological studies. McCulloch v. H.B. Fuller Co., 61 F.3d 1038, 1043-44 (2d Cir. 1995); Benedi v. McNeil-P.P.C., Inc., 66 F.3d 1378 (4th Cir. 1995); Kennedy v. Collagen Corp., 161 F.3d 1226 (9th Cir. 1998); Norris v. Baxter Healthcare Corp., 397 F.3d 878, 882 (10th Cir. 2005). Such a requirement would "doom from the outset all cases in which the state of research on the specific ailment or on the alleged causal agent was in its early stages." Heller v. Shaw Indus., Inc., 167 F.3d 146, 155 (3d Cir. 1999). It also would be inconsistent with Daubert because it would "effectively resurrect a Frye-like bright-line standard, not by requiring that a methodology be 'generally accepted,' but by excluding expert testimony not backed by published (and presumably peer-reviewed) studies." Amorgianos v. Nat'l R.R. Passenger Corp., 303 F.3d 256, 267 (2d Cir. 2002) (quoting Heller, 167 F.3d at 155).

There can be no question that the state of research on the link between oral bisphosphonates and ONJ is in its early stages. Before October 2007, there was no International Classification of Diseases ("ICD-9") code for ONJ, a testament to its relative obscurity until recent years. (PX 8.0004.)⁹ This made epidemiologic study infeasible, which is one of the professed reasons that Merck decided not to conduct any study. (PX 30009: 41:20-46:19; 1.0400.)

The absence of ONJ reports in the Fosamax clinical trials does not end the debate. The PSC's epidemiology experts have offered persuasive testimony that clinical trials can miss very rare, unexpected, and sometimes late-occurring adverse events. (Etminan Rep. at p. 4, 7-8; Furberg Rep. at 28; see also AAOMS Position Paper on Bisphosphonate-Related Osteonecrosis of the Jaw-2009 Update (DX 42) at 3 ("The low prevalence of BRONJ in osteoporosis patients poses a significant challenge for future clinical trials aimed at establishing accurate incidence data.")); In re Zyprexa Prods. Liab. Litig., 493 F. Supp. 2d 571, 575 (E.D.N.Y. 2007) (observing that clinical trials often fail to uncover important adverse effects for widely marketed prescription drugs). Merck's scientists have recognized that ONJ cases may have been unreported or misreported during the

⁹ "PX" refers to "plaintiff's exhibit," "DX" refers to "defendant's exhibit," and "Tr." refers to a page of a deposition or hearing transcript.

clinical trials for several different reasons. (PX 1.0073; 1.0424.)

A few controlled database studies have attempted to use surrogates for ONJ. While these add to the body of scientific knowledge, they have limitations and the Court finds them to be inconclusive on the issue of causation. One study examined medical claims data for 255,757 cancer patients, using jaw surgery as a surrogate for ONJ. (DX 48.) The study found that IV bisphosphonates strongly increased the risk for jaw surgery. Oral bisphosphonates were found to increase the risk by 15%, but the association was not statistically significant. When first approached by one of the study's authors, Merck decided not to participate in or sponsor the study because it believed that "not much could be done with epidemiology" due to the coding problems. (Px. 1.0400; 1.0522.) The same author published a subsequent study examining medical claims data for over 700,000 people, using various jaw problems as surrogates. (DX 50.) The study found that IV bisphosphonates increased the risk for adverse jaw outcomes but that oral bisphosphonates actually reduced it. Despite the favorable results, one of Merck's top scientists internally dismissed them because the study had an unacknowledged enrollment bias. (PX 1.0575; 3.0006: 217:13-218:2.)

The PSC, for its part, points to a database study by Dr. Etminan finding a statistically significant association between oral bisphosphonate use and reports of aseptic osteonecrosis. (PX 2.0272.) However, the study concedes that most of the reports likely were of necrosis of the hip, not ONJ, and that the study "could not establish causality." (Id.)

Considering the early state of the research, the lack of evidence from controlled epidemiological studies is not fatal. Under Daubert, an expert need not base his or her opinion on the best possible evidence, regardless of availability, but upon "good grounds, based on what is known." 509 U.S. at 590.

In McCulloch v. H.B. Fuller Co., the Second Circuit affirmed the admission of a doctor's testimony that plaintiff's exposure to glue fumes caused her respiratory ailment, even though the doctor "could not point to a single piece of medical literature" that specifically supported this conclusion. 61 F.3d at 1043-44. The Court found that the testimony rested on good science because the doctor based his opinion on a range of factors, including his care and treatment of plaintiff, her medical history, pathological studies, review of the substance's material safety data sheet, his training and experience, use of a scientific analysis known as differential etiology (which requires listing possible causes, then eliminating all causes

but one), and reference to various scientific and medical treatises. Id.

In Zuchowicz v. United States, the Second Circuit approved the admission of a pulmonary medical expert's opinion that a negligent overdose of a drug caused a fatal pulmonary disease. 140 F.3d at 386-87. The doctor based his opinion on the temporal relationship between the overdose and the start of the disease, the deceased's apparent good health prior to the overdose, and the differential etiology method of excluding other possible causes. Id. at 385. He also relied on the fact that the illness was similar in onset, timing and course of development to other cases of pulmonary diseases known to have been caused by other classes of drugs. Id. at 385-86. Although there had been no scientific studies of the drug at the high dosage ingested by the deceased, the Court affirmed the district court's conclusion that the doctor based his opinion on methods reasonably relied upon in his field. Id. at 387.

A third decision, Amorgianos v. Nat'l R.R. Passenger Corp., signaled the continuing authority of McCullock and Zuchowicz by repeatedly citing and relying on them. 303 F.3d at 266-67. The Court stated that an expert need not always "back his or her opinion with published studies that unequivocally support his or her conclusions." Id. at 266. It also cited decisions from other circuits holding that an opinion on medical

causation need not be based on evidence from controlled epidemiological studies. Id. at 266-67 (citing Bonner, 259 F.3d at 929; Heller, 167 F.3d at 155).

In Ruggiero v. Warner-Lambert Co., 424 F.3d 249 (2d Cir. 2005), the Court of Appeals affirmed the exclusion of a doctor's testimony that the drug Rezulin caused cirrhosis of the liver. The doctor apparently based his opinion on a differential diagnosis, but "was unable to point to any studies or, for that matter, anything else" that supported his conclusion. Id. at 252. The Court held that a differential diagnosis generally is insufficient by itself to support an opinion on general causation, except perhaps in rare cases due to the "the rigor of differential diagnosis performed, the expert's training and experience, the type of illness or injury at issue, or some other case-specific circumstance." Id. at 254. The Court explained that, "[w]here an expert employs differential diagnosis to rule out other potential causes for the injury at issue, he must also rule in the suspected cause, and do so using scientifically valid methodology." Id. The Court also stated that, in light of Joiner and Amorgianos, a district court must ensure that the expert's conclusion is supported at each step by the data and methodology upon which he or she relies. Id. at 255.

In this case, as detailed below, the PSC's oral maxillofacial experts do not base their general causation opinions on a single differential diagnosis, but upon many conducted over several years. They back up their conclusions with valid scientific evidence, albeit not from controlled studies. Merck implies that, after Ruggiero, a doctor must rely on such studies to "rule in" a suspected cause. This proposition is contrary to the precedent of this and several other circuits. McCulloch, 61 F.3d at 1043-44; Bonner, 259 F.3d at 929; Benedi, 66 F.3d at 1384; Heller, 167 F.3d at 155; Kennedy, 161 F.3d at 1228-29. More fundamentally, it is incompatible with the principle that a testifying expert is held to the standard of an expert in the relevant field. Kumho Tire, 526 U.S. at 152.

In the actual practice of medicine, physicians do not wait for conclusive, or even published and peer-reviewed, studies to make diagnoses to a reasonable degree of medical certainty. Such studies of course help them to make various diagnoses or to rule out prior diagnoses that the studies call into question. However, experience with hundreds of patients, discussions with peers, attendance at conferences and seminars, detailed review of a patient's family, personal, and medical histories, and thorough physical examinations are the tools of the trade

Heller, 167 F.3d at 155, cited in Amorgianos, 303 F.3d at 266-67; see also Kassirer et al. Inconsistency in Evidentiary Standards for Medical Testimony, JAMA, Sept. 18, 2002- Vol. 288 No. 11 (PX 2.1001) at 1384 ("In clinical medicine, a biologically plausible relationship, physiological studies of a drug, or even a handful of case reports can be useful in individual cases in helping a practitioner make judgments about cause and effect relationships.").

The following example illustrates the point. Merck's oral pathology expert, Dr. Ellen Eisenberg, believes that radiation therapy can cause ONJ. (04/15/09 Eisenberg Dep. Tr. 16:6-17:17, 21:23-24:17.) She bases her opinion upon years of clinical experience, case reports, and biologic plausibility, though she is not aware of a single study that demonstrates a statistical association between radiation therapy and ONJ. (Id.) This is not an unreliable methodology for a physician to rule in radiation therapy as a potential cause of ONJ.

The Court now turns to the reliability of the opinions of the PSC's oral maxillofacial experts and finds it established by the following factors.

(1) Qualifications and Professional Stature

The strength of an expert's qualifications provides circumstantial evidence of reliability. See Ambrosini v. Labarraque, 101 F.3d 129, 140 (D.C. Cir. 1996); United States v.

Downing, 753 F.2d 1224, 1239 (3d Cir. 1985). "[T]he more qualified the expert, the more likely that expert is using reliable methods in a reliable manner-highly qualified and respected experts don't get to be so by using unreliable methods or conducting research in an unreliable manner." Malletier v. Dooney & Bourke, Inc., 525 F. Supp. 2d 558, 616 (S.D.N.Y. 2007).

Dr. Marx is the Chief of Oral and Maxillofacial Surgery and the Director of Research at the University of Miami School of Medicine. He serves as an editor or on the editorial review board of eight journals, including the New England Journal of Medicine and the Journal of Oral and Maxillofacial Surgery. He has published three textbooks on oral maxillofacial diseases, one of which won the American Medical Writers Best Book of the Year Award in 2002. He has contributed to over 31 other textbooks and authored or co-authored more than 55 peer-reviewed articles on topics including osteoradionecrosis, osteomyelitis, and "bisphosphonate-induced ONJ." He frequently is invited to medical conferences around the country to speak on the topic of ONJ. In September 2006, Merck's scientists invited him to be the featured speaker at an expert consultants meeting on the topic.

Dr. Goss is a Professor of Oral and Maxillofacial Surgery at the University of Adelaide, Australia, and serves as the Director of Oral and Maxillofacial Surgery at the largest

maxillofacial surgery facility in Adelaide. He has published approximately 200 peer-reviewed articles in his field, several of which are on the relationship between bisphosphonates and ONJ. He also has published a nationwide study sponsored by the Australian health authority on the prevalence of ONJ among bisphosphonate users. Since 2003, he has devoted about half of his research efforts to bisphosphonates and ONJ. He too was invited by Merck to the 2006 consultant's meeting on ONJ.

Dr. Hellstein is a Clinical Professor at the University of Iowa, College of Dentistry, where he is also the Director of the Surgical Oral Pathology Laboratory. He is board-certified in oral pathology. The American Dental Association ("ADA") selected him to serve on its Expert Panel on Oral Bisphosphonates, which was convened to study bisphosphonate-associated ONJ. Dr. Hellstein has published numerous book chapters and peer-reviewed articles in leading journals, including several on the relationship between bisphosphonates and ONJ. He too was invited by Merck to the 2006 meeting as an expert on ONJ.

(2) Clinical Experience

Dr. Marx has 25 years of clinical experience at a national referral center for complex oral maxillofacial pathologies. Over the years, he frequently has managed ONJ in patients suffering from osteoradionecrosis, osteopetrosis, and,

more rarely, osteomyelitis. (Marx Rep. ¶ 16.) Beginning in 1999, he began to receive far more referrals of patients with exposed necrotic jawbone, the cause of he could not identify. (Id. ¶ 26.) He ruled out radiation therapy, osteopetrosis, and chemotherapy as alternative causes. (Id. ¶¶ 26-28.) The condition did not respond to treatments that had been proven effective to treat other forms of ONJ, such as that seen with osteomyelitis. (Id. ¶ 28.) Dr. Marx realized that only patients taking a bisphosphonate developed this unexplained ONJ. (Id. ¶ 29.) He noted that the clinical presentation was nearly identical to the exposed necrotic bone seen with osteopetrosis. (Id.) It made sense to him that a therapy that inhibits osteoclast function would lead to a condition also found in individuals whose osteoclast function is impaired by a genetic disorder. (Id.) As of September 2008, Dr. Marx has diagnosed and treated a total of 182 cases of bisphosphonate-associated ONJ: 129 cases in patients using IV bisphosphonates, and 53 cases in patients using oral bisphosphonates. (Id. ¶ 38.)

Practicing in Australia, Dr. Goss had a similar experience. In 2003, he saw a small cluster of patients who had areas of dead jawbone that would not heal. (3/27/09 Goss Dep. Tr. at 17.) He determined it to be a new disease that he had never before seen in 43 years of practice. (Id. at 18, 81.) He realized that the common link among the cases was the use of a

bisphosphonate. (Id. at 17-18.) He has received communications from oral maxillofacial surgeons throughout the country describing a similar experience. (Id. at 86-87.) As of March 2009, he has seen approximately 100 cases of bisphosphonate-related ONJ, about half of which involved the use of oral bisphosphonates. (Id. at 81.)

Dr. Hellstein concurs that reports of ONJ have exploded in recent years and that the use of bisphosphonates is the only consistent factor in these cases. (Hellstein Rep. at 17-20.) He bases this upon his clinical and laboratory experience at the University of Iowa, discussions with colleagues, and review of medical and dental literature. Over his career, Dr. Hellstein has treated patients with exposed bone from radiation therapy, osteomyelitis and, more rarely, spontaneous sequestration. (Id. at 18-19.) He also has been referred patients with bisphosphonate-associated ONJ and has managed their treatment. (Id. at 4.) He finds that these cases differ in clinical features and course of healing from other forms of ONJ. (Id. at 12, 18-19.)

According to all three witnesses, bisphosphonate-associated ONJ is a distinct disease with a unique set of clinical features. Each describes the objective factors that permit him to distinguish and diagnose the disease. Namely, the area of exposed necrotic bone is very slow to heal or never

heals and is unresponsive or even worsened by surgical and other treatments that have proven effective on other forms of ONJ.

That bisphosphonate-associated ONJ can be specifically diagnosed appears to have attained some measure of consensus among practitioners. In 2006, the AAOMS drafted a working definition for "bisphosphonate-related ONJ ('BRONJ')" intended to "distinguish BRONJ from other delayed healing conditions." (DX 42.) The working definition has remained unchanged. One of the criteria for a BRONJ diagnosis is exposed bone that has persisted for more than 8 weeks. The paper also reports that patients with BRONJ respond less predictably to surgical treatment than patients with osteoradionecrosis or osteomyelitis.

Without citing any authority on oral pathology, Merck argues that these doctors are unable to tell the difference between bisphosphonate-associated ONJ and other conditions involving exposed bone and delayed healing. This argument appears to be contrary to the views of one of Merck's own scientists. In 2005, Dr. Kimmel, a researcher and a dentist, gave an internal presentation in which he stated that ONJ is "somewhat like osteoradionecrosis" but that it "seems unlike" other conditions, including osteomyelitis, although osteomyelitis can occur subsequent to ONJ. (PX 1.0579.) He also stated that, while there are risk factors for delayed healing

after a dental extraction, the delayed healing lasted only 2-4 weeks and never as long as 6 weeks. (Id.)

The Court finds that the clinical experience of the PSC's oral maxillofacial experts is highly indicative of the reliability of their opinions.

(3) Biologic Plausibility

Biologic plausibility is a judgment about whether an agent plausibly could cause a disease, based on existing knowledge about human biology and disease pathology. (Michael D. Green et al., Reference Guide on Epidemiology at 388 in Federal Judicial Center, Reference Manual on Scientific Evidence (2d Ed. 2000)). The parties agree that the significance of this factor increases when epidemiological evidence is lacking or inconclusive. (PSC Opp. Mem. at 43; Merck Reply Mem. at 19.) However, the parties argue two separate points to the issue.

On the one hand, the PSC's experts identify a biologically plausible mechanism through which Fosamax may cause ONJ. This mechanism, the over-suppression theory, is detailed in a 2006 article in the New England Journal of Medicine by one of Merck's experts, Dr. John Bilezikian:

If there is a relationship between bisphosphonates and osteonecrosis of the jaw, what might explain it? The jaw is often subject to spontaneous, local trauma as well as trauma caused by dental procedures. The mucosa of the mouth is very thin and may therefore permit unroofing of

the alveolar bone immediately beneath it when trauma or infection occurs. As potent inhibitors of osteoclast activity, the nitrogen-containing bisphosphonates might retard skeletal repair processes associated with trauma to or infection of the oral mucosa that involves the underlying bone. Since the jawbones are in constant use and are characterized by active remodeling, bisphosphonates might accumulate there preferentially, resulting in concentrations that exceed those found elsewhere in the skeleton.

(DX 47 at 2280.)¹⁰ This theory is widely reported in the scientific literature as a plausible explanation for bisphosphonate-associated ONJ. As recently described in an exhaustive review article, "Nearly every report and review of BRONJ points to bisphosphonate-induced remodeling suppression as a likely mechanism." (PX 2.1002.) The ADA's Expert Panel on Oral Bisphosphonates concluded that biologic plausibility pointed in the direction of causality because the "event is defined by the mechanism of action of the drug," i.e., the suppression of bone turnover. (PX 2.1015.) In internal emails in 2005, Dr. Kimmel wrote that the reduction of bone remodeling likely reduces the jaws' natural ability to heal, and that placing too much of a healing demand on them in patients treated

¹⁰ The article goes on to state that other potential mechanisms are the antiangiogenic properties of nitrogen-containing bisphosphonates and their effect on T-cells. Contrary to Merck's argument, the Court does not view the existence of several plausible mechanisms to undermine the PSC experts' opinions on causation.

with bisphosphonates can lead to the death of jawbone. (PX 1.0549 at p. 00093701; 1.0986 at p. 00004310.)

The PSC's experts identify animal studies that offer support for the over-suppression theory. These studies involved rats or dogs, animals that Merck's scientists recognize as providing relevant and reliable information about the human skeleton. (PX 3.0006: 47:2-51:1, 79:18-80:8; PX 2.0152 at pp. 12535, 12538). The studies find higher rates of bone turnover in the jaws, (PX 2.0162), that bisphosphonates suppress remodeling in the jaws more than in other bones (Id.); that Fosamax treatment prior to tooth extraction delays initial healing, (PX 2.1005.); that Fosamax increases the incidence of bone matrix necrosis in the jaws; (2.1004 at p.987); that Fosamax inhibits resorption of necrotic bone; and that high doses of a first-generation bisphosphonate combined with severe periodontal disease induces ONJ. (PX 2.0144.)¹¹ Given this evidence, the Court cannot accept Merck's characterization of the over-suppression theory as mere untested speculation. (Merck Reply Mem. at 19-20.) Merck also cites animal studies that seem to reach contrary conclusions. (Id. at 23 & nn. 18-19.)

¹¹ Analogy to the pathogenesis of ONJ with osteopetrosis lends further support for biologic plausibility. (Marx Rep. ¶ 29; Hellstein Rep. at 33.) As Merck's expert, Dr. Eisenberg explained, the mechanism by which exposed necrotic bone sometimes appears in osteopetrosis patients involves the suppression of osteoclast activity and loss of blood supply. (04/15/09 Eisenberg Dep. Tr. at 234:21-236:12; see also PX 2.1002 at p.64 (noting that patients with a certain type of osteopetrosis develop clinical features similar to the bisphosphonate-associated ONJ).)

The Court's gate-keeping role does not require it to weigh the conflicting studies.

At oral argument, Merck presented a collection of articles and position papers stating that the mechanism underlying bisphosphonate-associated ONJ remains unknown or unclear. For example, the same review article mentioned above states that "Despite this large volume of work, there remain few data yet many hypotheses concerning the underlying pathophysiology." (PX 2.1002.) Similarly, the ADA Expert Panel paper concludes that, "The pathophysiological link between bisphosphonates and the development of BON [bisphosphonate-associated ONJ] remains unknown." (PX 2.1015 at 11.) Dr. Hellstein is a co-author of the paper and conceded at deposition that the statement is accurate. (03/25/09 Hellstein Dep. Tr. at 304-06.)

That the mechanism remains unknown does not mean that the one proposed by the PSC's experts is not widely accepted as plausible. See In re Neurontin Mktg Sales Practices and Prods. Liab. Litig., 612 F. Supp. 2d 116, 149 (D. Mass. 2009) (finding that biologic plausibility supported opinion on causation despite the fact that there was "robust debate in the scientific community" on the proposed mechanism); In re PPA Prods. Liab. Litig., 289 F. Supp. 2d 1230, 1247 (W.D. Wash. 2003) ("The fact that the mechanism remains unclear does not call the reliability

of the opinion into question.”). The Court finds that the existence of a biologically plausible mechanism bolsters the reliability of the proffered opinions on causation. However, this mechanism should not be represented as a matter of scientific certainty. Any testimony about it will be admitted only if qualified in substance by a statement that it remains a theory that, subject to further testing, might be proved or disproved.

(4) Peer-reviewed Publications & Independent Research

All three of the PSC’s oral maxillofacial experts have published their views on the relationship between bisphosphonates and ONJ in peer-reviewed articles appearing in top medical, dental, and oral maxillofacial journals. “That the research is accepted for publication in a reputable scientific journal after being subjected to the usual rigors of peer review is a significant indication that it is taken seriously by other scientists, i.e., that it meets at least the minimal criteria of good science.” Daubert v. Merrell Dow Pharmaceuticals, Inc. (“Daubert II”), 43 F.3d 1311, 1318 (9th Cir. 1995). In 2003, after accumulating the first 36 cases of ONJ in IV bisphosphonate patients, Dr. Marx reported his findings in an article published in the Journal of Oral and Maxillofacial Surgery. (Marx Rep. ¶ 34). He described it as an unrecognized

and unreported serious adverse effect of IV bisphosphonate treatment. (Id.) Since then, he has published at least six other articles in refereed journals and one textbook expressing the view that both IV and oral bisphosphonates cause ONJ. (Marx Rep. Ex. A.)

Similarly, after seeing his first small cluster of patients, Dr. Goss published letters to the editors of the Australian Dental Journal and the Australian Prescriber warning about a possible association between ONJ and bisphosphonate use. (3/27/09 Goss Dep. Tr. at 20.) He conducted and published a nationwide prevalence study that was sponsored by the Australian health authority. He has since authored or co-authored numerous articles on the relationship between bisphosphonates and ONJ, several of which have appeared in peer-reviewed journals. (Goss Rep. ¶ 5.) Likewise, Dr. Hellstein has published several peer-reviewed articles on the subject, in addition to his work on the ADA Expert Panel. (Hellstein Rep. at 6-7.) The Court finds that the peer-review process lends credibility to their opinions.

Also significant is the fact that the experts focused their research and published their views on the relationship between bisphosphonates and ONJ independently of litigation. "That the testimony proffered by an expert is based directly on legitimate, preexisting research unrelated to the litigation provides the most persuasive basis for concluding that the

opinions he expresses were 'derived by the scientific method.'" Daubert II, 43 F.3d at 1317 (9th Cir. 1995).¹²

(5) Case Reports, Case Series, and Adjudicated Adverse Event Reports

Case reports lack controls and therefore provide less information on causation than controlled studies. Mary Sue Henifin et al., Reference Guide on Medical Testimony at 633-34 in Ref. Manual on Scientific Evid., supra. "Causal attribution based on case studies should be viewed with caution. However, such studies may be carefully considered in light of other information available." Id. Moreover, a large number of case reports adds greater weight to the reliability of an opinion on causation. See In re PPA, 289 F. Supp. 2d at 1242 (finding "significant the sheer volume of case reports, case series and spontaneous reports associating PPA with hemorrhagic stroke to women"); Rider v. Sandoz Pharms. Corp., 295 F.3d 1194, 1202 (11th Cir. 2002) (stating in dicta that reliable evidence on causality includes, inter alia, "a very large number of case reports.").

¹² Merck points out that Dr. Marx first began meeting with plaintiffs' lawyers back in 2005, before he published his first case series of patients who developed ONJ with oral bisphosphonate use. (Merck Reply at 2 n.3.) While this might provide fodder for cross-examination, the inference of bias is undercut by the extent of his work before and since then and by the fact that the fees he earns as an expert witness go directly to the University of Miami.

Since 2004, there have been roughly 60 published reports of ONJ in patients treated with oral bisphosphonates. Many contain details about dosage, duration of use, concomitant medications, co-morbid conditions, and prior dental procedures, trauma, or infection. (See, e.g., PX 2.1018; PX. 2.0252). In addition, as of May 2008, Merck has received at least 1400 spontaneous reports of ONJ. Merck points out that the majority of these reports are unconfirmed and generated by the filing of lawsuits. In 2006, however, Merck adjudicated roughly 350 reports that it had received by then and verified that most of them were highly likely cases of ONJ. (PX 3.0006: 361:10-370:20; PX 1.2218, at pp. 837-38).

Additionally, there have been hundreds of published case reports of ONJ in IV bisphosphonate users, plus a few retrospective studies finding a strong association. Merck correctly notes that the IV bisphosphonates are more potent, administered in higher doses, and better absorbed than oral bisphosphonates. However, these distinctions might also suggest a dose-response relationship, which would tend to support causality. Merck also points out that IV bisphosphonates generally are used by cancer patients with co-morbidities and concomitant treatments that predispose them for ONJ. This difference, though important, does not completely undermine the reliability of extrapolating among nitrogen-containing

bisphosphonate drugs, all of which suppress bone turnover through the same mechanism of action. Merck also argues that ONJ has been reported in the absence of bisphosphonate therapy, but can point to relatively few involving non-irradiated patients in the medical literature over several decades. (See Merck Br. at 10 & n.6.) For example, one report cites a literature review finding 20 cases of ONJ reported with herpes zoster between 1955 and 1999. (DX 33.)

The Court finds that the relatively high number of recent ONJ reports, almost exclusively involving bisphosphonate use, confirms the clinical experience of the PSC's oral maxillofacial experts, and adds to the reliability of their opinions.

(6) Prevalence Studies

The experts also point to studies calculating the prevalence of ONJ among populations of oral bisphosphonate users. First, in 2007, Dr. Goss published a study sponsored by the Australian health authority calculating the nationwide prevalence of ONJ in IV and oral bisphosphonate users. (PX 2.0348.) The rate of ONJ in osteoporotic patients on oral bisphosphonates was between 1 in 2,260 to 8,470 (0.01% to 0.04%). For those who had dental extraction, the rate was 1 in 296 to 1,130 (0.09% to 0.34%).

The first large study in the United States was conducted by researchers at the University of Southern California ("USC"). (PX 2.085.) Published in early 2009, the USC study found 9 cases of ONJ among 208 patients with a history of Fosamax. All cases presented after a tooth extraction or dental trauma. The study found no ONJ cases among 13,522 patients without a history of Fosamax use, including 4,348 who had a dental extraction. According to the study, these "findings indicate[] that even short-term use of oral alendronate can lead to ONJ in a subset of patients after dental procedures such as extractions." (Id. at 66.) Most recently, an FDA-approved study by Kaiser Permanente, called the Predicting Risk of Osteonecrosis with Bisphosphonate Exposure ("PROBE") Study, calculated the prevalence of ONJ among oral bisphosphonate users to be 1 in 1,110, or 0.09%. (PX 2.1016.)

The Court appreciates the limitations of these studies. They do not compare the calculated rates against a control group of non-bisphosphonate users. Therefore, they provide no statistical evidence that oral bisphosphonate use increases the risk of ONJ. Their results take on greater significance in view of the rarity of ONJ, however. Merck has sought to ascertain the background rate of ONJ in the general population but was informed by expert consultants that it is essentially zero except in cases of radiation therapy and a few

serious diseases. (PX 1.0026; 3.0003: 229:9-231:9.) The prevalence rates found among persons with osteoporosis offer circumstantial support for the view that oral bisphosphonates increase the risk.

(7) Journal Articles and Position Papers

Dr. Marx notes that, since 2003, there have been over 400 published articles in refereed scientific journals addressing bisphosphonate-related ONJ. (Marx Rep. ¶ 37.) In his report, he quotes from a few that tend to support his views on causation. (Id. ¶¶ 49-51.) For example, one article states that, "Although the association between osteonecrosis of the jaw and bisphosphonates had been called into question, the sheer number of cases reported since the widespread use of bisphosphonates began, as well as the mode of action of this class of drugs, lend support to the view that there is a real and probable causal relationship." (Id. ¶ 49.) Similarly, Dr. Hellstein has surveyed the medical and dental literature on bisphosphonate-associated ONJ and has found several hundred articles published since the initial reports in 2003. (Hellstein Rep. at 17 & Ex. D). Likewise, Dr. Goss relies upon the published scientific literature in forming his opinion. (Goss Rep. ¶ 12 & Ex. D.)

As noted above, numerous medical, dental, and oral maxillofacial associations have commissioned expert panels to

study the topic of bisphosphonate-related ONJ. Most have concluded that more evidence is needed in order to establish a causal relationship. For example, the updated AAOMS position paper recently concluded that "the current level of evidence does not fully support a cause-and-effect relationship between bisphosphonate exposure and necrosis of the jaw." (AAOMS 2009 Position Paper (DX 42); see also Canadian Consensus Practice Guidelines (DX 43) (stating that "the relationship between bisphosphonate use and ONJ in the patient with osteoporosis remains unproven"); ASBMR Task Force Report (DX 40) (stating that "bisphosphonates have not proven to be causal").

Even Merck's experts have testified, however, that these papers result from a compromise of views and do not purport to speak for all members of the associations. (PX 4.0001: 211:10-212:21.) For example, the Chair of the AAOMS Task Force has testified in the Aredia/Zometa MDL that all bisphosphonates, including Fosamax, cause ONJ. (PX 8.0007: 38:13-38:19) In addition, Dr. Marx is a member of the AAOMS and published an article in the Journal of Oral Maxillofacial Surgery criticizing the task force's position that more epidemiological evidence is needed. (PX. 2.1012).

Furthermore, Merck does not account for the fact that expert panels of other respectable organizations have reached a different consensus. The ADA Expert Panel on Oral

Bisphosphonates recently published that, "[t]hough it is early in the investigative stage, the relationship between bisphosphonate exposure and the occurrence of osteonecrosis of the jaw appears to be consistent with Bradford-Hill's criteria for causality." (PX 2.1015 at p.8.) Similarly, the American Academy of Endodontists' Special Committee on Bisphosphonates advises its membership to "consider all patients taking bisphosphonates to be at some risk for ONJ," at least until "further information is available." (PX 2.1013 at p.2.). The American Academy of Oral Medicine Position Paper states that "[t]here is strong evidence that bisphosphonate therapy is the common link in patients with BON [bisphosphonate-associated ONJ]" and that both IV and oral bisphosphonate users are at risk. (PX 2.0338 at p. 1658.) This suggests that the opinions of the PSC's experts, though not generally accepted at this time, at least lay within the range where experts may reasonably differ. They certainly cannot be considered "junk science."

(8) Animal Studies

"Animal studies have the advantage of being able to be conducted as true experiments, with exposure controlled and measured. However, extrapolation from animal studies to humans entails some risks, as physiological differences and dosage differences can complicate comparisons." In re Neurontin, 612 F. Supp. 2d at 127. The PSC's experts identify a rat and a dog

study in which a bisphosphonate induced a form of jaw necrosis. A 1981 study published in the Journal of Periodontal Research found that high doses of clodrenate, a first-generation bisphosphonate, induced ONJ in rice rats with periodontal disease. (PX 2.0144.) In its Daubert motion, Merck points out that rice rats experience a particularly aggressive form of periodontal disease. However, Dr. Kimmel has suggested internally that, when a severe form of periodontitis in humans intersects with IV or oral bisphosphonate treatment, "ONJ is a high risk outcome". (PX 1.0412.) Merck also points out that clodronate is a non-nitrogen-containing bisphosphonate. Nevertheless, the Court finds there is adequate "fit" because all bisphosphonates have the primary effect of inhibiting bone resorption.

The second study, published in the Journal of Oral Maxillofacial Surgery in 2008, concluded that three years of daily Fosamax treatment in beagles significantly reduces bone turnover in the mandible and increases the incidence of matrix necrosis. (PX 2.1004.) As Merck points out, the beagles did not develop exposed necrotic bone and the connection between matrix necrosis and ONJ remains unclear. The study hypothesizes that matrix necrosis represents an early stage of ONJ that can become exposed after tooth extraction or periodontal disease. The Court finds that the gap here is not so great as to render the

study irrelevant, as Merck argues.

By themselves, these animal studies would not provide enough support for the conclusion that Fosamax can cause ONJ. Nonetheless, they serve as pieces of the scientific puzzle that contribute to the reliability of the experts' opinions.

In sum, the Court finds that the above factors, taken together, establish under Rule 702 that the general causation opinions of Drs. Marx, Goss, and Hellstein are sufficiently reliable for the jury to consider as evidence at trial.¹³

ii. Dr. Etminan

The PSC has not shown that Dr. Etminan reached his general causation opinion in this case by applying the same level of intellectual rigor that characterizes his work as an epidemiologist in the field. Therefore Merck's motion to exclude his testimony on general causation is GRANTED.

Epidemiology is the study of the relationship between exposures and diseases in large populations. Reference Guide on Epidemiology, supra, at 333, 337, 348. The first step in establishing causation in epidemiology is showing that the exposure is associated with the disease. Id. An association exists when the exposure and the disease occur more frequently together than one would expect by chance. Id. at 348.

¹³ Merck also raises several issue- or expert- specific challenges to the testimony of these witnesses. These challenges are addressed below.

Epidemiological studies frequently express the existence and strength of an observed association between exposure and disease as "relative risk." Id. If the relative risk is greater than 1.0, then there is a positive association because the risk in the exposed individuals or group is greater than the risk in unexposed individuals or groups. Id. at 349. Where there is a positive association between the exposure and disease, epidemiologists consider further whether the association represents a causal relationship between exposure to the agent and the disease. See id. at 348-49, 374-75. However, "epidemiology cannot objectively prove causation; rather causation is a judgment by epidemiologists and others interpreting epidemiological data." Id. at 374.

To assess causality, epidemiologists often apply a set of considerations described by Sir Austin Bradford Hill in a famous 1965 lecture, the Environment and Disease. The "Bradford Hill" factors are as follows: (1) strength of the association; (2) consistency; (3) specificity of the association; (4) temporality; (5) dose-response curve; (6) biological plausibility; (7) coherence (with other knowledge); (8) experiment; and (9) analogy.

In his report, Dr. Etminan arrives at his general causation opinion after applying a Bradford Hill analysis based upon his review of much of the evidence described above-case

reports, case series, prevalence studies, and animal studies. This is not the methodology that he usually follows in his professional work. He testified that his expertise is in observational epidemiology. (07/09/09 Hrg Tr. at 88.) His work focuses on conducting controlled studies using large administrative databases to determine the relative risk between an exposure and a rare adverse event. (Id. at 88-89; Etminan Rep. at 1.) In an article published early in his career, titled Evidence-Based Pharmacotherapy, he explained that controlled studies are useful for generating hypotheses only, not for determining causation, and that case reports and case series could not even generate hypotheses. (Hrg. DX A at p. 1194.)

Dr. Etminan has never written a paper applying the Bradford Hill factors because the drug safety questions that he has considered had "more detailed scientific evidence." (07/09/09 Hrg Tr. at 21-22.) He has not received any formal training in the application of the Bradford Hill factors. (Id. at 22; 60-61.) He asserts that training is not necessary because the factors are very simple to apply. (Id. at 60-61.) Despite his usual preference for more detailed evidence, he testified that, in forming his opinion in this case, he did not consider a controlled database study finding no association between oral bisphosphonates and adverse jaw outcomes. (Id. at 76, 79-80, Hrg. DX 5.)

According to Dr. Etminan, the Bradford Hill factors "set the minimal criteria for causal association" and are applicable in "situations where basically you are only left with case reports." (07/09/09 Hrg. Tr. at 19, 23.) This understanding seems to be contradicted by the text he described at his deposition as the "holy grail" of epidemiology textbooks, Rothman's Modern Epidemiology. (Id. at 54-58; Hrg. DX C.) It states that the factors are meant to be used to "distinguish causal from non-causal associations that were already 'perfectly clear-cut and beyond what we would care to attribute to the play of chance.'" (Hrg. DX C. at 26.) When confronted with this at the hearing, Dr. Etminan stated that it is correct, but only "if you're reading Rothman." (07/09/09 Hrg. Tr. at 56.) He claimed to have found support for his methodology in another text and referred to this new one as the "holy bible" of epidemiology. (Id. at 49.) But at the time of his deposition, he could not cite any authority stating whether it was appropriate to apply the Bradford Hill factors in cases where, as here, no epidemiological study has demonstrated an association between the drug and the disease. (03/17/2009 Etminan Dep. Tr. at 159.)

Several courts that have considered the question have held that it is not proper methodology for an epidemiologist to apply the Bradford Hill factors without data from controlled studies showing an association. See In re Neurontin, 612 F.

Supp. at 127; Dunn v. Sandoz Pharms. Corp., 275 F. Supp. 2d 672, 678 (M.D.N.C. 2003) (collecting cases). The record here is inconclusive on this point. Nevertheless, every indication is that Dr. Etminan applies in his own work a more rigorous methodology before making causal determinations than he has in forming his opinions in this case.¹⁴ Therefore, testimony from him on general causation is excluded.

The Court finds that Dr. Etminan's testimony on the limitations of clinical trials in detecting rare adverse events is reliable and would help the jury understand some of the evidence. Therefore, his testimony on this sole issue is admissible.

2. Motion to Exclude Dr. Suzanne Parisian

Dr. Suzanne Parisian is a board-certified Anatomic and Clinical Pathologist with a Master's Degree in Biology. From 1991 to 1995, she served as a Medical Officer with the FDA's Center for Devices and Radiological Health ("CDRH"). Since then, she has worked as a regulatory and medical consultant at a firm she founded.

Dr. Parisian's voluminous report of 143-pages is

¹⁴ Other statements by Dr. Etminan suggested a lack of expertise with the methodology he was applying. He referred to the "Brad Hill" factors in his report, (Etminan Rep. at 10); seemed uncertain whether there were 8, 9, or 10 factors, (07/09/09 Hrg. Tr. at 23); and recalled that he probably downloaded them from the internet to prepare his report. (*Id.* at 57.) The real issue though is the fact that Dr. Etminan seems to demand a higher level of epidemiological proof before making causal determinations in his professional work than he has in this case.

divided into four sections: (1) the general role of the FDA and the duties and obligations of prescription drug manufacturers; (2) the FDA's approval of the New Drug Application ("NDA") for Fosamax; (3) Merck's interactions with the FDA in reporting and investigating ONJ; and (4) Merck's communication of ONJ risks to health care professionals and patients. At the beginning of each section, she expresses a number of opinions as to the ways in which Merck's conduct failed to measure up to standards. (See Parisian Rep. at 8-10 (listing the opinions). The sections then extensively summarize or quote the record evidence that provides the bases for her opinions.

a. Merck's Position

Merck first claims that Dr. Parisian is not qualified to offer the opinions in her report. According to Merck, Dr. Parisian lacks expertise to opine on FDA regulations for pharmaceutical drugs, about Merck's duty of care as a pharmaceutical company, and about the labeling or promotion of Fosamax. Merck points out that she worked at the FDA for less than five years and claims that her experience was confined to medical devices, not pharmaceutical drugs. Merck also claims that she is unqualified to speak about medical issues like osteoporosis, ONJ, or bisphosphonates because she does not treat patients and has never performed research in these areas.

Second, Merck claims that Dr. Parisian's testimony consists of nothing more than her personal views on the weight of the evidence based upon a selective reading of the documents provided to her by plaintiff's counsel. As such, Merck contends, her testimony is excludable because it is not based on any valid methodology, supplants the role of plaintiff's counsel to make arguments at trial, and invades the province of the jury to weigh the evidence.

Third, Merck contends that Dr. Parisian's testimony about ethical issues or about Merck's state of mind, knowledge or intent is inadmissible. There is no scientific methodology or specialized knowledge that enables or qualifies a witness to determine the intent or knowledge of a pharmaceutical corporation, Merck contends. Such testimony also invades the province of the jury to determine intent.

Merck next claims that Dr. Parisian's opinion that Merck violated FDA regulations, about the FDA's purposes when it took various regulatory acts, and about the FDA's ability to carry out its regulatory mandate is inadmissible. Merck claims that such testimony will not be helpful both because it infringes upon the Court's role in instructing the jury on the law and also because it injects irrelevant issues into the case.

Finally, Merck claims that Dr. Parisian's testimony should be excluded under Rule 403. Merck asserts that her

personal views on the evidence and her speculation as to Merck's intent, presented under the guise of expert opinion, would be powerfully misleading. Such testimony lacks probative value because the jury can draw its own conclusions from the evidence to the extent it is admissible.

b. PSC's Position

The PSC first responds that, in her capacity as an FDA Medical Officer, Dr. Parisian gained expertise in various aspects of the regulatory process, including health risk assessment, product labeling and promotion, pre-marketing evaluation of product applications and clinical data, and post-marketing surveillance and compliance. The FDA relied on her to interpret the food and drug laws on medical devices, to train other employees, to represent the FDA in an administrative hearing, and to serve as the official agency representative at medical meetings and seminars. With respect to Merck's claim that her experience is limited to medical devices, the PSC points out that she worked on numerous projects involving both devices and drugs. The PSC also contends that the regulations governing the two products are similar. The fact that Dr. Parisian does not treat patients or specialize in ONJ is irrelevant, the PSC claims, because she does not offer an opinion on causation.

Next, the PSC contends that expert testimony is necessary to educate the jury on the complex regulatory requirements that bear upon a pharmaceutical company's duty of care. In reviewing the New Drug Application ("NDA") for Fosamax and Merck's internal company documents to assess compliance, Dr. Parisian employed the same methodology as she did at the FDA. Furthermore, according to the PSC, the documents she would review at trial are complicated, and the inferences that may be drawn from them are not simple. Therefore, her expert analysis is necessary to help the jury understand the evidence.

Finally, the PSC disputes Merck's claim that Dr. Parisian offers testimony on matters of ethics and Merck's state of mind. According to the PSC, she is testifying as to the standard of care of a pharmaceutical company in Merck's position and what Merck should have known in light of the information available to it. The PSC asserts that an expert may testify as to what a prudent pharmaceutical company would do and how Merck's actions measure up to that standard.

c. Court's Ruling

The Court finds that Dr. Parisian is qualified based upon her experience as a Medical Officer at the FDA to offer testimony about regulatory requirements relating to the development, testing, marketing, and surveillance of prescription drugs. As noted above, qualification is viewed

liberally and may be based on a broad range of skills, knowledge, training, and experience. In re TMI Litig., 193 F.3d at 664; In re MTBE, 2008 WL 1971538, at *5. Dr. Parisian's time at the FDA, though primarily spent on medical devices, included sufficient experience with various aspects of the regulation of pharmaceutical drugs. Moreover, in her report and at the Daubert hearing, she demonstrated specialized knowledge about the standards applicable to drug manufacturers.

The Court further finds that Dr. Parisian has followed an appropriate methodology. An expert is permitted to draw a conclusion from a set of observations based on extensive and specialized experience. In re MTBR, 2008 WL 1971538, at *6 (citing Kumho Tire, 526 U.S. at 156) Here, Dr. Parisian has drawn conclusions about Merck's conduct based on her review of pertinent portions of the regulatory filings for Fosamax and Merck's internal company documents. This is the methodology she applied as a Medical Officer, and Merck's regulatory experts have followed the same methodology to prepare their reports. (07/10/09 Hrg Tr. at 188-190, 250.)

To the extent Merck seeks to preclude Dr. Parisian from testifying about general FDA regulatory requirements and procedures or offering an opinion as to Merck's compliance therewith, the motion is DENIED. A lay jury cannot be expected to understand the complex regulatory framework that informs the

standard of care in the pharmaceutical industry. Dr. Parisian's assessment of the reasonableness of Merck's conduct in light of her experience and her understanding of FDA regulations will be helpful to the jury.¹⁵ An expert may offer testimony embracing an ultimate issue of fact that the jury will decide. Fed. R. Evid. 704(a).¹⁶ Cross-examination and competing expert testimony

¹⁵ See Reece v. Astrazeneca Pharmaceuticals, LP, 500 F. Supp. 2d 736, 744 (S.D. Ohio 2007) (admitting Dr. Parisian's expert testimony on "the regulations governing the approval, labeling, advertising and marketing of pharmaceutical and medical products; the processes by which the FDA determines the efficacy and safety of new drugs and new drug applications; the issues the FDA considers in the development of product labeling and marketing information; and a manufacturer's responsibility within this system"); Lillebo v. Zimmer, Inc., No. 03-2919 (JRT/FLN), 2005 WL 388598, at *5 (D. Minn. Feb. 16, 2005) (allowing Dr. Parisian "to testify to the general nature of the approval and regulatory process, the FDA's general expectations with respect to testing and marketing of new products, Zimmer's actions in that respect, and Parisian's opinion as to whether those actions were reasonable or appropriate," but not permitting her to detail specific FDCA and FDA standards); In re Guidant Corp. Implantable Defibrillators Prods. Liab. Litig., 2007 WL 1964337 (D. Minn. June 29, 2007) (admitting similar testimony from Dr. Parisian); see also American Home Assur. Co. v. Merck & Co., Inc., 462 F. Supp. 2d 435, 451 (S.D.N.Y. 2006) (permitting Merck to introduce expert testimony on proper interpretation of FDA regulations as they relate to licensing of vaccines because "testimony on these complex regulatory provisions will assist the trier of fact").

¹⁶ The Court disagrees with Merck that expert testimony about FDA regulations and procedures would "usurp either the role of the trial judge in instructing the jury as to the applicable law or the role of the jury in applying that law to the facts before it." United States v. Bilzerian, 926 F.2d 1285, 1294 (2d Cir. 1991). This principle is invoked to exclude expert testimony about the applicable law that governs the case. See, e.g., United States v. Scop, 846 F.2d 135, 139-40, modified, 856 F.2d 5 (2d Cir.1988) (in criminal prosecution for violation of securities laws, overruling admission of expert's testimony that defendants' conduct amounted to a manipulative fraudulent scheme within the meaning of the securities laws); Marx & Co., Inc. v. Diners' Club, Inc., 550 F.2d 505, 510-11 (2d Cir. 1977) (in dispute over whether defendant breached its contractual obligation to use best efforts, overruling admission of expert's interpretation of the meaning of best efforts within the contract); F.A.A. v. Landy, 705 F.2d 624, 632 (2d Cir. 1983) (in action seeking penalties for violation of airline regulations, affirming exclusion of expert's testimony about the meaning and applicability of

by Merck's regulatory experts will ensure that the jury carefully weighs her testimony.

Some opinions in Dr. Parisian's report are too conclusory or insufficiently based on expertise or analysis to be admitted. She asserts that "Merck failed to adequately disclose to physicians its use of ghostwriters to generate articles favorable to Merck." (Parisian Rep. ¶¶ 233-34.) At the hearing, she could not name any standard that prohibits such a practice, as long as the information presented is accurate. (07/10/09 Hrg. Tr. at 210-11.) She also asserts that "Merck attacks the credibility of physicians not favorable to Merck," but this statement is based upon a single email exchange between Merck employees. (Id. ¶ 233-34.) These are not expert opinions but mere "bad company" testimony with marginal relevance to the issues in controversy. If other opinions are shown at trial to be insufficiently based on expert analysis, they will be excluded.

To the extent Merck's motion seeks to preclude Dr. Parisian from offering a narrative history of Fosamax, it is GRANTED in PART. "[A]n expert cannot be presented to the jury

airline regulations). The cases in this MDL are not governed by federal regulations but by state law theories of negligence and strict liability. Expert testimony on regulatory compliance will assist the jury in determining whether Merck acted as a reasonably prudent pharmaceutical manufacturer. The Court will instruct the jury that it must take the law from the Court and not from any witness.

solely for the purpose of constructing a factual narrative based upon record evidence." Highland Capital Management, L.P. v. Schneider, 379 F. Supp. 2d 461, 469 (S.D.N.Y. 2005); Taylor v. Evans, 1997 WL 154010, at *2 (S.D.N.Y. Apr. 1, 1997) (rejecting portions of expert report on the ground that the testimony consisted of "a narrative of the case which a lay juror is equally capable of constructing"); In re Rezulin Products Liab. Litig., 309 F. Supp. 2d 531, 546 (S.D.N.Y. 2004) (rejecting portion of expert report presenting history of Rezulin for no purpose but to "provid[e] an historical commentary of what happened"). In detailing the factual basis for her opinions, Dr. Parisian's report presents a narrative of select regulatory events through the summary or selective quotation from internal Merck documents, regulatory filings, and the deposition testimony of Merck employees. The Court agrees with Merck that, to the extent such evidence is admissible, it should be presented to the jury directly. Dr. Parisian's commentary on any documents and exhibits in evidence will be limited to explaining the regulatory context in which they were created, defining any complex or specialized terminology, or drawing inferences that would not be apparent without the benefit of experience or specialized knowledge. She will not be permitted to merely read, selectively quote from, or "regurgitate" the evidence. In re Prempro Prods. Liab. Litig., 554 F. Supp. 2d

871, 880, 886 (E.D. Ark. 2008) (overturning a punitive damages award based on Dr. Parisian's testimony in part because she "did not explain the documents, provide summaries, or tie them in to her proposed regulatory testimony" and "did not provide analysis, opinion, or expertise").

To the extent Merck's motion seeks to preclude Dr. Parisian from testifying as to the knowledge, motivations, intent, state of mind, or purposes of Merck, its employees, the FDA, or FDA officials, it is GRANTED. Dr. Parisian conceded at the hearing that her regulatory expertise does not give her the ability to read minds. Nevertheless, her report is replete with such conjecture. This is not a proper subject for expert or even lay testimony. See In re Rezulin, 309 F. Supp. 2d at 546 (stating that "the opinions of [expert] witnesses on the intent, motives, or states of mind of corporations, regulatory agencies and others have no basis in any relevant body of knowledge or expertise"); In re Diet Drugs Prods. Liab. Litig., MDL No. 1203, 2000 WL 876900, at *9 (E.D. Pa. June 20, 2000) (same).

To the extent Merck challenges Dr. Parisian's testimony on Rule 403 grounds, the Court believes that the above restrictions will minimize unfair prejudice or the danger of confusion. Therefore, the motion is DENIED.

As a caveat, Dr. Parisian's report discusses events

occurring over a wide span of time. The portions of her testimony relevant in any particular case likely will depend on the dates of the plaintiff's alleged ingestion of Fosamax and onset of ONJ. Thus, transferor courts will have to determine what portions of her testimony fit the facts of the specific cases before them.

3. Motion to Exclude Dr. Curt D. Furberg

Dr. Curt D. Furberg is a medical doctor admitted to practice in Sweden and a Professor of Public Health Sciences at Wake Forest University School of Medicine. He has served as an investigator on over 50 clinical trials, including the Fracture Intervention Trial ("FIT") trial that led to Fosamax's approval. The PSC has designated Dr. Furberg as an expert on clinical trials and drug safety. The first part of his report describes general industry standards governing the conduct of clinical trials and the reporting of safety information. (Furberg Rep. ¶¶ 21-28) He then opines that Merck failed to actively pursue emerging safety signals through research of analysis of available databases; denied evidence and ignored advice by expert that Fosamax causes ONJ; has refused to broadly inform physicians and patients about the risk of ONJ; and aggressively promotes Fosamax even for off-label use.¹⁷ He also would testify

¹⁷ Near the end of his report, in a section called "Sponsor's Failures," Dr. Furberg lists specific things that Merck allegedly failed to do properly with respect to monitoring, warning, and promotion.

about the limitations of clinical trials in detecting rare and unexpected adverse events.

a. Merck's Position

Merck first claims that Dr. Furberg has withdrawn many of the opinions in his report because, at deposition, he allegedly admitted that he lacked the expertise to offer them. According to Merck, Furberg and/or his counsel stated that Furberg was not an expert on interpreting animal studies; the biology of the jaw, osteoporosis, or ONJ; regulatory affairs; or drug labeling, marketing or promotion. Therefore, Merck argues, Furberg cannot opine on alleged failures in pursuing safety signals raised in animal studies; the inadequacy of the clinical trials for Fosamax; its violation of FDA regulations; or its improper promotion, marketing, or labeling of the drug.

Next, Merck reasserts several of the challenges it raised to Parisian's testimony, claiming that Furberg (1) merely presents personal views in the guise of a narrative history based on a selective reading of the evidence; (2) offers opinions on matters of ethics or Merck's knowledge, motive, or

(Furberg Rep. ¶ 58(a)-(n)) At the hearing, the PSC stated that he would not be offering two of those opinions at any trial. (Id. ¶ 58(e) (stating that Merck "failed to accept promptly FDA's request for a class label change"; (1) (stating that Merck "fail[ed] to warn prescribers and patients about the ONJ risk in the drug label). In addition, parts of Dr. Furberg's report contain the implicit or express opinion that Fosamax causes ONJ. (See, e.g., id. ¶¶ 30, 44, 60.) The PSC states that Dr. Furberg will not offer his opinion on general causation at any trial.

intent; and (3) invades the province of the judge by testifying about FDA regulations and Merck's noncompliance therewith, and (4) the testimony should be excluded under Rule 403. Merck also points out that similar testimony by Dr. Furberg was excluded in the Rezulin litigation.

b. PSC's Position

The PSC claims that Dr. Furberg's three decades of expertise in the fields of clinical trials, drug safety, and public health qualifies him to offer the opinions in his report. His experience includes service on the safety monitoring boards of over fifty clinical trials sponsored by government entities and pharmaceutical companies and his testimony before Congress on drug safety issues on two occasions. According to the PSC, Dr. Furberg need not be an expert in the specific area of bisphosphonates or ONJ because he has evaluated clinical trials for many types of drugs. Similarly, he need not be an expert on drug labeling to interpret clinical trial data and opine on whether it was clearly and accurately conveyed in a drug's label. Finally, he need not be an expert in interpreting animal studies to opine that Merck should have pursued safety signals from the 1981 rat study to inform their human trials.

Next, the PSC argues that testimony about the duty of care and the reasonableness of a pharmaceutical company's actions is necessary to educate the jury on this complex issue.

Industry standards and how a defendant's actions measure up against those standards are not mere "personal opinions" but are a proper subject for expert testimony, the PSC claims.

Finally, the PSC asserts that Dr. Furberg's testimony with respect to the limitations of clinical trials is unchallenged by Merck. In its reply, Merck clarifies that it does in fact challenge Dr. Furberg's qualifications to opine on Merck's conduct of the clinical trials because he has no expertise in the field of bone metabolism, osteoporosis, bisphosphonates, or ONJ.

c. Court's ruling

The Court finds that Dr. Furberg's extensive experience as a clinical trial investigator qualifies him to offer some of the testimony in his report. He may testify about the utility and limitations of clinical trials with respect to obtaining information about drug efficacy and safety. In addition, his review of the published data from Merck's clinical trials and his experience in the field qualify him to interpret that data as it relates to the efficacy and safety of Fosamax treatment.

To the extent Merck challenges testimony about purported general ethical standards governing the conduct of clinical trials, Merck's motion is GRANTED. In the first section of his report, Dr. Furberg references authorities such

as the 1964 Declaration of Helsinki as providing generally accepted international standards such as "The health of my patient will be my first consideration." (Furberg Rep. ¶ 23, see also id. ¶ 59 (stating that "[t]rust and honesty are essential virtues that permeate all aspects of human life, including the drug approval process"). As Judge Kaplan held in Rezulin, such standards are "so vague as to be unhelpful to a fact-finder." 309 F. Supp. 2d at 543, 545 n. 37 (excluding similar ethics testimony by Dr. Furberg).

To the extent Merck challenges testimony by Dr. Furberg about Merck's alleged failure to pursue safety signals, the motion is GRANTED in PART. Dr. Furberg's opinion that Merck should have followed up on the 1981 rat study involving clodronate lacks an adequate foundation because he does not know what types of animal testing Merck conducted with Fosamax. (07/10/09 Hrg. Tr. 293-95.) Similarly, his opinion regarding Merck's failure to report a 2002 ONJ case from Japan is unreliable because he does not even know when that report was sent to Merck. (Id. at 304-305.) He may offer testimony about the adequacy of Merck's response to the other safety signals identified in his report insofar as such testimony is relevant and admissible in specific cases.

To the extent Merck challenges testimony by Dr. Furberg about regulatory standards or alleged regulatory

violations by Merck, the motion is GRANTED. Counsel for the PSC has stated on several occasions that Dr. Furberg is not being proffered as a regulatory expert. Despite this, his report contains numerous references to FDA regulations and assertions that Merck failed to comply with them.¹⁸ At oral argument, counsel for the PSC confirmed that these opinions are withdrawn. (07/16/09 Hrg. Tr. at 429-430.)

To the extent Merck's motion seeks to preclude Dr. Furberg from speculating about the knowledge, motivations, intent, state of mind, or purposes of Merck, its employees, the FDA, or FDA officials, it is GRANTED. As discussed above, this is not an appropriate subject for expert testimony.

To the extent Merck seeks to preclude Dr. Furberg from testifying about Merck's promotion or marketing of Fosamax, the motion is GRANTED. At the Daubert hearing, Dr. Furberg admitted that he is not an expert on marketing, but stated that he was exposed to it and "can have opinions without being an expert" on the subject. (07/10/09 Hrg. Tr. at 301-02.) His non-expert opinions are not admissible.

¹⁸ See, e.g., Furberg Report ¶ 26 ("For regulatory approval, a drug has to be shown to be safe and efficacious for its use"); ¶ 28 ("The pre- and post-approval processes for new drugs are governed by many federal regulations in the United States . . ."); ¶ 41 ("According to FDA regulations, a commercially approved drug can only be promoted for approved indication(s)"); ¶ 42 ("Merck repeatedly violated the federal regulations governing the safety and efficacy of their drug through false and misleading promotion of Fosamax.").

To the extent Merck challenges Dr. Furberg's testimony on Rule 403 grounds, the Court believes that the above restrictions will minimize unfair prejudice or danger of confusion. Therefore, the motion is DENIED.

4. Motion to Exclude Dr. Gordon Guyatt.

Dr. Gordon Guyatt is a Professor in both the Department of Clinical Epidemiology and Biostatistics and the Department of Medicine at McMaster University. He is a medical physician and epidemiologist. He has authored over 650 peer-reviewed journal articles in the area of evidence-based medicine. His research areas include measuring quality of life in patients with chronic disease; measuring the effectiveness of therapy in patients with chronic diseases; health technology assessment; systematic overview methodology; evidence-based healthcare; and guidelines development. He has co-authored a published article entitled, "Drugs for pre-osteoporosis: prevention or disease mongering?" Prior to this litigation, Dr. Guyatt served as a consultant to Merck and performed and published meta-analysis of Fosamax's fracture reduction efficacy, at the request and sponsorship of Merck. As PSC's expert, he plans to explain the limited fracture reduction efficacy of Fosamax. The PSC has clarified that Dr. Guyatt will not offer any opinion testimony on the topic of ONJ; his

testimony will be limited to the fracture reduction efficacy of Fosamax and other related issues.

a. Merck's Position

Merck offers a number of arguments to exclude Dr. Guyatt's testimony. First, Merck claims that he presents no relevant professional qualifications, underlying knowledge, or study or review to support the personal opinions that he presents in his report and deposition. Merck asserts that the opinions set forth in his report range far beyond any area of expertise that he may claim as a medical doctor who lacks clinical experience relating to osteoporosis or ONJ. Merck points out that he does not have his own patients at the university hospital in which he works, and he is not the primary care physician for any patient who may have osteoporosis. Furthermore, Merck points out that he does not make medical decisions relating to osteoporosis, such as whether or when a patient needs bone mineral density ("BMD") testing and he rarely makes decisions about whether or not a patient will receive a bisphosphonate.

Second, Merck argues that Dr. Guyatt should not opine as to osteoporosis or bone mineral density testing because, by his own admissions, he only has superficial knowledge of those areas. Merck points out that Dr. Guyatt has made no methodological analysis to determine when postmenopausal women

should have BMD tests performed, and he admits that he is not an expert in the relationship between bone mineral density and fracture risk.

Third, Merck argues that Dr. Guyatt should not be able to present an expert opinion criticizing the use of oral bisphosphonates for the treatment of osteoporosis or for the prevention of osteoporosis in osteopenic women because he has no relevant expertise with those medical conditions, does not believe osteoporosis is a disease, and cannot say when it is or is not appropriate to use oral bisphosphonates. In support, Merck points out that Dr. Guyatt has never produced or worked on guidelines to determine whether or when to prescribe oral bisphosphonates, nor could he state his opinion as to whether bisphosphonate should or should not be prescribed at a particular level of bone mineral density.

Additionally, Merck argues that Dr. Guyatt cannot properly criticize Merck's promotion of Fosamax because he has no identifiable expertise relating to the promotion of pharmaceutical products and cannot identify any facts relating to Merck's promotion of Fosamax on which to base his views. Merck points out that Dr. Guyatt has not identified any experience or study to support his opinions on the marketing and promotion of Fosamax. Merck asserts that his opinions as to Merck's role in the alleged expansion of osteoporosis treatment

are based on information that he can no longer identify, information from a colleague, and on a single scientific article. Merck asserts that Dr. Guyatt's views as to the promotion of Fosamax were based on his article, "Drugs for pre-osteoporosis: prevention or disease-mongering?," an opinion piece that he wrote in conjunction with others, but without any underlying facts that he can cite to support those opinions.

Finally, Merck argues that the meta-analysis of Fosamax clinical trials that he conducted prior to this litigation has no bearing on his opinions in this case. Here, Merck argues, Dr. Guyatt purports to present opinions about the overselling of the disease osteoporosis and about pharmaceutical marketing. And given his scant review of Merck's internal documents, Merck argues that he is wholly unqualified to render views as to Merck's promotion of Fosamax. Merck argues that Dr. Guyatt's opinions should be excluded because they are not based upon any specific facts relating to any individual Plaintiff or to any specific actions by Merck.

b. PSC's Position

According to the PSC, Dr. Guyatt is qualified to offer the opinions set forth in his report regarding Fosamax's fracture reduction efficacy because Dr. Guyatt is a medical doctor, he is experienced and trained as a methodologist, and his research is focused on risk-analysis. The PSC asserts that

the focus of Dr. Guyatt's testimony and his opinions presented in his report have previously been presented, peer-reviewed, and published in his article, "Drugs for pre-osteoporosis: prevention or disease-mongering?" In this article, Dr. Guyatt explains that the diagnosis of osteoporosis is controversial because the main criterion upon which the bone mineral density T-score evaluation is based is somewhat arbitrary. He explains that he does not necessarily consider osteoporosis "a disease," but merely a part of the aging process.

In addition, the PSC argues that Dr. Guyatt, through his experience and training as a methodologist focused on risk-benefit analysis, is well qualified to opine on the clinical propriety of promoting Fosamax use for women without osteoporosis, since the condition "osteopenia" includes more than half of all white post-menopausal women in the United States. The PSC asserts that Dr. Guyatt puts Merck's fracture reduction data into context and warns against inferring a small benefit for a high risk group, such as severe osteoporotics with prior vertebral fracture, to a low risk group, such as osteopenic women. The PSC asserts that Dr. Guyatt reviewed the fracture reduction data himself to reach his conclusions.

Finally, the PSC challenges Merck's assertion that Dr. Guyatt is attempting to express opinions related to Merck's marketing. The PSC asserts that Dr. Guyatt has simply placed

Merck's marketing efforts to non-osteoporotic women in the context of the data about which he opined.

c. Court's Ruling

Dr. Guyatt is qualified to interpret the clinical trial and meta-analysis data for Fosamax as it relates to fracture reduction efficacy. He is also qualified to opine on what that data means in terms of the risk-benefit profile for Fosamax treatment. That he does not have experience treating patients with osteoporosis does not disqualify him because he does not offer an opinion on whether or when Fosamax is appropriate for any specific patient. Rather, he testifies from an epidemiological perspective about how the limited anti-fracture efficacy data affects the risk-benefit analysis. This testimony is within his expertise and would be helpful to the jury.

To the extent Merck seeks to preclude Dr. Guyatt from testifying about the marketing of osteoporosis drugs in general or Merck's marketing of Fosamax in particular, the motion is GRANTED. Dr. Guyatt stated at deposition that he spent less than an hour reviewing Merck marketing documents, didn't read them in detail, could not recall any of them, and that his views about Merck's marketing were based mostly on conversations with colleagues. (03/09/09 Guyatt Dep. at 12-13; 84-90, 171-72) Although he states in his report that "the propriety of []

marketing efforts will be for others to discuss," he nevertheless makes broad assertions about improper industry-wide marketing practices.¹⁹ The Court finds such opinions lack adequate foundation and are insufficiently tied to any conduct by Merck.

Insofar as Merck seeks to preclude Dr. Guyatt from testifying about the utility of bone mineral density testing, the motion is GRANTED. Dr. Guyatt admitted at deposition that he only has "superficial knowledge" of the subject and that he is not knowledgeable about the relationship between bone mineral density and fracture risk. (03/09/09 Guyatt Dep. at 32-38, 126-27.) Despite this, his report criticizes the use of BMD testing as a diagnostic tool. (Guyatt Rep. at 3, 9.)

To the extent Merck seeks to preclude Dr. Guyatt from testifying that osteoporosis is "controversial" or that it is not really a disease, the motion is GRANTED. The Court finds that such testimony is mere personal opinion going beyond his expertise and, as such, would not be helpful to the jury.

To the extent Merck challenges Dr. Guyatt's testimony on Rule 403 grounds, the Court believes that the above

¹⁹ See Guyatt Rep. at 5 (stating that "drug marketing in the United States and elsewhere has encouraged treatment of younger postmenopausal women at relatively low risk of fracture"); *id.* at 3 (claiming that "[a]n informal global alliance of drug companies, doctors and sponsored advocacy group portray and promote osteoporosis as a silent but deadly epidemic bringing misery to tens of millions of postmenopausal women").

restrictions will minimize unfair prejudice or the danger of confusion. Therefore, the motion is DENIED.

5. Specific Challenges

At the end of its Daubert brief, Merck sets forth in bullet point fashion a number of issue- or expert- specific challenges. These are addressed in turn.

a. Testimony by Etminan or Hellstein about Mechanisms of BRONJ

Merck argues that Drs. Etminan and Hellstein should be precluded from testifying about the biological mechanism through which Fosamax allegedly causes ONJ because they have testified that the mechanism is not known. As ruled above, any testimony about the mechanism is admissible only if qualified in substance with a statement that it remains a theory that, subject to testing, may be proved or disproved. Furthermore, as Dr. Etminan's testimony about general causation has been excluded, he will not be permitted to testify about mechanisms of causation.

b. Dr. Marx's Testimony that Fosamax is Toxic to Bone

Merck moves to exclude any testimony by Dr. Marx that Fosamax is toxic to bone because it kills or impairs osteoclasts. The motion is DENIED provided that Dr. Marx's testimony about the mechanism is accompanied by the qualification stated in the paragraph above. Cross-examination and competing testimony by Merck's experts are the appropriate ways to expose for the jury what Merck believes to be flaws in Dr. Marx's testimony.

c. Testimony about Parallels between BRONJ and Phossy Jaw

Merck moves to exclude testimony about the supposed similarities between bisphosphonate-associated ONJ and "phossy jaw," a condition observed in the 19th and early 20th centuries in factory workers exposed to white phosphorus. Dr. Hellstein is the only PSC expert who mentions phossy jaw in his report. He

would testify that exposure to white phosphorus interferes with bone remodeling and has "eerily similar effects on the jaws" as bisphosphonates. (Hellstein Rep. at 29.) The bulk of his report on this subject consists of lengthy excerpts from toxicological profiles offered with little explanation. (Id. at 29-33.) While Dr. Hellstein has published on the analogy between phossy jaw and bisphosphonate-associated ONJ, he also has written that there is a "current lack of scientific support for the theory," though he "personally feel[s] that time will provide a more scientific link." (07/16/09 Hrg. Tr. at 373; Hrg. DX O.) The Court finds that the link is not yet scientific enough for the courtroom.

In addition, these trials will be long and will force the juries to digest difficult scientific evidence and terminology. If testimony about phossy jaw is introduced, Merck will have to present its organic chemistry expert, Dr. Paul Bartlett, to explain the different chemical structures and properties of white phosphorus and bisphosphonate and how these two substances react differently in the human body. Whatever probative value the topic of phossy jaw has for causation or notice is substantially outweighed by the corresponding waste of time, danger of confusion, and unfair prejudice to Merck.

Accordingly, Merck's motion to exclude testimony about phossy jaw is GRANTED pursuant to Rules 702 and 403.

d. Qualifications of Etminan

Merck challenges Dr. Etminan's expertise on bisphosphonates and ONJ. As held above, Dr. Etminan's testimony on general causation is excluded, so any challenge to his qualifications on this subject is moot. To the extent Merck challenges his qualifications to offer testimony about the limitations of clinical trials, which has been ruled admissible, such challenge is rejected.

e. CTX Levels as Measurement of Risk for ONJ

Merck seeks to preclude Dr. Marx from opining that the testing of CTX levels, which are a marker for bone turnover, provides a measurement of risk for ONJ. Merck argues that "CTX testing shows only that the level of bone resorption declines when a patient takes a medicine that is intended to reduce the level of resorption." (Merck Reply at 25.) Merck points out that the AMBR Task Force has criticized Dr. Marx's use of the test as reflecting a "significant lack of understanding." (DX

67.) Furthermore, the ADA Expert Panel and the AAOMS Task Force have stated that studies are needed to demonstrate that CTX testing is a valid risk assessment tool. (DX 68, 42.)

While Dr. Marx has published his opinion that CTX testing can predict the risk of ONJ, he does not express this opinion in his expert report. In its opposition brief, the PSC cites Dr. Marx's research on CTX testing only to show that Fosamax treatment indeed suppresses bone turnover, in support of the PSC's argument that the over-suppression theory is biologically plausible. (See PSC Mem. in Opp'n to Merck's Daubert Motion at 47-48.) When asked about the subject at oral argument, counsel for the PSC replied that the evidence is "not so much for CTX as a predictor" and that the PSC was not basing its case on this. (07/16/09 Hrg. Tr. at 428-29.)

Therefore, Merck's motion to preclude Dr. Marx from testifying about the usefulness of CTX testing to predict the risk of ONJ in Fosamax users is GRANTED. However, Merck has not challenged testimony about CTX testing to show that Fosamax suppresses bone turnover.

f. Efficacy of Drug Holidays in Preventing ONJ

Merck seeks to preclude Dr. Marx from opining that cessation of Fosamax treatment is appropriate before major dental surgery. As Merck points out, the position papers of several task forces and expert panels have noted the lack of evidence supporting the efficacy of such "drug holidays." (DX 42, 43, 44.) None of the PSC's experts offer in their reports an opinion that a drug holiday reduces the risk of ONJ. In its opposition brief, the PSC does not defend the reliability of such an opinion. Therefore, Merck's motion to preclude testimony that a drug holiday alters the risk of ONJ is GRANTED.

g. Dr. Goss's Testimony About Matters Outside of His Report

Merck claims that portions of Dr. Goss's de benne esse deposition, conducted in Adelaide, Australia, on March 29, 2009, should be excluded because he testifies about matters not covered in his expert report. Specifically, Merck challenges Dr. Goss's testimony about the mechanism through which Fosamax allegedly causes ONJ and his use of photographs of patients with ONJ.

The Court reserves decision on this issue and will

hear from the parties on it at oral argument on the pending motions in limine.

h. Testimony on General Causation Before Three Years of Continuous Use

Merck seeks to exclude testimony by any PSC expert that Fosamax can cause ONJ in patients who have taken the drug continuously for less than three years, based on Dr. Marx's prior publications and testimony that there is no or minimal risk before then. Merck also has filed a motion for summary judgment in 26 cases involving less than three years of use. The Court reserves decision on the admissibility question and will decide it in connection with the summary judgment motions.

In its brief, Merck additionally argues that Dr. Marx's inconsistency on the three year issue undermines his entire opinion on causation, whether before or after three years of Fosamax use. The Court rejects this argument. His new view that exposure can cause the disease before three years is consistent with his longstanding view that it causes it in general.

i. Specific Causation Testimony in *Boles v. Merck & Co., Inc.*, No. 1:06-cv09455-JFK; *Maley v. Merck & Co., Inc.*, No. 1:06-cv04110-JFK; *Fleming v. Merck*, No. 1:06-cv-07631-JFK.

As noted supra note 7, the Court will decide Daubert challenges to the specific causation experts designated in the bellwether cases in the ruling on the summary judgment motions filed in those cases.

j. Admissibility of Adverse Event Reports

Merck seeks to preclude the PSC's experts from referring to adverse event reports ("AERs") in their testimony. This question is governed by Federal Rule of Evidence 703, which allows experts to base opinions on evidence of a type reasonably relied upon by experts in the relevant field. As held above, the Court finds that the PSC's experts have reasonably relied in part on adjudicated AERs to form their general causation opinions. Merck cites several decisions holding that experts in the field do not rely on AERs as proof of causation. See *In re Baycol Prods. Liab. Litig.*, 532 F. Supp. 2d 1029, 1040 (D. Minn. 2007); *DeLuca v. Merrell Dow Pharms., Inc.*, 791 F. Supp.

1042, 1051 (D.N.J. 1992) aff'd 6 F.3d 778 (3rd Cir. 1993). But see In re PPA, 289 F. Supp. 2d at 1242 (allowing expert testimony that was based in part on AER data and finding "significant the sheer volume of case reports, case series and spontaneous reports associating PPA with hemorrhagic stroke to women"). The rarity of ONJ, the relatively high number of recent reports from bisphosphonate users, and the fact that the reports were adjudicated by Merck distinguishes this case. Furthermore, one of Merck's clinical experts, Dr. Bilezikian, agreed at deposition that "someone who is prescribing [a] drug such as Fosamax really would like to know how many adjudicated cases there are of an adverse event like osteonecrosis of the jaw in association with a drug which that clinician is prescribing." (04/17/09 Bilezikian Dep. Tr. at 194:19-195:2).

Whether the AERs may be disclosed at trial depends on whether they are otherwise admissible or whether "their probative value in assisting the jury to evaluate the expert's opinion substantially outweighs their prejudicial effect." Fed. R. Evid. 703. Both questions may depend on case-specific circumstances. Therefore, the Court will defer to trial courts on this question.

B. The PSC's Motions

1. Motion to Exclude Expert Testimony on General Causation or Medical Issues by Certain Merck Witnesses

a. Dr. Paul Bartlett

Dr. Paul Bartlett is a Professor of Chemistry at the University of California, Berkeley. The PSC challenges portions of his report in which he discusses the effects of Fosamax on the human bone and the historical disease phossy jaw. In its opposition brief, Merck states that Dr. Bartlett's entire opinion in this case is presented in response to claims that ONJ

is similar to phossy jaw. At oral argument, counsel for Merck confirmed that it would not present Dr. Bartlett as a witness if plaintiff's experts did not present testimony about phossy jaw. (07/16/09 Hrg. Tr. 403.)

As ruled above, testimony about phossy jaw is inadmissible pursuant to Rules 702 and 403. Therefore, Merck will not present expert testimony from Dr. Bartlett, and the PSC's challenge to his testimony is moot.

b. Merck's Regulatory Experts

Dr. Daniel Shames is a former FDA manager and is now a consultant to drug companies. Dr. Lisa Rarick is medical doctor who worked for 15 years at the FDA's Center for Drug Evaluation and Research. Merck has designated these witnesses to testify on regulatory issues, including Merck's adherence to FDA regulations and the appropriateness of Merck's conduct during the FDA approval process and the post-marketing phase.

The PSC moves to exclude testimony by Drs. Shames and Rarick on general causation. Merck responds that there is no basis for such a motion because these witnesses will not offer an opinion on general causation. The Court agrees. With the understanding that Merck will not seek to elicit general causation testimony from these witnesses on direct examination, the PSC's challenge is DENIED as moot.

c. Dr. John Bilezikian

Dr. John Bilezikian is a Professor of Medicine and Pharmacology at Columbia University, Chief of the Division of Endocrinology, and Director of the Metabolic Bone Diseases Program at Columbia University Medical Center. He also maintains a private practice and treats patients with osteoporosis and other metabolic bone diseases. In his report, he discusses the biological mechanics of osteoporosis and bone remodeling, the development and efficacy of bisphosphonates as a treatment for osteoporosis, and the biological mechanism by which bisphosphonates act. He also discusses the incidence of ONJ among oral bisphosphonate users and criticizes the theories of the PSC's experts about the mechanism through which Fosamax supposedly causes ONJ. In particular, he opines that the chances of developing ONJ while taking oral bisphosphonates are very small and that a mechanistic or causal relationship between bisphosphonates and ONJ has not been demonstrated. (Bilezikian Rep. ¶¶ 38-39.)

i. PSC's Position

The PSC argues that Dr. Bilezikian should be precluded from offering any opinion about general causation because he lacks qualifications to opine on ONJ. According to the PSC, Dr. Bilezikian admitted at deposition that he is not an expert on ONJ, does not diagnose it, and would be incompetent to

adjudicate a bisphosphonate/ONJ study because he is not an oral and maxillofacial surgeon. In addition, the PSC argues, Dr. Bilezikian testified at deposition that experts in the medical and dental field are unsure whether bisphosphonates pose a risk for ONJ. The PSC also notes that, in his New England Journal of Medicine article on bisphosphonates and ONJ, he cites Merck's figure of one ONJ case per 100,000 patient-years as a reasonable estimate of frequency. However, at deposition he admitted that he heard this figure at professional meetings and that it was not based on rigorous studies or subjected to peer review.

ii. Merck's Position

According to Merck, Dr. Bilezikian is well qualified to discuss oral bisphosphonates, their mechanism of action in the bone, including whether they cause ONJ, and their use and efficacy in the treatment or prevention of osteoporosis. Merck points out that Dr. Bilezikian has devoted his 40-year career to the treatment of patients with metabolic bone diseases such as osteoporosis, as well as to the study of those diseases and the medications used to treat them.

Merck notes Dr. Bilezikian's extensive experience and involvement in clinical research at all levels, including numerous trials studying the cellular and molecular effects of medications for metabolic bone diseases like osteoporosis. In addition, Merck points out that Dr. Bilezikian has authored more

than 550 publications in his field, including dozens of articles specifically on bisphosphonates and osteoporosis, and is the co-editor of a seminal treatise, Principles of Bone Biology. He also has served as an editor to numerous endocrinology journals and has reviewed many articles relating directly to the mechanism of action and pharmacology, pharmacokinetics, pharmacodynamics, and the clinical, cellular, and molecular effects of medications used to treat osteoporosis and other metabolic bone diseases. In addition, he has extensive clinical experience, treating countless patients with osteoporosis and other metabolic bone diseases and routinely prescribing bisphosphonates.

Finally, with respect to his expertise on ONJ, Merck points out that Dr. Bilezikian was selected by the New York Academy of Sciences to chair its international panel of ONJ experts, and that, in 2006, The New England Journal of Medicine invited Dr. Bilezikian to write its perspective article on bisphosphonates and ONJ. Prior to this litigation, Dr. Bilezikian and other endocrinologists and bone biologists have publicly criticized the over-suppression theory. Thus, Merck argues, Dr. Bilezikian is amply qualified to present his opinions, and nothing in his report requires clinical experience in diagnosing or treating ONJ.

iii. Court's Ruling

The Court finds that Dr. Bilezikian is qualified to testify to the matters in his report, including the mechanism of action of bisphosphonates on bone and the relationship between bisphosphonates and ONJ. As set forth above, qualification is viewed liberally and is determined by comparing the area in which the witness has superior knowledge, skill, experience, or education with the subject matter of the witness's testimony. In re TMI Litig., 193 F.3d at 664; In re MTBE, 2008 WL 1971538, at *5; Carroll, 896 F.2d at 212. This requires a determination of a witness's actual qualifications and knowledge of the subject matter and not his title. In re Agent Orange Prod. Liability Litig., 611 F. Supp 1223 (E.D.N.Y. 1985). A witness's qualification on areas of knowledge by no means qualifies him to express opinions outside of his field. Nimely v. City of New York, 414 F.3d 381, 399 n. 13 (2d Cir. 2005). However, the fact that a physician is not a specialist in the field in which he is giving expert opinion does not affect the admissibility of the opinion, but rather the weight the jury may place on it. Payton v. Abbott Labs, 780 F.2d 147, 155 (1st Cir. 1985).

Dr. Bilezikian has extensive experience researching and treating bone diseases and studying the effects of bisphosphonates on bone. Notably, he has been involved in at least six clinical trials involving Fosamax that led to peer-

reviewed publications, and another six to eight trials involving other osteoporosis medications. Additionally, he has written extensively on bisphosphonates and their effects on bone, including, in his New England Journal of Medicine piece, the relationship between bisphosphonates and ONJ. His experience and knowledge qualify him to discuss oral bisphosphonates and their mechanism of action on bone. This includes his discussion of the scientific evidence on the link between bisphosphonates and ONJ and his criticism of the causal mechanism proposed by plaintiffs. The fact that the affected bone is the jaw does not require that he be an oral maxillofacial surgeon, nor do the opinions in his report require clinical experience in diagnosing or treating ONJ. Accordingly, the PSC's motion to exclude his testimony on these subjects is DENIED.

d. Dr. David Dempster

Dr. David Dempster holds a Doctorate in Physiology and is a Professor of Clinical Pathology at Columbia University and the Director of The Regional Bone Center at Helen Hayes Hospital. He has conducted his own research on bones since 1982 and is a member of two multi-disciplinary task forces on ONJ. Merck has designated Dr. Dempster to testify as an expert on the mechanism of action of Fosamax in the prevention and treatment of osteoporosis, the effect of Fosamax on bone turnover, and the lack of scientific evidence supporting the theories of the PSC's

experts that Fosamax causes ONJ by over-suppressing bone turnover. He also opines that an association between Fosamax and ONJ has not been scientifically established.

i. PSC's Position

The PSC argues that Dr. Dempster lacks the necessary expertise to opine on general causation because he is not an oral surgeon, dentist, or medical doctor, and because he has not researched the topic of ONJ himself. According to the PSC, Dr. Dempster is not qualified to testify about ONJ because he lacks expertise with the human jaw and with the jawbone's ability to heal. In addition, the PSC argues that he is unqualified because he has never examined a biopsy of an ONJ patient treated with bisphosphonates and has never conducted any original research on the topic of bisphosphonate action and ONJ. Instead, the PSC argues, Dr. Dempster merely relies on the research of others to support his conclusions.

ii. Merck's Position

According to Merck, Dr. Dempster is qualified to offer his opinions on the biological mechanism of bone and the effects of Fosamax on bone, including whether or not bisphosphonates have been scientifically established to be associated with or to cause ONJ. Dr. Dempster holds a Doctorate in Physiology and is a Professor of Clinical Pathology. He is a prominent histomorphometrist and bone researcher who has devoted his

decades-long career to the study of bone physiology and metabolism and the pathogenesis and treatment of osteoporosis and other metabolic bone diseases, and specifically to the study of cell biology of the osteoclast and the pathogenesis and treatment of osteoporosis and other metabolic bone diseases.

In addition, Merck points out that Dr. Dempster has been involved with numerous clinical and preclinical trials studying the clinical, cellular, and molecular effects of medications for metabolic bone diseases such as osteoporosis. This experience includes trials involving Fosamax and other osteoporosis medications.

Additionally, Merck notes that most of Dr. Dempster's more than 100 publications are directed to bone biology and metabolic bone diseases, including the workings of the medications used to treat such diseases. Dr. Dempster has been the associate editor for Osteoporosis International and many of the articles that he reviewed and approved related directly to the mechanism of action and the clinical, cellular, and molecular effects of medications used to treat osteoporosis and other metabolic bone diseases.

Merck also points out that Dr. Dempster serves on ONJ task forces created by the American Society for Bone & Mineral Research and the Canadian Association of Oral & Maxillofacial Surgeons. Thus, Merck asserts, his expertise with bone

mechanisms and his knowledge of bisphosphonates are well recognized, and he is qualified to render the opinions in his report.

iii. Court's Ruling

Dr. Dempster is qualified to testify about the matters set forth in his report. His testimony relates to his area of expertise, bone biology and physiology and the effects of bisphosphonates on bone. He is qualified to discuss the scientific evidence on the link between bisphosphonates and ONJ and to criticize the causal mechanism proposed by the PSC's experts. These issues do not require experience with diagnosing ONJ, examining biopsies of necrotic jawbone, or conducting original experimental research on ONJ. Accordingly, the PSC's motion to exclude Dr. Dempster's testimony on these issues is DENIED.

e. Dr. Elizabeth Holt

Dr. Elizabeth Holt is an Assistant Professor of Medicine in the Section of Endocrinology and Metabolism at Yale University. She has a Doctorate in Cellular and Molecular Physiology and her research has focused specifically on the effect of certain hormones on bone disease. She is also co-director of the Yale Bone Center and was Chief of Endocrinology at VA-Connecticut Healthcare. As Merck's expert, Dr. Holt would

testify about the diagnosis, treatment, and impact of osteoporosis, the efficacy of Fosamax, and its effect on bone. In the final section of her report, she critiques the evidence linking Fosamax to ONJ and the causal mechanism proposed by the PSC's experts.

i. PSC's Position

The PSC argues that Dr. Holt's opinions on ONJ, the incidence of ONJ in Fosamax users, and any testimony regarding the relationship between ONJ and Fosamax should be excluded. First, the PSC argues that Dr. Holt lacks direct experience with or knowledge of ONJ. Further, the PSC argues, she has no knowledge about the relationship between bisphosphonates and ONJ other than through reading the work of others. She has never performed any original research on ONJ herself and admits that dentistry and oral surgery are beyond her area of expertise. The basis for her opinions on ONJ attendance at some lectures, her review of literature prepared by others, and scant clinical experience. She has only seen one patient with ONJ but did not offer that patient any treatment. She has never published anything on the topic of ONJ.

Furthermore, the PSC argues, Dr. Holt's ONJ opinions should be excluded because they lack a factual foundation. She accepts Merck's estimate on the prevalence of ONJ among Fosamax

users but does not know what methodology Merck used to come up with it. She does not know how many reports of ONJ in Fosamax patients Merck has received to date. The PSC suggests that Dr. Holt merely is serving as a "mouthpiece" for a Merck study that she admits she does not understand.

ii. Merck's Position

Merck responds that Dr. Holt is qualified to testify that the PSC's theory of causation is unsupported. Merck points out that she has considerable experience treating osteoporosis and that it her responsibility to be knowledgeable about the risks and benefits associated with oral bisphosphonate treatment. According to Merck, Dr. Holt's knowledge of the physiology of bones and how bisphosphonates operate qualify her to criticize the theories of biological mechanism presented by the PSC's experts. She is also qualified to criticize the level of evidence linking ONJ and oral bisphosphonates. According to Merck, none of these opinions require experience with diagnosing or treating ONJ.

iii. Court's Ruling

The Court finds that Dr. Holt's experience as a professor of endocrinology and director of the Yale Bone Center, her clinical experience treating osteoporosis and prescribing

oral bisphosphonates, and her knowledge of bone physiology and the effects of bisphosphonates qualify her to testify to the matters set forth in her report. This includes her discussion of the scientific evidence linking Fosamax and ONJ and her criticism of the causal mechanisms proposed by the PSC's experts. Again, the Court rejects the PSC's argument that clinical experience treating ONJ or training as an oral maxillofacial surgeon are the only ways to obtain expertise on these topics.²⁰ The PSC's challenge to the factual foundation to some of Dr. Holt's opinions can be explored on cross-examination but are not grounds for exclusion.

f. Dr. Jane Cauley

Dr. Jane Cauley is a Professor of Public Health at the University of Pittsburgh and has a Doctorate in Public Health and Epidemiology. Her specialty is osteoporosis epidemiology, prevention, and treatment. Merck has designated her to testify as an expert witness on the epidemiology of osteoporosis, the efficacy of Fosamax, the causal relationship between bisphosphonates and Fosamax, and the risks and benefits of

²⁰ However, the Court notes that Dr. Holt testified at deposition that Fosamax does not cause ONJ, an opinion not directly stated in her report. In its opposition brief, Merck states that "Dr. Holt has ample background and experience to discuss the reasons why she has . . . concluded that it has not been proven that Fosamax can cause ONJ." (Merck Mem. in Opp'n to PSC Daubert Motion at 19 (emphasis added)). Merck has not sought to show the reliability of Dr. Holt's opinion that Fosamax does not cause ONJ, and the Court has not ruled that such an opinion would be admissible on direct examination.

Fosamax treatment. In her report, Dr. Cauley surveys and critiques the scientific literature on bisphosphonates and ONJ. She concludes that no causal relationship has been established between ONJ and oral bisphosphonates. (See Cauley Rep. at 15.)²¹

i. PSC's Position

The PSC argues that the Court should preclude Dr. Cauley from offering her general causation opinion relating to ONJ as well as the risk/benefit profile of Fosamax treatment. First, the PSC claims that Dr. Cauley has no medical credentials to support her general causation opinion, relies entirely on studies conducted by others, and bases her opinion on an incomplete factual basis. The PSC points out that Dr. Cauley is not a dentist, oral surgeon, doctor, or bone biologist; she is not an expert on the human jaw or ONJ, has no research interest in ONJ, and is not qualified to diagnose or treat ONJ.

The PSC next challenges Dr. Cauley's testimony relating to the risk/benefit analysis for Fosamax patients. First, the PSC argues that she does not know the standard of care for treating osteoporosis patients because she is not a

²¹ At her deposition, Dr. Cauley went further to say that the lack of evidence establishing causation actually disproves causation. ((04/29/09 Cauley Dep. Tr. at 183:16-23; 187: 2-9.) In its motion, the PSC challenges the reliability of this opinion. At oral argument, Merck's counsel clarified that, on direct examination, Dr. Cauley will offer the opinion stated in her report--that there is no proof of causation--rather than the opinion that Fosamax does not cause ONJ. (07/16/09 Hrg. Tr. at 436.)

clinician. Second, the PSC points out that Dr. Cauley has testified that she is not legally allowed to conduct a risk/benefit analysis on behalf of any patient. Thus, the PSC contends that her opinion on the risk-benefit profile for Fosamax treatment strays far from her area of expertise.

ii. Merck's Position

According to Merck, as a trained epidemiologist, Dr. Cauley is qualified to opine on the causal relationship between oral bisphosphonates and ONJ, the efficacy of Fosamax, and the risk/benefit issue based upon the published scientific record. Merck argues that Dr. Cauley is qualified to discuss the causation because as an epidemiologist, she is an expert in the study of the incidence, distribution and etiology of disease and there is no need for an epidemiologist to be a clinician in order to render an opinion that is based on sound epidemiological principles. Merck claims that epidemiologists rely on published scientific studies to determine whether a proven causal connection exists. Merck asserts that PSC presents no evidence to show that Dr. Cauley utilized a methodology inconsistent with the principles of epidemiology. In addition, Merck points out that Dr. Cauley has extensive experience with clinical trials and studies related to osteoporosis, including the clinical trials relating to Fosamax

such as Merck's Fracture Intervention Trial, and she has authored more than 400 publications.

As to the risk and benefit analysis for Fosamax, Merck asserts that Dr. Cauley presents her analysis under epidemiological principles based on the available research relating to the efficacy and risks of Fosamax. The fact that Dr. Cauley does not herself treat Fosamax patients is irrelevant because she is not testifying as to whether or when Fosamax is appropriate for any specific, individual patient.

iii. Court's Ruling

Dr. Cauley is qualified to offer the opinions stated in her report. Her primary area of research is the epidemiology of osteoporosis, osteoporosis treatment and the consequences of osteoporosis in both men and women. Her opinions are based on proper epidemiological methodology. Epidemiologists rely on published scientific studies to determine whether a causal association exists. Dr. Cauley's training in epidemiology qualifies her to discuss the epidemiological data relating to osteoporosis (including the incidence and severity of the disease), the data on the efficacy of Fosamax, and the available data on the relationship between Fosamax and ONJ. Her lack of experience treating osteoporosis or ONJ patients in no way disqualifies her offering these opinions. In addition, she need

not be a clinician to opine from an epidemiological standpoint about the risk-benefit profile for Fosamax treatment. Accordingly, the PSC's motion to exclude portions of her proffered testimony is DENIED.

g. Dr. Jeri Nieves

Dr. Nieves is an Associate Professor of Clinical Epidemiology at Columbia University and holds a Doctorate in Epidemiology. She is the principal investigator for the New York State Osteoporosis Prevention and Education Program, which involves educating both the public and health care professionals about the risks of osteoporosis and the need to promote the prevention, diagnosis, and treatment of the disease. As Merck's expert, Dr. Nieves offers her opinion on general causation, which is that there is no known or proven causal relationship between bisphosphonates and ONJ. She also would testify that, while there may be many risk factors for ONJ, Fosamax has not been scientifically proven to be one of them. In addition, she offers the opinion that the mechanism of action by which bisphosphonates could cause ONJ is uncertain.

i. PSC's Position

The PSC claims that Dr. Nieves is not qualified to offer an opinion on general causation or the mechanism underlying ONJ. First, the PSC argues that she is unqualified

to testify on general causation because she does not have a medical degree and is not a dentist or oral surgeon; she has never studied ONJ or any other dental condition in a clinical trial; she has not published anything on ONJ, and none of her opinions related to ONJ have even been submitted for peer review. Second, the PSC challenges Dr. Nieves' ability to offer an opinion concerning causation and causal mechanisms because she has not conducted any original research on the link between bisphosphonates and ONJ. The PSC points out that, at the time of her deposition, she had only spent twenty hours researching ONJ.

Third, the PSC alleges that Dr. Nieves displays a willful blindness toward the possibility that there may be a causal relationship between Fosamax and ONJ. The PSC points out that, at deposition, she was unfamiliar with the data supporting the secondary sources that she cited to in her expert report, yet she insisted that there were no data to support the causal relationship between bisphosphonates and Fosamax. In addition, the PSC claims that Dr. Nieves is biased. The PSC asserts that, in reaching her opinions, Dr. Nieves applied an arbitrarily selected filter for the studies she would consider and that Merck has paid her tens of thousands of dollars in lecturing fees over their twelve-year relationship. Finally, the PSC

argues that Dr. Nieves' testimony should be excluded from trial because she relied on an incomplete and biased factual foundation based entirely on Merck's data. Therefore, PSC argues, Dr. Nieves' testimony is unreliable.

ii. Merck's Position

According to Merck, Dr. Nieves is qualified to discuss ONJ because she has been practicing epidemiology for more than 20 years and most of her research involves osteoporosis, including studies of treatments for osteoporosis. She has been involved in the design, implementation, and evaluation of numerous epidemiological studies on these issues. In her report, Dr. Nieves addresses the published scientific data on the epidemiology of osteoporosis, the efficacy of Fosamax, the types and quality of scientific evidence used to assess associations or causation, and the available scientific evidence relating to Fosamax and ONJ. She concludes that there are numerous studies showing that Fosamax is an effective agent in the prevention and treatment of osteoporosis and that all evidence to date suggests that the risk of developing ONJ while taking Fosamax is extremely rare.

Merck asserts that Dr. Nieves is qualified to offer opinions as to the causation of ONJ because she followed the standard methodology of epidemiologists by making her

determinations as to whether there is an association or a causal relationship on the basis of the published scientific studies that were available at the time. Merck attempts to clarify her testimony by pointing out that in her report, Dr. Nieves states that (1) the mechanism of ONJ is uncertain; (2) there have been some suggestions of possible risk factors for ONJ; (3) several of these risk factors are also risk factors for osteoporosis, which makes it difficult to isolate and determine whether it is the disease itself or similar risk factors for both osteoporosis and osteonecrosis of the jaw; and (4) the term "bisphosphonate-associated ONJ" does not necessarily assume that bisphosphonate therapy is a risk factor for ONJ because association does not mean causation.

As to the PSC's challenge that Dr. Nieves did not conduct original research, Merck asserts that, in developing her opinions, she utilized a methodology consistent with the principles of epidemiology. In addition, Merck claims that Dr. Nieves did not review case reports because she found them to be scientifically unreliable in that they lack a control group and there are biases in the reporting of cases.

iii. Court's Ruling

Dr. Nieves is qualified to render the opinions in her report. She is a trained and experienced epidemiologist and has

reached conclusions using the standard methodology of her field. She has extensive experience researching osteoporosis and osteoporosis treatments and has performed sufficient research on the topic of ONJ. Her lack of clinical experience treating patients with osteoporosis or ONJ does not disqualify her from interpreting epidemiological evidence on osteoporosis, the efficacy of Fosamax treatment, and the link between Fosamax and ONJ. The PSC's arguments about the factual foundation for her opinions and her financial ties to Merck are a proper subject for cross-examination but do not warrant exclusion. Therefore, the PSC's motion is DENIED.

2. Motion to Restrict Testimony by Merck Witnesses about the Anti-Fracture Efficacy of Fosamax

The PSC seeks an order excluding any Merck witness from testifying that Fosamax reduces the risk of fracture (a) in patients without osteoporosis, (b) before 18 months of use, or (c) after 36 months with respect to vertebral fractures and after 48 months of use with respect to hip fractures.

(a) Efficacy for Patients Without Osteoporosis

The PSC seeks to preclude Merck's witnesses from testifying that Fosamax treatment reduces the risk of fracture in patients who use it for the prevention of osteoporosis. The PSC cites Merck's clinical trial data showing no statistically

significant reduction in fracture incidence among non-osteoporotic patients over the placebo group. The PSC also cites deposition testimony by Merck scientists and an analysis by an FDA reviewer stating that there is no fracture reduction for non-osteoporotic patients.

Merck responds that Fosamax has been proven to help non-osteoporotic patients maintain bone mineral density and thereby prevent them from developing osteoporosis. Because bone mineral density correlates strongly with fracture risk, Merck contends that the prevention of osteoporosis in turn lowers the risk of future fractures. In fact, this is an FDA-approved indication for Fosamax: "For the prevention of osteoporosis, FOSAMAX may be considered in postmenopausal women who are at risk of developing osteoporosis and for whom the desired clinical outcome is to maintain bone mass and to reduce the risk of future fracture." Merck also cites published meta-analysis studies finding that, when used for the prevention of osteoporosis, Fosamax treatment reduces the risk of spine fractures.

The Court sees nothing wrong with Merck's efficacy argument and no grounds to enter the order requested by the PSC. Cross-examination and competing expert testimony by the PSC's experts are the appropriate ways for the PSC to expose what it

believes are flaws in Merck's position. Therefore, the motion is DENIED.

(b) Short-term Efficacy

The PSC seeks to preclude Merck's witnesses from testifying that Fosamax reduces the risk of vertebral fractures before 12 months of use or hip fractures before 18 months of use. The PSC cites clinical trial data, FDA analysis of the data, and deposition testimony by two of Merck's experts that there is no statistically significant data to support claims of fracture reduction with shorter periods of Fosamax use.

Merck responds that the absence of statistically significant fracture reduction data before 12 or 18 months does not mean the absence of any fracture risk reduction before then. According to Merck, there is necessarily some period of time in a clinical trial to accumulate enough fracture data before statistically significant results can be achieved. Furthermore, Merck contends that the FDA analysis cited by the PSC only looked at data from one of the two arms in a clinical trial.

The parties are simply drawing different conclusions from the same data. The Court does not find the analytic gap between the data and Merck's conclusions to be so wide as to justify exclusion. Cross-examination and competing expert testimony by the PSC's experts are the appropriate ways for the

PSC to expose what it believes are flaws in Merck's reasoning. Therefore, the PSC's motion with respect to short-term efficacy is DENIED.

(c) Long-term Efficacy

The PSC seeks to preclude Merck's witnesses from testifying that Fosamax reduces the risk of vertebral fractures after 36 months of use or hip fractures after 48 months of use. The PSC cites clinical trial data, an FDA analysis, the deposition testimony of two Merck experts, and studies from the United Kingdom (the "ICARO studies") to support that there is no evidence of reduced fracture risk with longer periods of Fosamax use.

Merck responds that an extension study of the largest Fosamax trial (the "FLEX study") found that patients who discontinued treatment after five years saw a dramatic worsening in their bone mineral density levels, whereas patients who continued treatment for an additional five years maintained bone mineral density at the hip and spine and experienced statistically significant fewer vertebral fractures. Merck also contends that a subgroup analysis found a statistically significant decrease in non-vertebral fractures as well. Merck claims that the ICARO studies have numerous flaws and therefore

Merck's experts have ample reason to disagree with their results.

The PSC replies that the FLEX study was not a true placebo-controlled trial because all participants had taken Fosamax for five years and the study did not measure fracture reduction as a primary endpoint. The PSC also criticizes the use of bone mineral density changes as a surrogate marker for fracture reduction efficacy.

The Court again finds that the parties are simply interpreting the data differently, that Merck's conclusions are sufficiently reliable to be admitted, and that cross-examination and competing testimony by the PSC's experts are the proper ways to expose what the PSC believes are flaws in Merck's arguments. Therefore, the PSC's motion with respect to long-term efficacy is DENIED.²²

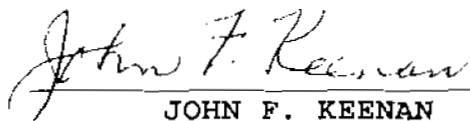
²² The PSC also claims that admission of expert testimony on efficacy outside of the 18 to 36 month window would violate Fed. R. Civ. P. 26(a)(2)(B)(i), which requires that an expert's report contain a complete statement of all opinions he or she will express and the basis and reasons for them. The PSC points out that several of Merck's experts have admitted at deposition that Fosamax has limited fracture reduction efficacy. Therefore, according to the PSC, the admission of "different opinions at trial would constitute serious surprise and prejudice to plaintiffs." (PSC Mem. at 26.) Because this argument is not based on any alleged deficiency in expert witness reports, the Court finds that Rule 26(a)(2)(B)(i) is not applicable. Impeachment with prior inconsistent statements is the appropriate way to prevent a witness from changing his or her testimony between deposition and trial. The PSC also cites authority prohibiting the submission of an affidavit contradicting prior deposition testimony to defeat a summary judgment motion, (PSC Mem. at 26), but does not attempt to explain how this is relevant in a Daubert motion.

IV. Conclusion

This constitutes the Court's ruling on the omnibus Daubert motions. The Court has considered all other arguments by the parties and finds them to be without merit.

SO ORDERED.

Dated: New York, New York
July 27, 2009



JOHN F. KEENAN
United States District Judge