192 N.J. 81, 98-104 (2007); Lopez v. Swyer, 62 N.J. 267, 273-76 (1973). B. Adequacy-of-Warning Laws "> Original Wordprocessor Version
(NOTE: The status of this decision is .)

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SUPERIOR COURT OF NEW JERSEY

APPELLATE DIVISION

DOCKET NO. A-3280-07T13280-07T1

ANDREW MCCARRELL,

Plaintiff-Respondent,

v.

HOFFMAN-LA ROCHE, INC., and

ROCHE LABORATORIES, INC.,

Defendants-Appellants.

0x08 graphic

Argued December 1, 2008 - Decided

Before Judges R. B. Coleman, Sabatino and Simonelli.

On appeal from the Superior Court of New Jersey, Law Division, Atlantic County, Docket No. L-1951-03.

Paul W. Schmidt (Covington & Burling LLP) of the Washington bar, admitted pro hac vice, argued the cause for appellants (Gibbons P.C., attorneys; Michael X. Imbroscio (Covington & Burling LLP) of the Washington bar, admitted pro hac vice, and Mr. Schmidt, of counsel; Diane E. Lifton, on the brief).

David R. Buchanan argued the cause for respondent (Seeger Weiss

LLP, attorneys; Michael D. Hook (Hook & Bolton, P.A.) of the Florida bar, admitted pro hac vice, and Mr. Buchanan, of counsel; Mr. Buchanan, on the brief).

Riker, Danzig, Scherer, Hyland & Perretti, LLP, attorneys for amicus curiae Pharmaceutical Research and Manufacturers of America (Anne M. Patterson and Maha M. Kabbash, on the brief).

McCarter & English, LLP, attorneys for amicus curiae The New Jersey Lawsuit Reform Alliance (David R. Kott, of counsel; Mr. Kott and Zane C. Riester, on the brief).

McCarter & English, LLP, attorneys for amicus curiae The Healthcare Institute of New Jersey (Edward J. Fanning, Jr., of counsel and on the brief).

PER CURIAM

This appeal arises out of a lawsuit filed by plaintiff Andrew McCarrell, a resident of Alabama, against defendants Hoffman-LaRoche and Roche Laboratories (collectively, "Roche"), which manufactured and distributed the prescription drug Accutane. Plaintiff alleged that as a result of taking Accutane for an acne condition, he developed inflammatory bowel disease ("IBD"). The IBD led to the surgical removal of his colon and other serious medical complications. A jury returned a verdict in plaintiff's favor on his products liability claim against Roche, but not on his consumer fraud claim, and awarded him compensatory damages.

On appeal, Roche challenges several rulings by the trial court, including the court's admission of the testimony of plaintiff's causation expert; the admission and use of various internal Roche documents, including records known as causality assessments; the exclusion of certain defense proofs relating to the number of Accutane users; and the denial of Roche's motions for judgment on various grounds.

We affirm the trial court's admission of testimony from plaintiff's causation expert. We also affirm the trial court's other rulings appealed by Roche, with a significant exception. Specifically, we hold that the court's restrictions upon the defense presenting to the jury

certain background evidence about the number of Accutane users constituted reversible and harmful error. Consequently, the judgment must be vacated, and the matter remanded for a new trial. On remand, the trial court shall also consider Roche's contention that plaintiff's failure-to-warn claims are preempted by federal law, in light of the United States Supreme Court's recent opinion in Wyeth v. Levine, 555 U.S. ___, ___ S. Ct. ____, ____ L. Ed.2d ____, No. 06-1249 (March 4, 2009).

I.

We shall not attempt to state comprehensively the proofs that emerged in the extensive pretrial proceedings and at the lengthy jury trial that consumed fifteen days. We instead summarize the facts most significant to the issues Roche has raised on appeal.

A. Accutane

Accutane is a prescription medication developed by Roche. It was approved by the Food and Drug Administration ("FDA") in 1982 to treat recalcitrant nodular acne, a severe and disfiguring skin disease characterized by large, inflamed cystic lesions on the patient's face and back.

Chemically, Accutane is isotretinoin, or 13-cis-retinoic acid. It is part of the family of drugs known as retinoids, vitamin A derivatives. Roche initially studied the use of retinoids as potential chemotherapy for the treatment of cancer. As a result of its research, Roche discovered that retinoids were effective in treating nodular acne.

Although the exact "mechanism of action" for how Accutane works is unknown, Roche discovered that the drug was effective in suppressing the production of oil and waxy material

produced in the sebaceous glands. Nodular acne is caused by the accumulation of sebum under the skin, which ultimately ruptures the follicle wall, forming an inflamed nodule. Accutane was found to be highly effective in treating nodular acne that has been recalcitrant to standard treatments.

Accutane is a teratogen, meaning that there is a high risk that if a woman takes the drug while pregnant, her child will be born with life-threatening birth defects. Additionally, common adverse effects from Accutane include dry skin, lips, and eyes, conjunctivitis, decreased night vision, muscle and joint aches, and elevated triglycerides.

Prior to receiving FDA approval for Accutane, Roche conducted several pre-clinical studies of the drug, using dogs. Those studies revealed instances of gastrointestinal bleeding in the treated dogs.

Roche also conducted a pre-FDA approval clinical study of Accutane on 523 patients, 21.6% of whom suffered some gastrointestinal side effects. Nevertheless, Roche did not include any warnings about IBD on the original 1982 Accutane label.

B. IBD

IBD is a chronic idiopathic inflammation of the small bowel and the colon. IBD most commonly presents as one of two diseases: Crohn's disease or ulcerative colitis. Ulcerative colitis is a chronic inflammation and ulceration of the inner lining of the cells of the colon. Crohn's disease is similar to ulcerative colitis, in that it causes inflammation and ulcers, but it can attack any part of the digestive tract from the mouth to the anus. Patients with Crohn's disease commonly experience abscesses, fistulae, and fissures within the bowel and around the rectum and anus. IBD occurs when a trigger sets off an immune reaction, or inflammation,

and for some reason the patient is unable to regulate the body's response.

The causes of IBD remain largely unknown. However, several factors are associated with a statistically-increased rate of IBD, including family history, prior infections, and the frequent use of antibiotics. The peak age of onset of IBD is young adulthood.

IBD is a permanent condition, although the symptoms may remit and recur. The common symptoms of IBD include diarrhea, gastrointestinal bleeding and rectal bleeding. About seventy percent of patients diagnosed with Crohn's disease undergo surgery to remove their colon.

C. Roche's Warnings About Accutane

After it began selling Accutane, Roche received several post-marketing reports of patients who had developed IBD following their use of the drug. By 1983 Roche had received "more than a handful" of reports of IBD and peptic ulceration in Accutane users, particularly in patients taking the drug outside of the clinical trial. Dr. William Cunningham, director of medical affairs for Roche, testified that he could not then determine

> what the relationship was, because we only had a handful [of reports]. . . . [B]y this time [i.e., 1983] . . . we estimated about 300,000 patients had been treated . . . so we had about six or seven or eight patients with these two diseases in a total population of about 300,000.

Roche did not perform clinical trials to test the relationship between Accutane and IBD. Nonetheless, it made certain labeling changes after it received this additional risk information in the early 1980s.

Specifically, in March 1984, Roche revised the Accutane warning, explaining in a "Dear Doctor"

letter that:

> Ten Accutane patients have experienced gastrointestinal disorders characteristic of inflammatory bowel disease (including 4 ileitis [inflammation of the small intestine] and 6 colitis [inflammation of the colon, a form of ulcerative colitis]). While these disorders have been temporally associated with Accutane administration, i.e., they occurred while the patients were using the drug, a precise cause and effect relationship has not been shown. Roche is continuing to monitor adverse experiences in an effort to determine the relationship between Accutane . . . and these disorders.
>
> [(Emphasis added).]

Roche also amended the "WARNINGS" section of the Accutane label (or package insert provided to physicians) to include the following:

> Inflammatory Bowel Disease: Accutane has been temporally associated with inflammatory bowel disease (including regional ileitis) in patients without a prior history of intestinal disorders. Patients experiencing abdominal pain, rectal bleeding or severe diarrhea should discontinue Accutane immediately.
>
> [(Emphasis added).]

Dr. Cunningham was involved in developing Accutane and in designing the product's label. He explained that the term "temporal," (or "temporally") as used in the "Dear Doctor" letter, meant "somehow relating to the time, implying the time of administration [of the drug]."

Nurse Eileen Leach, medical director of dermatology at Roche, offered similar testimony. She contended that the term "temporal," as used in this context, meant that "during the time that the patient was taking Accutane, they developed symptoms, or they reported symptoms." She elaborated that the word "associated" meant that Roche had received reports of an adverse event. According to Leach, such language contrasts with the term "cause," which would connote a biological connection between the adverse event and the use of the drug.

Roche's Sales Desk Reference, a manual used by the company's sales personnel in answering

questions about its drug products, stated that some Accutane patients had experienced symptoms characteristic of IBD. The manual added that "[t]hese disorders have been temporally associated with Accutane administration, that is to say, the symptoms occurred while the patients were receiving the drug."

Dr. Martin Huber, head of drug safety for Roche, differed with the definition of "temporally" contained in the sales manual. He claimed the term meant that "it occurs in a reasonable temporal association," or within a reasonable time after taking the drug. Dr. Huber acknowledged that if Accutane caused IBD, the symptoms might not become readily apparent until after a patient had stopped taking the drug.

Roche also published a patient brochure for Accutane. The brochure contained a warning about the drug's possible gastrointestinal side effects. The brochure stated, in pertinent part, that "ACCUTANE MAY CAUSE SOME LESS COMMON, BUT MORE SERIOUS SIDE EFFECTS" and patients should be "ALERT" for "SEVERE STOMACH PAIN, DIARRHEA, RECTAL BLEEDING." Patients were advised in the brochure that if they "EXPERIENCE ANY OF THESE SYMPTOMS" they should discontinue taking Accutane and check with their doctor.

Patients were further warned in the brochure that these symptoms "MAY BE THE EARLY SIGNS OF MORE SERIOUS SIDE EFFECTS WHICH, IF LEFT UNTREATED, COULD POSSIBLY RESULT IN PERMANENT EFFECTS." The same warnings were reprinted on the blister packaging for Accutane. These warnings remained unchanged as of 1995, when plaintiff began using the drug.

D. Post-Marketing Monitoring and Causality Assessments

After Accutane was approved for sale, Roche was obligated to monitor the safety of the drug

on a continual basis and to report safety findings to the FDA. Dr. Alan Bess, then head of drug safety for Roche in the United States, was responsible for collecting the data on adverse drug reaction ("ADR") reports the company received about Accutane. As Dr. Bess indicated, Roche received such reports through its call center. The calls came from physicians, pharmacists, patients, family members, and attorneys. Roche also received information indirectly through MedWatch, the FDA's voluntary reporting program.

Various Roche employees, generally nurses and drug safety associates, responded to adverse event reports that came into the call center. These employees recorded each caller's responses on the MedWatch form. That form included entries for the duration of the Accutane therapy, the drug dosage, the age and sex of the patient, his or her family and medical history, the onset of symptoms, the ultimate outcome, and whether the adverse event abated after the patient stopped using the drug. A Roche medical reviewer typically examined each ADR report and contacted the patient, doctor, or reporter to obtain missing information, including copies of the patient's medical reports. Dr. Bess explained that the goal of this ADR review process was to obtain as much accurate information as possible to enable Roche to "make a determination as to whether the drug was in any way responsible for causing" the adverse event. Dr. Bess described the process as a "pretty vigilant system," and said his group was often successful in getting all of the necessary information.

Roche logged the information from the ADR reports into a database known as "ADVENT." If the reporter of an ADR provided the company with his or her assessment of an alleged relationship between Accutane and the adverse effect, Roche would record that assessment. Roche would do so by noting the reporter's assessment in the ADVENT data field.

The ADVENT database also contained a specific field that reflected the company's own assessment of potential relatedness of the adverse event to the drug. A "yes" response in this

data field could signify that the company had found a reasonable probability that the adverse event is related to the drug. In that regard, Roche reviewed the individual reports of adverse events, obtained additional information when necessary, and made its own assessments of causality. The ADVENT database also contained a Council for International Organizations of Medical Sciences ("CIOMS") field, in which Roche supplied a narrative discussion of the potential causal relationship between the adverse event and the drug treatment.

Dr. Huber explained that such so-called "causality assessments" are performed by Roche to identify cases that warrant a more thorough evaluation. They are required by regulation to be conducted in Europe, but not in the United States. He testified that, despite the nomenclature, "causality" assessments are not conducted to determine actual causality, but rather to determine whether there is simply evidence of an "association" between the adverse effect and use of the drug. He contended that the causality assessments help Roche personnel understand if "we see enough evidence that we need to take action."

Dr. Bess, on the other hand, defined a causality assessment differently than Dr. Huber. Dr. Bess described the term as one "used in the world of drug safety to demonstrate a relationship, a cause and effect relationship, between the drug and an adverse event."

In assessing causality, Roche utilized the "Naranjo algorithm," a questionnaire created to help determine the likelihood of whether an adverse drug reaction is related to the drug's use. The Naranjo algorithm was scientifically designed to decrease, in particular, inter-observer variability. It consists of ten "yes" or "no" questions, expressed as follows:

Question	Yes	No	Do Not Know	Score
1. Are there previous conclusive reports on this reaction?	+1	0	0	
2. Did the adverse event appear after the suspected drug was administered?	+2	-1	0	
3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	
4. Did the adverse reactions appear when the drug was readministered?	+2	-1	0	
5. Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	+2	0	

6. Did the reaction reappear when a placebo was given?	-1	+1	0	
7. Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	0	
8. Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	+1	0	0	
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	
10. Was the adverse event confirmed by any objective evidence?	+1	0	0	

Points are added or subtracted to the Naranjo algorithm based on the answer to each of the questions, generating a total score ranging from -2 to +10. The total score classifies each particular case as either "highly probable" (>8 points), "probable" (5-8 points), "possible" (1-4 points), or "doubtful" (0 points).

Health care professionals at Roche used this Naranjo scoring method to conduct the primary review of the reported ADR information. The results were then sent to Roche's headquarters in Switzerland, where, according to Dr. Huber, a physician would review the results to "see if there was anything they felt from a medical point of view needed to be adjusted."

Dr. Daniel Reshef, a physician and director of drug safety at Roche, conducted a final review of the Accutane causality assessments. Dr. Reshef made his own independent medical judgment as to whether they were correct. The reviewed assessments were included in the ADVENT database, but Roche was not required to submit them to the FDA.

Periodically, Roche, like other pharmaceutical companies, prepared internal reports evaluating the ADR reports. In one such document, entitled "Internal Causality Assessment," Roche stated that through January 6, 1994, 104 colitis and related syndromes, including Crohn's disease, had been reported in Accutane users. Of those 104 cases, 33 were given a "possible" or "probable" causality rating. Based on that information, Dr. H. Lefrancq, a physician with Roche, commented in a February 24, 1994 internal memorandum that "[i]t is reasonable to conclude from this data, that in rare cases Roaccutane [Accutane's brand name in Europe] may induce or aggravate a preexisting colitis."

Dr. Peter Schifferdecker, also a physician employed by Roche, reviewed the post-marketing ADR reports received from patients using Roaccutane for the six-month period from January 1 through June 30, 1988. In his internal report dated August 17, 1988, Dr. Schifferdecker wrote that "[s]ince [the drug's] introduction, Roche Drug Safety received 38 case reports of colitis and proctitis in association with Roaccutane treatment." He added that "[a] history of diarrhea, or colitis, or rectal bleeding was reported in six patients, suggesting a preexisting irritability of the intestinal mucosa in these patients with a possible exacerbation or aggravation of these

symptoms by Roaccutane." Dr. Schifferdecker concluded:

> It appears that cases of colitis and proctitis reported to Roche . . . are within the spontaneous incidence rates of the background population, although underreporting of such cases may occur. It should be stressed that approximately one half of the patients were at a certain risk for the development of colitis prior to Roaccutane treatment. Although there is evidence from in vitro and animal experiments that Roaccutane may protect the organism from experimental colitis, Roche . . . will further monitor closely cases of colitis and proctitis reported in association with Roaccutane treatment.
>
> [(Emphasis added).]

Despite this recognition by Dr. Schifferdecker in 1988 of the need for close monitoring, Roche did not thereafter conduct any clinical trials or epidemiological studies as to whether Accutane caused IBD.

E. Plaintiff's Use of Accutane and His Injuries

On March 6, 1995, plaintiff, who was then twenty-three years old, saw Dr. Ann Gerald, an Alabama dermatologist, for treatment of acne. Dr. Gerald's records indicate her perception at the time that plaintiff had "been treated for the past 5 or 6 years with antibiotics" and that he was "getting afraid" to continue taking them. However, plaintiff testified that he told Dr. Gerald that he had taken antibiotics "five or six years ago," not that he had been on a continuous course of antibiotics.

It is undisputed that during her initial consultation with plaintiff, Dr. Gerald discussed Accutane and certain of its side effects with him. Dr. Gerald stated it was her practice to discuss with her patients only Accutane's common side effects, which included teratogenicity, elevated triglycerides and lipids, dry eyes, dry skin, chapped lips, vision problems, and headaches.

The information provided in the Accutane label about IBD did not indicate to Dr. Gerald that IBD was a significant risk for plaintiff because he did not have a family history of bowel disorders. Moreover, she understood the phrase "temporally associated," as used in the "Dear Doctor" letter, to mean that the identified side effects would appear only at the time of Accutane's administration to the patient and not after the drug had been discontinued.

Dr. Gerald also typically gave her patients the Accutane patient brochure. As we have already noted, the brochure contained the warning that Accutane may cause less common, but more serious, side effects, such as severe stomach pain, diarrhea, and rectal bleeding. Dr. Gerald admitted, however, that there was no indication in her file, as she claimed was her practice, that she had specifically given plaintiff the brochure.

Plaintiff insisted that Dr. Gerald never warned him that Accutane could cause permanent IBD. He claimed that if he had been so warned, he would not have taken the drug because his acne was not severe enough as to risk such a permanent injury.

As prescribed by Dr. Gerald, plaintiff began treatment for his acne with Accutane on June 22, 1995. He did so after an unsuccessful course of treatment with Bactrim, an antibiotic. Plaintiff received a dosage of 40 milligrams (mgs) of Accutane twice a day, or slightly over 1 mg per kilogram of body weight per day (1 mg/kg/day). During that treatment with Accutane, Dr. Gerald monitored plaintiff every thirty days for possible side effects. Plaintiff initially experienced chapped lips, dry eyes, and pain in his knee, but no gastrointestinal effects.

Plaintiff stopped taking Accutane on October 19, 1995, after about four months of treatment and after his acne had been successfully cleared. As of February 6, 1996, plaintiff was not experiencing any side effects.

However, in the summer of 1996, plaintiff began having abdominal pain and diarrhea. As that summer progressed, his symptoms worsened. He experienced stomach cramping, burning diarrhea, and rectal bleeding. Plaintiff was admitted to the hospital in November 1996, suffering from pain, diarrhea, vomiting, and fatigue. He was treated at the hospital for an ulcer, and given a course of antibiotics.

On November 27, 1996, plaintiff was diagnosed with ulcerative colitis. The diagnosis was later changed to Crohn's disease. He was treated with steroids. Around this time, some of the side effects that plaintiff had previously experienced while he was taking Accutane reemerged, including chapped lips and joint pain.

In December 1996, plaintiff underwent a proctocolectomy, a procedure in which his entire colon and rectum were surgically removed and replaced with an ileoanal pouch. He continued to suffer from chronic diarrhea, and had additional surgeries for a rectal abscess. He also was hospitalized for bowel obstructions.

By April 1998, plaintiff's IBD had spread to his ileoanal pouch. He suffered from excessive diarrhea, fever, blood and mucous discharge, abdominal cramping, incontinence and fatigue. To address those persisting symptoms, plaintiff underwent a diverting ileostomy, a surgical procedure in which the small intestine is brought through the abdominal wall to drain into an ileostomy bag. Despite this additional surgery, plaintiff continued to experience problems with incontinence. He had leakage of fecal matter, excess gas and pain. He also claimed humiliation as a result of noises emanating from the bag.

In 2002, plaintiff underwent another surgery, this time to reverse the ileostomy and to reform the ileoanal pouch. The ensuing absence of the ileostomy bag was an improvement, but plaintiff continued to endure a host of complications, including incontinence, pain, cramping,

fatigue and diarrhea. On an average day, plaintiff had eight to ten bowel movements during the day, and two or three at night.

These difficulties prompted plaintiff to retain an attorney. The attorney submitted an ADR report on his behalf to Roche. Based upon that information, internal Roche documents entered into the ADVENT database concluded that plaintiff's IBD was possibly related to his use of Accutane. In the CIOMS comments field, Roche indicated that "ulcerative colitis is listed in the CDS [database] for isotretinoin. Based on the information received for [plaintiff's] case, a causal relationship between the reported event and the treatment with isotretinoin is assessed as possible. Company causality is based on the Naranjo algorithm." (Emphasis added).

F. Plaintiff's Lawsuit

On July 23, 2003, plaintiff filed a complaint against Roche, whose principal place of business is in New Jersey. Plaintiff sought compensatory and punitive damages under the applicable product liability laws, as well as economic losses under the New Jersey Consumer Fraud Act, N.J.S.A. 56:8-1 to -20 ("CFA"). Roche filed an answer and separate defenses. Plaintiff subsequently filed an amended complaint, adding a common-law negligence claim.

By order dated May 2, 2005, the Supreme Court designated all pending and future statewide actions involving Accutane as a mass tort, pursuant to Rule 4:38A. All Accutane cases, including plaintiff's lawsuit, were consequently transferred to Atlantic County to be heard on a coordinated basis. Discovery in the state cases proceeded in tandem with discovery in the federal Accutane multidistrict ("MDL") litigation.

Roche made numerous pre-trial motions, including a motion to dismiss plaintiff's complaint as time-barred under Alabama's statute of limitations, motions for summary judgment on the

adequacy of its warnings, and motions to exclude the testimony of plaintiff's causation expert. The trial court denied all of these motions.

G. Plaintiff's Expert Proofs

1. Causation - Dr. Sachar

Plaintiff retained as his causation expert David Sachar, M.D., a gastroenterologist. Dr. Sachar is board-certified in internal medicine and the past chairman of the FDA advisory committee on gastroenterology. He had been specializing in IBD for thirty years, and has published over 220 articles on IBD, ulcerative colitis, and Crohn's disease. Dr. Sachar is a Professor of Medicine at the Mount Sinai School of Medicine, where he has been teaching since the 1980s.

Dr. Sachar opined that, as a general matter, Accutane in regularly-prescribed doses is a cause of IBD in humans. More specifically, Dr. Sachar contended that Accutane was the cause of plaintiff's IBD.

Dr. Sachar stated that the pharmaceutical industry generally determines whether there is a causal relationship between a patient taking a drug and experiencing an adverse effect by conducting a case controlled, or epidemiological, study. Such studies, according to Dr. Sachar, provide "compelling scientific evidence for a certain factor being a measurably statistically quantifiable risk factor for a certain disease." Because Roche had not conducted such a study with respect to Accutane and IBD, Dr. Sachar claimed that he spent hundreds of hours reviewing other evidence to determine causation.

a. Dog Studies

In reaching his conclusions about Accutane's causation of IBD, Dr. Sachar relied, in part, on

animal studies. These studies included a fifty-five week oral toxicity study of Accutane that Roche conducted on beagles in 1979. The beagles were divided into two control groups. They were further divided by three dose levels: (1) high doses (initially 120 mg/kg/day, thereafter lowered to 60 mg/kg/day); (2) mid-doses (20 mg/kg/day); and (3) low doses (3 mg/kg/day). Among other things, Roche scientists learned from this study that:

> A variety of gross anatomic changes were observed in the gastrointestinal tract at autopsy and their nature is suggestive of gastrointestinal irritation. The frequency with which these changes were observed is clearly dose related; they were observed in the mid- and low-dose groups only in dogs sacrificed at the end of the study but were observed in some high-dose dogs sacrificed at 30 weeks. These findings and the relatively high incidence of gastrointestinal bleeding in treated dogs suggest that treatment with . . . [Accutane] is associated with gastrointestinal irritation. On the other hand, only one high-dose dog and one mid-dose dog had microscopic findings qualitatively different from unmedicated dogs suggesting that the gastrointestinal changes associated with [Accutane] . . . are neither profound nor irreversible.
>
> [(Emphasis added).]

The 1979 beagle study further revealed that high doses of Accutane caused "severe toxicity." Many of the high-dose dogs had what the study described as "signs of gastrointestinal irritation as judged by frequent episodes of black, tarry stools and spots or streaks of fresh blood in the feces." On autopsy, these dogs had an "increased incidence of focal gross lesions in the gastrointestinal tract." By comparison, dogs in the mid-dose group experienced "focal gross anatomic lesions suggestive of gastrointestinal irritation," although not with the same frequency as the high-dose group. The frequency with which blood was observed in the feces of the low-dose animals did not distinguish them from the control group.

Dr. Sachar also reviewed a seven-week oral toxicity study Roche conducted in 1981 on nine dogs. The dogs in this 1981 study were divided into two groups, with six dogs receiving a 120 mg/kg/day dose of Accutane, and three dogs receiving a placebo. The focus of the 1981 study

was to determine the location of gastrointestinal bleeding. The treated dogs had frequent visible blood in their stools, and dark tarry stools associated with stomach bleeding. Treatment-related findings included gastrointestinal upset, diarrhea and bloody mucoid stools.

Dr. Sachar explained that it was important to review and consider the results of these animal studies, which are a prerequisite to FDA approval. He opined that adverse effects in animal studies for a drug should raise a "red flag" as to suspected adverse events in humans. Dr. Sachar acknowledged that some of the dog studies had used extremely high doses. However, he contended that such "megadosing" was "good for suggesting mechanisms of action" in humans, even humans taking Accutane at normal doses.

As part of his review, Dr. Sachar took note of animal studies "in which the end products of the metabolism of the drug produced those effects in the animals at concentrations comparable to those achieved in human patients actually taking Accutane the way it is normally prescribed." Thus, he found that some of the animal studies had, in fact, utilized doses "that were actually achieved in human therapy so that there is a direct plausible link [between Accutane use and the reported gastrointestinal symptoms]."

b. Pre-Approval Human Clinical Study

Dr. Sachar also reviewed Roche's 1981 pre-approval study of Accutane conducted on 523 patients. As we have already noted, this study showed that 21.6% of the patients reported gastrointestinal side effects, primarily adverse impacts on mucous membranes. Dr. Sachar testified that this result was to be expected, given his understanding of the biological mechanism of the drug. He explained that Accutane is effective in curing acne because it affects epithelial cells. Epithelial cells line the surfaces of structures throughout the body, including the skin and the entire gastrointestinal tract. Mucous membranes, which line and

protect the intestines, are comprised of epithelial cells.

As Dr. Sachar noted, cystic acne occurs when the epithelial skin cells multiply and secrete excessive amounts of mucous and sebum. Although he agreed that the exact mechanism of action of Accutane is unknown, Dr. Sachar posited that the drug affects epithelial cells by inhibiting cell growth and inhibiting sebaceous gland function. He opined that since the intestines are lined and protected by a mucosal lining of epithelial cells, it is biologically plausible that Accutane, which has a "direct toxic effect" on epithelial cells, disrupts the mucosal lining of the intestines, leading to damage. The lining and walls of the intestines would become inflamed as a result of this damage. In some individuals that immune reaction would become chronic, resulting in IBD. Accordingly, Dr. Sachar linked intestinal damage caused by Accutane to IBD.

c. Challenge/Dechallenge/Rechallenge Reports

Dr. Sachar also reviewed over a dozen MedWatch case reports for Accutane containing so-called "challenge," "dechallenge" and "rechallenge" events. A "challenge" occurs when a patient suffers an adverse event while taking a prescription drug. A "dechallenge" occurs when a patient is taken off the drug and the adverse effects are abated, and a "positive rechallenge" occurs when the adverse effects reappear on the drug's reintroduction.

The MedWatch form contains a section asking the drug manufacturer whether the adverse event "abated after use stopped or [the] dose reduced," and whether the "[e]vent reappeared after reintroduction." Dr. Sachar stated these MedWatch reports are taken "very seriously," and are "very important" in determining whether there is a causal relationship between a drug and an adverse event.

For example, in MedWatch Report No. 3379, a seventeen year-old female patient began Accutane treatment in 1995. She stopped in 1996, at that time without incident. In 1997 she recommenced treatment with Accutane. In June 1997, she experienced symptoms of Crohn's disease and stopped taking the drug. By December 1998, her Crohn's disease was in remission. In August 1999, she recommenced treatment, and in September 1999, she once again experienced symptoms of Crohn's disease, including abdominal pain and diarrhea.

Report No. 3470 presented a comparable scenario. It involved a twenty-three year-old male patient who began Accutane treatment in November 1981. After experiencing a "flareup" of Crohn's disease, he stopped treatment in February 1982 and the symptoms subsided. The patient recommenced treatment in May 1983, and his symptoms recurred in June 1983. He ultimately underwent an ileostomy in January 1992, after suffering from weight loss, diarrhea, gastrointestinal bleeding, and anemia.

Dr. Sachar further cited to positive challenge/rechallenge reports submitted for (1) a twenty-three year-old male who developed IBD, (2) a twenty-seven year-old male who developed colitis with bloody diarrhea, (3) an eighteen year-old male who developed IBD, and (4) a thirty-six year-old male who developed bloody diarrhea.

Given these various reports of adverse events, Dr. Sachar opined that Roche should have conducted tests to verify if there was a relationship between IBD and Accutane. He asserted that "whether or not a company chooses to do full-fledged case control studies, it must . . . at a minimum, pay special attention and invest special concern about that issue." He added that "rather than pay special attention to this problem . . . [Roche] as a matter of policy, chose to minimize and downplay this risk and, as a matter of policy, deliberately inhibited the dissemination of this concern to the profession and the public."

d. Vesanoid Comparison

Dr. Sachar also reviewed side effects reported about users of Vesanoid. Vesanoid is a chemically-similar retinoid manufactured by Roche, which is used to treat acute promyelocytic leukemia ("APL"). Chemically, Vesanoid is tretinoin, an all-trans retinoic acid. Accutane, or isotretinoin, another retinoid, metabolizes into tretinoin and 4-oxo-isotretinoin. Like Accutane, the exact "mechanism of action" of tretinoin is unknown.

The Vesanoid package insert stated that gastrointestinal disorders, including gastrointestinal hemorrhage, were reported in 34% of clinical trial patients. Dr. Sachar opined that these results were significant, because such a high percentage of gastrointestinal disorders would not be expected, even in APL patients. He criticized Roche for failing to conduct an analysis of disorders reported by patients who took Vesanoid, given its asserted similarity to Accutane.

Dr. Sachar also reviewed a four-week toxicity study of 4-oxo-isotretinoin conducted by Roche in 2001 on a small group of dogs. The dogs in this particular study were divided into two groups, one receiving 40 mg/kg/day and the other 80 mg/kg/day. Several of the dogs suffered from intestinal irritation, watery mucous-containing feces, blood in feces, intestinal adhesions, thickening of the mucosa, and epithelial damage. These symptoms, according to Dr. Sachar, were evidence of intestinal injury and inflammation. Dr. Sachar said that the study supported his overall causation opinions because 4-oxo-isotretinoin is an Accutane metabolite.

e. Causality Assessments

Dr. Sachar also found significance in Roche's internal causality assessments for colitis and apparent IBD syndrome cases, as reported to the company from the time of the FDA's approval of Accutane through January 6, 1994. This data was reflected on the following table:

EVENTS	Total	Ins. Info.	Not related	Remote	Possible	Probable	Highly Probable	Not App.	Not Coded
Colitis	34	8	1	4	7	2	0	8	4
Colitis hemorrhagic	5	1	0	0	3	1	0	0	0
Colitis Pseudo-Membranous	1	0	0	0	0	0	0	1	0
Colitis ulcerative	30	2	1	7	9	2	0	7	2
Colitis ulcerative aggravated	6	1	1	0	1	2	0	0	1
Crohn's disease	9	3	0	3	1	0	0	2	0
Enteritis	2	0	0	0	2	0	0	0	0
Enterocolitis	14	1	0	1	3	0	0	5	4
Ileocolitis	2	1	0	1	0	0	0	0	0

Ileitis regional aggravated	1	0	0	0	0	0	0	1	0
Total	104	17	3	16	26	7	0	23	11

Dr. Sachar also reviewed an internal Roche document, dated December 17, 2002, which stated that there were 159 reports of adverse events from exposure to Accutane received from worldwide sources. Of those patients, sixty-four had Crohn's disease. Roche assessed causality as being "related" in twenty-seven of the sixty-four cases, with the remainder designated either as "unrelated" or "unknown." Additionally, there were twenty-nine cases of IBD reported, of which causality was assessed as "related" in thirteen cases, and sixteen remained "unknown." Dr. Sachar found these assessments significant because "assessment of causality is what all this argument [in this litigation] has been about."

f. Published Scientific Literature

As further support for his opinions on causation, Dr. Sachar relied on medical literature in peer-reviewed journals. He testified about an article detailing a study of isotretinoin by physicians from Massachusetts General Hospital and the University of Chicago Hospitals. See Deepa Reddy, M.D., et al., Possible Association Between Isotretinoin and Inflammatory Bowel Disease, 10 Am. J. Gastroenterology 1569 (2006) (the "Reddy article").

The two groups of university physicians who authored the Reddy article obtained every pertinent MedWatch report filed with the FDA. They also reviewed all ADR reports on file with Roche involving isotretinoin and IBD. Each group of physicians then independently collected

data from the MedWatch reports, including the patient's age and sex, the date of onset of symptoms, the dates of usage, the dosage, diagnostic information, history, the ultimate outcome and dechallenge/rechallenge data.

The separate lists in the Reddy study were assembled and independently reviewed for the likelihood of a causal connection by using the Naranjo scale. The Reddy study treated that scale as a validated and widely-used causality assessment tool. Dr. Sachar similarly considered the Naranjo scale a "validated" instrument, characterizing it as "the medical community's best effort . . . to achieve some kind of objective measurement, free of bias."

The Reddy article stated that between 1997 and 2002, the FDA had received eighty-five reports of patients suffering from IBD following isotretinoin use. The authors found that "[a]ccording to the Naranjo ADR probability scale, 4 cases (5%) scored in the 'highly probable' range for isotretinoin as the cause of IBD, 58 cases (68%) were 'probable,' 23 cases (27%) were 'possible,' and no cases were doubtful." Id. at 1571. The article concluded that:

> In the cases reported to the FDA between 1997 and 2002, isotretinoin appears to be a potential precipitant of IBD. It is conceivable that isotretinoin is acting as a trigger for IBD in already predisposed individuals, or unmasking symptoms in patients with preexisting but subclinical disease. The incidence of the phenomenon is unknown and the data obtained from MedWatch have limitations. Physicians and patients should be made aware of this possible association and it should be included in the already extensive consent process required before isotretinoin is prescribed. We do not think that this should prohibit the use of isotretinoin, but careful consideration should be made in those patients at higher risk for IBD (prior personal history, family history) or with symptoms suggestive of IBD. We hope that our study will increase awareness of the possible association between isotretinoin use and IBD, encourage more reporting of appropriate cases to the FDA, and stimulate further research in this area.
>
> [Id. at 1572 (emphasis added).]

Dr. Sachar also reviewed a peer-reviewed article published in 1987 in the official journal of the

American Gastroenterological Association. See P. Martin et. al., Isotretinoin-Associated Proctosigmoiditis, 93 Gastroenterology 606 (1987) (the "Martin article"). The Martin article focused upon a case report involving a seventeen-year-old boy who had developed acute proctosigmoiditis (a form of IBD), after taking isotretinoin for the treatment of acne. Withdrawal of the drug resulted in a prompt resolution of the boy's symptoms and a reduction in his inflammation. The symptoms returned on rechallenge, but abated when the boy again stopped taking the drug.

The Martin article concluded that "[a]lthough the pathogenesis of the colonic mucosal inflammation remains unknown, the relationship of the [patient's] bouts of proctosigmoiditis to the administration of isotretinoin strongly suggests that the drug was directly responsible." Id. at 606. Dr. Sachar characterized the phrase "strongly suggests," as used in this context, as conveying the "most extreme causation language" that can be found in published medical reports.

Another peer-reviewed medical article cited by Dr. Sachar, published in a 1991 pharmacological journal (the "Reniers & Howard article"), reported that:

> Individuals without a prior history of intestinal disorders have developed IBD while on isotretinoin therapy, making it difficult to assess who is at most risk of developing this complication. Our patient developed rectal bleeding one week after completion of a five-month course of isotretinoin. Given his negative family history for IBD and the strong temporal relationship between the acute onset of ulcerative colitis and recent treatment with isotretinoin, the drug is a probable cause of his diagnosis according to the Naranjo probability scale. It is unlikely that ulcerative colitis occurred in temporal association with, but independent of the use of isotretinoin (i.e., the idiopathic ulcerative colitis).
>
> Many of the toxic effects of isotretinoin can be extrapolated to the early changes seen in IBD, and retinoids may act as a trigger for IBD. There are more than 200 reports to the Food and Drug Administration of gastrointestinal pathology patients treated with isotretinoin, and a large number of unreported cases have been cited through an Internet news

> group. Rectal bleeding has been reported to occur during or several years after treatment with isotretinoin. Individuals with IBD may experience vague symptoms for years prior to diagnosis, which makes the potential association between IBD and past isotretinoin use go unrecognized. . . .
>
> The mechanism by which isotretinoin may induce IBD is unknown. Proposed mechanisms include inhibition of the epithelial cell growth resulting in ulceration and inflammation of the gut mucosa, inhibition of glycoprotein synthesis affecting the integrity of the mucosal wall, and stimulation of killer T cells leading to epithelial cell injury and a resulting inflammatory response.
>
> [Denise E. Reniers & John M. Howard, Isotretinoin-Induced Inflammatory Bowel Disease in an Adolescent, 35 Annuals Pharmacology 1214, 1215 (October 2001) (emphasis added) (footnotes omitted).]

In addition, Dr. Sachar cited a 2006 article from a Netherlands medical journal, which reported that three cases of IBD had been diagnosed from a very small population of patients exposed to isotretinoin. J.L.M. Passier et. al., Isotretinoin-induced Inflammatory Bowel Disease, 64 J. Med. 52 (2006) (the "Passier article"). With respect to that article, Dr. Sachar considered it "a remarkably high frequency for three cases to occur out of a small cohort." This published research "strengthen[ed]" his opinions on causation.

Lastly, Dr. Sachar discussed an excerpt from the Textbook of Gastroenterology 1803 (Tadataka Yamada et. al. eds., vol. 2, 4th ed. 2003). The textbook indicated that "[i] sotretinoin . . . has been linked to acute colitis and to the reactivation of quiescent IBD." Id. at 1803. The textbook also referred to the rechallenge data that Dr. Sachar had also found significant.

g. Plaintiff's Medical History

In assessing what caused plaintiff's IBD, Dr. Sachar reviewed plaintiff's extensive medical history. Dr. Sachar began his analysis by noting that while plaintiff was taking Accutane, he

suffered from the drug's common side effects. These effects included chapped lips, bloodshot eyes (produced by the drying of a mucosal surface) and joint pain. Within a year of taking the drug, plaintiff developed IBD. Significantly for Dr. Sachar, those chronic complications of IBD were accompanied by a recurrence of Accutane's common side effects, even though plaintiff was no longer taking the drug.

Dr. Sachar explained that plaintiff's IBD was "mimicking in these extraintestinal manifestations the same symptoms that the Accutane had induced before [his] bowel disease . . . had become symptomatic." Dr. Sachar further noted that Roche had reviewed plaintiff's case report and had concluded that a causal relationship was "possible."

Dr. Sachar ruled out any other potential cause of plaintiff's IBD, including his family history and his prior use of antibiotics. Dr. Sachar explained that antibiotic-induced colitis occurs at any time within a day or two of taking an antibiotic through about a month after cessation. This contrasts with Accutane-induced IBD which, according to Dr. Sachar, can have a very long latency period.

In sum, Dr. Sachar opined that plaintiff's IBD, a permanent condition, was caused by his use of Accutane. He rendered that opinion "within a reasonable degree of medical probability."

2. Adequacy-of-Warning

Dr. Cheryl Blume, a pharmacologist, testified as plaintiff's expert in drug development and labeling. Dr. Blume holds a doctorate in medical pharmacology and is the vice president of a firm that, among other things, consults drug companies on new drug applications before the FDA. She opined that Accutane's label, which Roche had not changed since 1984, did not accurately reflect the knowledge the company possessed about IBD prior to plaintiff's

treatment.

Dr. Blume noted that from 1984 to 1995, Roche received many ADR reports relating to IBD. These include four MedWatch reports of positive rechallenges, and one positive rechallenge report in a recognized medical journal. According to Dr. Blume, these reports constituted "critically important" information in evaluating the relationship between a drug and an adverse effect. She noted that it was "unusual" for a pharmaceutical company not to change its label after the receipt of five positive rechallenges.

Dr. Blume opined that the Accutane label should have used stronger and more specific language to communicate clearly the risks of IBD from use of Accutane. She was particularly critical of Roche's use of the term "temporally associated" in the package materials. Dr. Blume asserted that Roche should instead have warned that IBD may be a permanent condition, not a condition that will abate once a patient ceases taking the drug.

Additionally, Dr. Blume opined that Roche failed to monitor adequately the ADR reports to determine any potential relationship between Accutane and IBD, as it had promised in its 1984 letter to health care professionals. She was surprised that Roche had not conducted post-marketing randomized clinical studies, which she described as the "gold standard," nor any epidemiologic studies, to follow up on the ADR reports.

Dr. Blume proposed that the Accutane label should have read, in part, that "[b]ased on the scientific analysis of post-marketing adverse events reported in patients following the use of Accutane and evaluation of the dechallenge and rechallenge data, Accutane can induce inflammatory bowel disease in patients without a prior history of intestinal disorders." Roche also should have warned that in some cases symptoms of IBD "persisted even after Accutane treatment has stopped," and that "[e]ven with treatment, inflammatory bowel disease and

Crohn's disease may be permanent."

H. Defendants' Expert Testimony

Dr. Peter Davies, a physician with a Ph.D. in biochemistry and molecular endocrinology and a professor at the University of Texas Health Sciences Center, testified on Roche's behalf regarding causation matters.

Disagreeing with Dr. Sachar, Dr. Davies opined, within a "reasonable degree of medical and pharmacologic probability and certainty," that there was no evidence that Accutane causes IBD. Nor was there any evidence, according to Dr. Davies, of a latency effect.

Dr. Davies contended that isotretinoin passes through the intestinal wall and does not destroy intestinal cells. He differed with Dr. Sachar about the significance of the dog studies, noting that no inflammation was found in the intestinal tracts of the dogs that were sacrificed at the end of the 60 mg/kg/day high-dose toxicity study. Dr. Davies also maintained that adverse reports concerning Vesanoid should not have been considered by Dr. Sachar in evaluating Accutane, because the two drugs, although they are related, produce different effects.

Another defense expert, Dr. Ellen Scherl, a gastroenterologist and director of the Roberts Center for Inflammatory Bowel Disease of Cornell University, likewise opined that Accutane does not cause IBD, and thus Roche's label was accurate. Her opinions were also rendered within a reasonable degree of medical probability and certainty. She contended that plaintiff developed IBD as a result of taking tetracycline and Flagyl (metronidazole) for an ulcer, not from taking Accutane.

Dr. Scherl acknowledged that Roche had not initially provided her with copies of the pre-approval human or animal studies of Accutane, the case reports, the Schifferdecker

memorandum, or Roche's internal causality assessments. She also conceded on cross-examination that Dr. Sachar had once been her mentor, describing him as "one of the leading experts in inflammatory bowel disease."

I. Other Proofs

Apart from these competing medical experts, the parties presented several other trial witnesses, some through deposition testimony and some in person. They included Dr. Gerald, Dr. Cunningham, Dr. Huber, Dr. Bess, Dr. Reshef, Dr. John McClane (a former Roche research scientist), Dr. Leonard Ou-Tim (plaintiff's treating gastroenterologist), Dr. David Wynne (plaintiff's internist), Dr. Phillip Dean (plaintiff's colorectal surgeon), Dr. Willard Stockfisch (plaintiff's family practice physician), Dr. Lisa Columbia (plaintiff's pain management physician), Heather Mayer (a Roche product knowledge manager), plaintiff, plaintiff's mother, and plaintiff's sister. The trial proofs and the summations of counsel focused heavily upon liability issues, devoting far less time to the damages aspect of the case.

J. The Verdict and Judgment

At the close of the evidence, the trial judge granted Roche's motion to dismiss plaintiff's demand for punitive damages. Following deliberations, the jury returned a verdict in plaintiff's favor on the product liability claim, finding that Roche had failed to provide an adequate warning to plaintiff's prescribing physician about the risks of IBD from Accutane. On the other hand, the jury found in Roche's favor on the CFA claim. The jury awarded plaintiff $119,000 for past medical expenses and $2.5 million in compensatory damages.

Thereafter, Roche moved for a new trial or judgment notwithstanding the verdict. After considering oral argument, the trial judge issued an order and an extensive written decision on

February 8, 2008, denying Roche's motion. The court subsequently entered final judgment in favor of plaintiff on March 12, 2008.

Roche's appeal ensued. Plaintiff did not file a cross-appeal on any of the pretrial or trial determinations that went against him, including the jury's rejection of his consumer fraud claim.

Roche specifically argues that (1) the trial court erred in admitting the opinion testimony of Dr. Sachar because his methodology was unreliable and thus improper under N.J.R.E. 702; (2) the court denied Roche a fair trial in admitting the testimony about the Accutane causality assessments and in restricting the defense in presenting competing quantitative proofs, including the actual number of Accutane users; (3) its IBD warnings were adequate as a matter of state law, and also federal law preempted plaintiff's warning claims; and (4) plaintiff's claims should have been dismissed as time-barred under either Alabama law or New Jersey law. The amicus parties have collectively made the same or similar arguments, particularly as to the admission of Dr. Sachar's testimony. We now address those contentions.

II.

We first consider Roche's claim that the trial judge should have barred the expert testimony on causation presented by Dr. Sachar.

To establish liability, plaintiff must, among other things, prove through expert testimony that his use of Accutane caused him to develop IBD. Kemp ex rel. Wright v. State, 174 N.J. 412, 417 (2002). Plaintiff's satisfaction of this causation element hinged upon Dr. Sachar's expert testimony.

Prior to trial, Roche moved in limine to bar Dr. Sachar's testimony and also for summary

judgment on the causation issues. The trial judge was supplied with Dr. Sachar's expert report, as well as the transcripts of Dr. Sachar's thirteen hours of deposition testimony. The judge also considered briefs from the parties on the admissibility issue, as well as oral argument. Given the extensive nature of these presentations, and with the acquiescence of the parties, the judge did not require Dr. Sachar to appear in court for an evidentiary hearing under N.J.R.E. 104. The judge issued an oral decision, ruling that Dr. Sachar's proposed testimony would be admissible at trial, and denying Roche's summary judgment motion.

In denying Roche's motion, the trial judge observed that Dr. Sachar was "one of the premier experts in the field of IBD" and was "highly qualified." Although Dr. Sachar's qualifications alone did not "overcome the question of scientific validity," the judge found that they added "credibility to his opinion." The judge found that the underlying data relied upon by Dr. Sachar was generally followed by experts in the field and that his opinions were based on a proper scientific methodology. In particular, the judge concluded that Dr. Sachar's opinions, predicated on "animal studies, related retinoids, published literature, [and] his own experience and training would be a sufficient basis for him to overcome the [in limine] challenge."

N.J.R.E. 702 governs the admissibility of scientific expert testimony in the courts of our State. It provides that

> [i]f 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 a opinion or otherwise.
>
> [Ibid.]

As construed by our Supreme Court, N.J.R.E. 702 imposes three requirements for the admission of expert testimony:

> (1) the intended testimony must concern a subject matter that is beyond the ken of the average juror; (2) the field testified to must be at a state of the art such that an expert's testimony could be sufficiently reliable; and (3) the witness must have sufficient expertise to offer the intended testimony.
>
> [Creanga v. Jardal, 185 N.J. 345, 355 (2005) (quoting Landrigan v. Celotex Corp., 127 N.J. 404, 413 (1992)).]

At issue here is the second requirement, that is whether Dr. Sachar's causation testimony was sufficiently reliable in the field of scientific research to be admitted.

Traditionally, the proponent of scientific evidence had to demonstrate that the opinions were "generally accepted, within the relevant scientific community" ("the Frye standard"). State v. Chun, 194 N.J. 54, 91 (2008); accord State v. Harvey, 151 N.J. 117, 169-70 (1997) (citing Frye v. United States, 293 F. 1013, 1014 (D.C. Cir. 1923)). Our Supreme Court has relaxed the Frye "general acceptance" standard, particularly in "tort cases involving novel theories of causation offered to connect a plaintiff's injuries to a drug or a toxic substance." Biunno, Current N.J. Rules of Evidence, comment 3 on N.J.R.E. 702 (2008); see Kemp, supra, 174 N.J. at 430-31 (involving defective vaccine); Landrigan, supra, 127 N.J. at 413 (involving exposure to asbestos); Rubanick v. Witco Chem. Corp., 125 N.J. 421, 449 (1991) (involving exposure to a chemical).

Under this more expansive standard, "a scientific theory of causation that has not yet reached general acceptance may be found to be sufficiently reliable if it is based on a sound, adequately-founded scientific methodology involving data and information of the type reasonably relied on by experts in the scientific field." Rubanick, supra, 125 N.J. at 449; accord Kemp, supra, 174 N.J. at 430. Thus, our Supreme Court has "changed the focus of the inquiry from the scientific community's acceptance of the substance of the opinion [as in Frye] to its acceptance of the methodology and reasoning underlying it." Clark v. Safety-Kleen Corp., 179

N.J. 318, 337 (2004).

The initial rationale behind the New Jersey Supreme Court's expansion of the admissibility standard beyond Frye's "general acceptance" test was "the extraordinary and unique burdens facing plaintiffs who seek to prove causation in toxic-tort litigation." Rubanick, supra, 125 N.J. at 433. "In toxic tort cases, the task of proving causation is invariably made more complex because of the long latency period of illnesses caused by carcinogens or other toxic chemicals." Ayers v. Jackson, 106 N.J. 557, 585 (1987). Likewise, the Court has recognized some drug cases "in which a medical cause-effect relationship has not been confirmed by the scientific community but compelling evidence nevertheless suggests that such a relationship exists." Kemp, supra, 174 N.J. at 430.

Under the post-Frye standard, a trial judge assesses "'the soundness of the proffered methodology and the qualifications of the expert.'" Id. at 426 (quoting Rubanick, supra, 125 N. J. at 454). "The court's role is to 'determine whether the expert's opinion is derived from a sound and well-founded methodology that is supported by some expert consensus in the appropriate field.'" Id. at 427 (quoting Landrigan, supra, 127 N.J. at 417). "Support for an expert's methodology may be found in professional journals, texts, conferences, symposia, or judicial opinions accepting the methodology." Ibid. "Courts also may consider testimony from other experts in the field who use similar methodologies." Ibid.

Recently, these reliability-based standards of admissibility were reaffirmed by the Court in Hisenaj v. Kuehner, 194 N.J. 6 (2008). We discuss that case in detail, not only because of its recency but also because of its useful guidance as to the pertinent standards of appellate review.

In Hisenaj, the Court held admissible under N.J.R.E. 702 the expert testimony of a

biomechanical engineer who had been retained by a defendant in a personal injury case. The case arose out of a rear-end automobile collision. The defense expert had opined that the so-called "low impact" nature of the collision made it "highly improbable" that the collision had caused disc herniations in plaintiff's cervical and lumbar spine. Id. at 13. In rendering that opinion, the expert considered, among other things, seventeen biomechanical engineering studies of other persons who had been involved in low-impact vehicular collisions. Id. at 17. None of the persons in those studies sustained chronic spinal injuries. Extrapolating from those studies, the expert opined that the rear-end collision at a low speed did not cause plaintiff's herniations. The expert also relied on literature published in the field. Id. at 22. The expert did no testing of his own. Ibid.

Plaintiff contended that the defense expert's methodology in Hisenaj was seriously flawed, in part because the studies he cited did not include a passenger of the same age and physical characteristics. Id. at 21. Plaintiff also claimed that defense expert overlooked other factors, apart from vehicle speed, that would play a causal role in producing plaintiff's chronic injury. Id. at 23. Plaintiff further argued that the defense expert's testimony contained improper net opinions. Id. at 23-24.

The trial judge in Hisenaj found the defense expert's methodology sufficiently reliable to present to the jury. A panel of this court reversed that finding, determining from its own independent review of the record that the expert's methodology was seriously flawed and in violation of Rule 702. 387 N.J. Super. 262 (App. Div. 2006). As part of its analysis, the panel considered materials that had not been considered by the trial judge when he ruled on the expert's admissibility. Id. at 272-77.

The Supreme Court reversed our decision in Hisenaj and reinstated the trial judge's ruling that

the defense expert's testimony was admissible. 194 N.J. at 25. In its analysis, the Court repeated the "three well-known prerequisites" of Rule 702: "(1) the intended testimony must concern a subject matter that is beyond the ken of the average juror; (2) the field testified to must be at a state of the art such that an expert's testimony could be sufficiently reliable; and (3) the witness must have sufficient expertise to offer the intended testimony." Id. at 15 (citations omitted). The Court found that we had too stringently applied those standards in reversing the trial judge's decision to admit the defense expert. Id. at 23-25. The Court recognized in Hisenaj that "the relationship between the studies and literature on which [the expert] relied and [his] opinions in this matter could be attacked as tenuous." Id. at 24. Even so, the Court emphasized that the flaws in the expert's reasoning could be explored by opposing counsel on cross-examination. Id. at 24. The Court further sustained the trial court's ruling that the expert's causation testimony was not inadmissible as "net opinion," but rather that he had sufficiently provided the "why and wherefore" underlying his conclusions. Id.; see also State v. Townsend, 186 N.J. 473, 494 (2006) (quoting Rosenberg v. Tavorath, 352 N.J. Super. 385, 401 (App. Div. 2002)).

The Supreme Court's analysis in Hisenaj is consistent with our State's developing case law on the admissibility of expert testimony. As we noted in State v. Dreher, 302 N.J. Super. 408, 464 (App. Div.), certif. denied, 152 N.J. 10 (1997), cert. denied, 524 U.S. 943, 118 S. Ct. 2353, 141 L. Ed.2d 723 (1998), "[e]xpert testimony should not be excluded merely because it fails to account for some condition or fact that the opposing party considers relevant." The opposing party "may, on cross-examination, supply the omitted conditions or facts and ask the expert if his or her opinion would be changed by them." Ibid.

Moreover, "[a]lthough trial courts are expected to act as gatekeepers to the proper admission of expert testimony, we do not expect courts to investigate sua sponte the extent to which the scientific community holds in esteem the particular analytical writings or research that a

proponent of testimony advances as foundational to an expert opinion." Hisenaj, supra, 194 N. J. at 16; see also Landrigan, supra, 127 N.J. at 414 (noting that "the trial court should not substitute its judgment for that of the relevant scientific community"); Rubanick, supra, 125 N. J. at 451 (noting that a court should not "directly and independently determine as a matter of law that a . . . complex scientific methodology is sound"). "The court's function is to distinguish scientifically sound reasoning from that of the self-validating expert, who uses scientific terminology to present unsubstantiated personal beliefs." Landrigan, supra, 127 N.J. at 414.

Significantly, as a guide to our assessment of the trial court's decision to admit Dr. Sachar's testimony, the Supreme Court in Hisenaj made clear that our standard of review of such rulings under Rule 702 is a narrow one. "In reviewing a trial court's evidential ruling, an appellate court is limited to examining the decision for abuse of discretion." Hisenaj, supra, 194 N.J. at 12. On appeal, a decision should not be overturned "'unless it can be shown that the trial court palpably abused its discretion, that is, that its finding was so wide off the mark that a manifest denial of justice resulted.'" Brenman v. Demello, 191 N.J. 18, 31 (2007) (quoting Green v. N.J. Mfrs. Ins. Co., 160 N.J. 480, 492 (1999)).

Appellate courts are not to engage in "an unconstrained review" of the merits of the expert's methodology, at least in considering on appeal materials that had not been presented to the trial court. Hisenaj, supra, 194 N.J. at 25. Applying that deferential review standard and "Rule 702's tilt in favor of admissibility," see State v. Berry, 140 N.J. 280, 290-93 (1995), the Court concluded that the trial judge's decision to admit the defense expert's testimony in Hisenaj "was not so 'wide off the mark' as to constitute 'a manifest denial of justice' and an abuse of discretion." Ibid.; see also State v. Wakefield, 190 N.J. 397, 435 (2007), cert. denied, ____ U. S. ____, 128 S. Ct. 1074, 169 L. Ed.2d 817 (2008).

Bearing in mind our limited scope of review, as clarified by Hisenaj, we now turn to the substance of Roche's arguments concerning Dr. Sachar's testimony.

The main thrust of Roche's argument is that Dr. Sachar's methodology in determining causation was scientifically unreliable. In particular, it criticizes Dr. Sachar's reliance upon various Accutane "data points," including (a) the dog studies, (b) case reports, (c) causality assessments, (d) the Lefrancq memorandum, (e) the information on the Vesanoid label and (f) biological theories. Roche contends that Dr. Sachar did not understand much of the data and literature that he considered, and that he misused those materials in rendering his causation opinions here.

Roche also argues that this court should reject Dr. Sachar's testimony as unreliable because the testimony of a different causation expert, proffered by another plaintiff who suffered from IBD after taking Accutane, was rejected as unreliable by the federal MDL court in Florida. See In re Accutane Prods. Liab., 511 F. Supp.2d 1288 (M.D. Fla. 2007), aff'd, Rand v. Hoffman-LaRoche, Inc., 291 Fed. Appx. 249 (11th Cir. 2008) ("Rand"). Roche further asserts that Dr. Sachar overlooked or unfairly discounted information favorable to the defense, and that his testimony contained impermissible net opinions.

For the reasons that follow, we are satisfied that the trial judge did not abuse her discretion or otherwise violate N.J.R.E. 702 in admitting Dr. Sachar's expert testimony.

A. The Animal Studies

We first address Dr. Sachar's partial reliance on the animal studies. In denying Roche's motion to exclude Dr. Sachar's testimony, the trial judge found that the use of animal studies to help establish causation in humans was a "scientifically acceptable methodology." The judge

observed that those studies "show that this drug has a severe impact on the gastrointestinal tract of the animals on which it was tested." Later, in denying Roche's motion for a new trial, the trial judge reiterated that point, noting that "a properly conducted animal study on a drug is an accepted scientific method."

The trial judge did acknowledge that "[t]he two drawbacks of animal studies are, first, that they are done on animals and the results have to be extrapolated to predict the results on humans, and, second, animal testing usually uses larger doses than are used on humans." Even so, the judge concluded that:

> These limitations don't make the methodology unscientific. They do affect the weight to be given and animal studies alone would usually not be enough to give an opinion on causation. However, the scientific community, including the FDA and the scientists at Hoffman-La Roche, clearly believe there is important scientific information to be gained from animal studies. The FDA requires them to evaluate new drugs before approval.
>
> There was a scientific purpose to these studies and it was obviously to investigate the effects of the drugs on a species similar enough to humans that the results would matter. Dr. Sachar testified that he relied on not one, but multiple[,] dog studies in forming his opinion. One of the advantages to dog studies is that the animal can be and usually is autopsied at the end of the study and the scientists can look at animal tissue after the drug has been administered . . . . This is an accepted scientific method to evaluate the effects of a drug. It is not conclusive proof of cause and effect, but it is of the type of information scientists rely on in forming an opinion.

Our Supreme Court has previously recognized that animal studies can be an accepted scientific method to study the safety and efficacy of drugs. See Rubanick, supra, 125 N.J. at 450 (holding that an expert's methodology, which included a review of animal studies, could be deemed "sound and well-founded"). "A finding that experts in the field rely on certain data raises a presumption that such reliance is reasonable." Landrigan, supra, 127 N.J. at 420.

To be sure, "in order for animal studies to be admissible to prove causation in humans, there

must be good grounds to extrapolate from animals to humans . . . ." In Re Paoli R.R. Yard PCB Litig., 35 F.3d 717, 743 (3d Cir. 1994), cert. denied sub nom. General Elec. Co. v. Ingram, 513 U.S. 1190, 115 S. Ct. 1253, 131 L. Ed.2d 134 (1995). However, "a cause-effect relationship need not be clearly established by animal . . . studies" before a expert can testify that, in his or her "opinion, such a relationship exists." Ferebee v. Chevron Chem. Co., 736 F.2d 1529, 1535 (D.C. Cir.), cert. denied, 469 U.S. 1062, 105 S. Ct. 545, 83 L. Ed.2d 432 (1984).

Roche argues that "[Dr.] Sachar offered no basis for comparing the dog gastrointestinal tract to the human tract, and literature recognizes that they are not comparable." However, the potential difference in Accutane's impact upon the human body, as opposed to the dogs in the studies, was ameliorated by the fact that Roche conducted the dog studies as clinical trials to substantiate FDA approval. That endeavor reasonably suggests that, contrary to its present argument, Roche believed the dog testing results were indeed relevant to humans.

Roche further argues that Dr. Sachar's causation opinions were refuted by the "large universe of other animal data," data he allegedly ignored. In support of this point, Roche cites to two studies, the first of which it contends showed "a positive gastrointestinal effect." This first study involved the effect of tretinoin, not isotretinoin, on chemically-induced colitis in mice. Roche's causation expert, Dr. Davies, presented very limited testimony about the mice study, stating simply that it "showed that tretinoin markedly reduced the amount of inflammation in this animal model of inflammatory colitis." Defense counsel did not cross-examine Dr. Sachar about the study. Even on this limited record, the mice study can be reasonably differentiated because it was conducted on a different species and for a different purpose.

The second animal study cited by Roche was said to reveal "no gastrointestinal effect." That study was conducted on eight dogs who suffered from severe canine idiopathic seborrhea (a

skin disorder), to determine the efficacy and safety of treatment with isotretinoin. This animal study also can be reasonably differentiated from the studies relied on by Dr. Sachar.

In addition, Roche claims that Dr. Sachar's methodology was unreliable because he failed to address sufficiently the human studies conducted with Accutane. In particular, Roche points to human studies about the effect of Accutane on malignant intracranial tumors (a 23-patient study), chemoprevention of lung cancer (an 18-patient study), skin cancer prevention (a 523-patient study with retinol and isotretinoin), isotretinoin as treatment for oral leukoplakia (a 44-patient study), and low-dose isotretinoin (the 981-person "Tangrea" study).

Roche did not question Dr. Sachar about any of these human studies except for the 523-patient study. Dr. Davies, the competing defense expert, testified as to the results of only one human study, the Tangrea study. Dr. Davies stated that there were no reports of gastrointestinal effects in the group of patients taking Accutane in that particular study. However, the study indicated that the patients were only taking a dose of .014 mg, not adjusted for weight, and thus heavier patients effectively received even lower doses of the drug than thinner patients. Even at these low doses, seventy percent of the patients in the Tangrea study suffered mucocutaneous adverse effects, namely, chapped lips. Hence, the results of the Tangrea study are not necessarily inconsistent with Dr. Sachar's opinions.

The defense also contends that Dr. Sachar overlooked another human clinical study that did not support his hypothesis. Roche refers in this regard to a study involving seventy-five patients, of whom twenty-five received isotretinoin, twenty-five received tretinoin, and twenty-five received a placebo. As the trial court noted, defense counsel asked Dr. Sachar only "minimal questions" about this study on cross-examination. He admitted that only two patients in the study, one taking isotretinoin and one taking tretinoin, experienced diarrhea. However, on re-direct examination, Dr. Sachar explained that this study actually supported his opinions

on causation because diarrhea was a symptom of IBD, and "in at least 10 percent of the patients, the blood levels of the 4-oxo-isotretinoin were at or above the same levels in the dogs that got the bloody diarrhea."

Moreover, the remainder of the human studies cited by Roche, even if they had been specifically considered by the trial judge in making her evidentiary rulings, do not appear to have been designed to test the causal relationship between isotretinoin and IBD. Consequently, they can be reasonably differentiated on that basis. The fact that Dr. Sachar did not consider these studies himself does not necessarily render his methodology unscientific.

Next, Roche argues that in considering the animal studies Dr. Sachar "gave no justification for extrapolating from the high doses used in these dog studies to the treatment doses used by humans." Plaintiff received a dose slightly over 1 mg/kg/day, whereas the dogs in the other studies highlighted by Roche received doses from 120 mg/kg/day to 3 mg/kg/day.

"Trained experts commonly extrapolate from existing data." Gen. Elec. v. Joiner, 522 U.S. 136, 146, 118 S. Ct. 512, 519, 139 L. Ed.2d 508, 519 (1997). In assessing the results of animal studies, which frequently involve high doses, experts should be careful to consider the dose-response differential between animals and humans. Magistrini v. One Hour Martinizing Dry Cleaning, 180 F. Supp.2d 584, 593 (D.N.J. 2002), aff'd, 68 Fed. App'x. 356 (3d Cir. 2003). See also West's Reference Manual, supra note 13, at 346.

In his testimony, Dr. Sachar acknowledged that some of the doses in the animal studies were "tremendously higher than in humans." He explained that the high-dose studies are ordinarily used to identify "red flags" for human experiences. However, Dr. Sachar stated that some of the dosages in the animal studies upon which he relied were "at concentrations that were actually achieved in human therapy so that there is a direct plausible link." He added that he

had reviewed animal studies "in which the end products of the metabolism of the drug produced those effects in the animals at concentrations comparable to those achieved in human patients actually taking Accutane the way it is normally prescribed." Such testimony reasonably indicates that Dr. Sachar addressed the issue of dosage in a scientific manner.

In a similar vein, Roche argues that Dr. Sachar wrongfully ignored the dose-dependent results in the animal studies, particularly the results for the low-dose dogs. In determining whether there is an association between a drug and an adverse effect, scientists commonly look to whether there is a dose-response relationship, that is, if an increase in exposure yields an increase in risk. The dose-response relationship also involves consideration of whether there is some dose below which there are no permanent effects.

The record indicates that there were observable dose-dependent effects on the dogs in at least some of the animal studies. When the dosage was increased, the gastrointestinal side effects, including visible blood in the dogs' feces, often increased. These dose-dependent relationships lend support to Dr. Sachar's opinion that Accutane disrupts the mucosal lining of the intestines.

Finally, Roche argues that Dr. Sachar ignored the animal studies showing that the dogs' intestinal irritation was temporary, not permanent. For example, the report of the fifty-five-week dog study concluded that the "gastrointestinal changes" associated with Accutane are "neither profound nor irreversible." Roche argues that because IBD is a permanent condition, although the symptoms may remit and recur, the gastrointestinal effects experienced by the dogs in the study could not be extrapolated to IBD in humans. However, Dr. Sachar reasonably addressed this point in his testimony. As Dr. Sachar explained, the dogs were sacrificed at the end of the study. Thus, any conclusions as to the lack of permanency of the condition were premature.

B. ADRs or Case Reports

Apart from Dr. Sachar's alleged misuse of the animal studies, Roche maintains he impermissibly relied upon anecdotal case reports or ADR reports. It contends that Dr. Sachar's testimony should have been excluded because, in forming his opinion, he relied upon over a dozen case reports that described challenge/dechallenge/rechallenge events with Accutane, as well as a case report published in the Martin article.

In denying Roche's motion for a new trial, the judge noted that Dr. Sachar had testified that the case reports were "considered very significant to scientists based on his experience as chairman of an FDA advisory committee." Crediting that testimony, the judge observed that "[a] scan of medical literature will demonstrate that scientists use this method to evaluate causal links between a drug and an adverse effect. Again, this is just one other piece of evidence that Dr. Sachar testified that he relied upon in his opinion." Moreover, defense counsel was given ample opportunity to cross-examine Dr. Sachar about the weaknesses in such case report evidence, including the general tendency of IBD to remit and recur.

We recognize that "[c]ausal attribution based on case studies must be regarded with caution." Federal Judicial Center, Reference Manual on Sci. Evidence 497 (2d ed. 2000). That is so because case reports typically reflect reported data, and do not themselves contain scientific analyses. For instance, case reports may lack medical controls, may fail to screen out alternative causes, and may omit relevant facts about the patient's condition that can be pertinent to causation. Consequently, a number of courts have concluded that anecdotal case reports are not a scientifically reliable basis for an expert's opinion on causation. Nevertheless, several other courts have allowed consideration of case reports as an acceptable basis for showing causation, particularly when accompanied by other reliable scientific evidence.

We have previously upheld the admission of expert testimony that has relied, at least in part, upon case reports or comparable anecdotal evidence. For instance, in State v. Smith, 262 N.J. Super. 487, 498 (App. Div.), certif. denied, 134 N.J. 476 (1993), the State called an expert on the transmission of the AIDS virus. The expert cited to a case report, published in "a well-respected medical journal," in which a nurse was bitten by an AIDS patient and later tested positive for HIV. Ibid. The expert also cited to a second case report submitted to the medical journal's editor, documenting a child who had contracted HIV after he had been bitten by his brother who became infected with AIDS through a blood transfusion. Ibid. Although the expert acknowledged that these case reports were anecdotal in nature, he testified that the reported incidents supported his view that, within a reasonable degree of medical probability, it is possible for the HIV virus to be transmitted through a bite injury. Ibid.

On appeal, defendant argued in Smith that the State's causation expert should have been excluded under Rule 702 as unscientific and unreliable. Id. at 518. We rejected that argument, noting that the expert's testimony had a sufficient foundation to be admitted, given the expert's "background as an infectious disease specialist," "the case reports in a leading medical journal," and the expert's discussions with another doctor who had authored a study confirming HIV transmission through bites. Id. at 521. "Whether these sources and the expert's background were persuasive went to the weight of the opinion, not to its admissibility." Ibid.

In a later case arising in a toxic tort context, Harris v. Peridot Chem. (N.J.), Inc., 313 N.J. Super. 257 (App. Div. 1998), we found no error in the admission of testimony about case reports from an expert in occupational and environmental medicine. The expert opined that plaintiffs' exposure to hydrogen sulfide and sulfur dioxide from a nearby chemical plant had

caused them to sustain respiratory and other injuries. Id. at 273-75. Among other things, the expert relied upon "toxicology literature within occupational medicine." Id. at 274. Her review included a study of the catastrophic release of hydrogen sulfide in Mexico, an incident which resulted in the death or hospitalization of numerous victims. Id. at 299. The expert correlated the Mexico incident to plaintiffs' exposure in New Jersey. Ibid.

The expert in Harris concluded that the symptoms of one of the named plaintiffs were "'almost totally consistent with the symptomatology exhibited in case reports in the medical literature of other individuals with high level acute gas exposure who survived long enough to tell about it.'" Id. at 274 (emphasis added). Defendant challenged the reliability of the expert's methodology. Applying Rubanick, we rejected that challenge, concluding that the "[t]rial court could reasonably have found that the data and information cited by [the expert] was 'of a type reasonably relied on by experts in the scientific field' of occupational medicine." Id. at 300 (citing Rubanick, supra, 125 N.J. at 449).

Roche cites to no published New Jersey decision treating case reports so inherently unreliable as to preclude their consideration as part of a scientific expert's methodology under N.J.R.E. 702. We see no reason to deviate from our past decisions in Smith and Harris and to hold that such case studies are per se excludable from an expert's consideration.

Here, Dr. Sachar's causation opinions were independently supported by peer-reviewed journals, the animal studies, a pre-clinical human study, and a biologically plausible explanation. Additionally, many of the case reports upon which Dr. Sachar relied contained detailed descriptions of the underlying events, including details about the patients' conditions. In fact, Dr. Bess confirmed that Roche's well-trained employees carefully reviewed the ADR reports and were "pretty vigilant" in obtaining all necessary information. Furthermore, Dr. Sachar relied on more than a dozen such reports, lending further reliability to the information.

As in Hisenaj, supra, 194 N.J. at 14, the proffered expert here did not do his own testing, and it was not mandatory for him to do so.

We also find significant that the case reports here included dechallenge and rechallenge reports. Dechallenge and rechallenge reports are included in, or are a type of, a case report. Dunn v. Sandoz Pharms. Corp., 275 F. Supp.2d 672, 682 (M.D.N.C. 2003). Such reports, although they surely have limitations, have been considered valuable in ascertaining causation because they measure a patient's reaction to a drug. Id. at 683. Dr. Sachar described such reports as "very important" in determining whether there is a relationship between the drug and an adverse event. A positive dechallenge/rechallenge case report was also the subject of the Martin article, which was published in a peer-reviewed scientific journal. The authors concluded that the profiled case "strongly suggest[ed]" that isotretinoin use was "directly responsible" for the patient's condition.

We are mindful that the probative value of the dechallenge/rechallenge reports considered by Dr. Sachar is lessened by the fact that the symptoms of IBD can remit and recur. But, as the trial judge found, that concern was a proper subject of cross-examination. See Hisenaj, supra, 194 N.J. at 24 ("'[t]he jury is to determine the credibility, weight, and probative value of expert's testimony.'") (quoting Lanzet v. Greenberg, 126 N.J. 168, 186 (1991)). We are satisfied that the trial court did not abuse its discretion in finding that an expert in this particular scientific field would reasonably rely, at least in part, on such case reports.

C. Causality Assessments

Roche next argues that Dr. Sachar's testimony should have been excluded because he improperly considered Roche's causality assessments as support for his opinions. We disagree.

Prior to trial, the court initially held that "[c]ausality reports based on adverse events and case study reports are admissible but not to prove causation." Shortly thereafter, the court reconsidered its ruling and reversed its decision on how the causality documents could be used at trial. The court ultimately held that "Roche's causality assessments may be considered by the jury in deciding notice and causation."

At trial, the judge admitted three causality documents into evidence: Roche's individual CIOMS causality assessment for plaintiff, and Roche's internal causality assessments for 1984 and 2002. In denying Roche's motion for a new trial, the judge found that these causality assessments represented an accepted and scientifically-validated method of evaluating causation.

The judge's rulings concerning the causality assessments are supported by the regulatory context. Post-marketing reporting of adverse drug experiences is governed by 21 C.F.R. • 314.80 (2008). Pharmaceutical companies are required to report such adverse drug experiences to the FDA. 21 C.F.R. • 314.80(c) (2008). As one of the amicus parties supporting Roche's position acknowledges, post-marketing surveillance, or "pharmacovigilance," is a "crucial aspect of the safe marketing of prescription medicines." That is so "because even the largest pre-approval clinical trials may not detect some rare risks."

Some companies, including Roche, employ causality assessments to analyze individual ADR reports. As we have already noted, in performing its causality assessment, Roche uses the Naranjo scale. That scale is a widely-used causality assessment tool. Roche used the scale to help assess the probability that an adverse reaction was connected to the patient's use of Accutane. The Naranjo scale, according to Dr. Huber of Roche, "structured the assessment in a more consistent manner."

Dr. Sachar demonstrated ample familiarity with the methodology used by Roche in generating the causality assessments. Significantly, he testified at length, both at trial and earlier during depositions, as to the use and purpose of the Naranjo scale. He understood how the scale was used, and he knew that Roche had listed the results in the ADVENT database. Although Dr. Sachar had not specifically reviewed Roche's Naranjo coding manual, he gave "consideration to how those determinations were made." He also demonstrated a detailed understanding of the Naranjo scoring method.

Dr. Sachar acknowledged that physicians generally do not use the Naranjo scale as a clinical tool in their practice. Even so, he explained that the Naranjo scale was "the best, most widely used, and most validated objective causality index used for the purpose of determining causality in research studies, as opposed to private practice."

Ample evidence is presented in the record that the process Roche used in preparing causality assessments involved more than simply logging subjective views about causation into a computer. Indeed, Dr. Reshef, Roche's director of drug safety, described the process as a "very serious effort and investment of resources." Dr. Reshef explained that in making a scientific evaluation of the adverse event, he considered well-established scientific criteria, including temporal association, dechallenges/rechallenges, dose-response, class effect and the absence of alternatives. Dr. Reshef testified that he personally conducted a final review of the assessments, and made his own independent medical judgment as to whether they were correct.

Furthermore, the Naranjo algorithm was used as a validated scientific methodology by physicians in the Reddy study on the causal relationship between Accutane and IBD. As we have noted, the Reddy study appeared in a peer-reviewed journal. The physicians in that study assembled every available adverse event report, and they independently reviewed them

for the likelihood of a causal connection by using the Naranjo scale. The Reddy authors noted that the scale "was found to have high within-rater and between-rater retest reliability[,] in addition to consensual, content, and concurrent validity." Reddy article, supra, 10 Am. J. of Gastroenterology at 1570. Based on their research, they concluded that "isotretinoin appears to be a potential precipitant of IBD." Id. at 1572.

Roche argues that, in spite of their nomenclature, causality assessments are not actually used to determine causation, and therefore they were improperly considered by Dr. Sachar in forming his opinion. Dr. Huber testified that causality assessments are instead conducted to determine only whether there was evidence of an "association" between the adverse effect and the drug use.

However, during depositions, and before he was represented by counsel for Roche, Dr. Bess more expansively defined a causality assessment as "a term used in the world of drug safety to demonstrate a relationship, a cause and effect relationship, between the drug and an adverse event." According to Dr. Bess, the fact that a significant number of cases had been given a "possible" or "probable" causality rating would tend to support a conclusion that the adverse effect was caused by the drug. In fact, Dr. Lefrancq of Roche apparently formed such a conclusion from his own review of causality assessments back in 1994.

We agree with Roche that causality assessments, standing alone, are not sufficient to support an admissible scientific opinion on causation. In this case, however, the assessments were just one part of Dr. Sachar's analysis. We are persuaded that the trial judge did not abuse her discretion or violate the reliability tenets of N.J.R.E. 702 in finding that causality assessments have been accepted in medical or scientific fields as potential indicia of causation, and could, when combined with other evidence, be rationally used to support Dr. Sachar's opinion on

causation.

D. Dr. Lefrancq's Internal Memorandum

Roche next argues that Dr. Sachar's testimony should have been excluded because he erred in considering only that portion of Dr. Lefrancq's 1994 internal company memorandum that supported his opinion. In advancing this argument, Roche does not dispute that internal memoranda prepared by scientists may qualify as the type of data reasonably relied on by experts in the scientific field. N.J.R.E. 702.

In his memorandum, Dr. Lefrancq reviewed the company's internal causation assessments existing at that time and wrote that "[i]t is reasonable to conclude from this data, that in rare cases Roaccutane may induce or aggravate a preexisting colitis." Dr. Sachar referred to this conclusion from Dr. Lefrancq on direct examination, stating that it was supportive of his own causation opinions.

The Lefrancq memorandum did note that it was "reasonable to assume that the drug has the same effect on the internal mucosa as on the other mucosae in the body . . . . As these reactions have always been reversible, the colitis which may develop in a relatively limited number of patients can as well be regarded as reversible." (Emphasis added). Dr. Sachar did not testify as to this portion of the memorandum on direct examination.

Dr. Sachar's failure to comment on the entire Lefrancq memorandum goes to the weight of his opinions, not admissibility. Defense counsel could have cross-examined Dr. Sachar about the rest of the memorandum, but chose not to do so. See State v. Dreher, supra, 302 N.J. Super. at 464 (noting that expert testimony should not be excluded merely because it may omit certain facts or conditions "that the opposing party considers relevant," and thus such

omissions may be explored on cross-examination). Furthermore, Dr. Lefrancq's specific comment that Accutane affects intestinal mucosa (a portion of the memorandum Dr. Sachar did not cite) does not appear helpful to Roche. Instead, that omitted aspect of his memorandum could be read to support Dr. Sachar's biological mechanism theory.

E. The Vesanoid Comparison

Additionally, Roche argues that Dr. Sachar's testimony should have been excluded because his reliance on "Vesanoid data to support his conclusion that Accutane causes IBD" was manifestly unscientific. We are not so persuaded.

To be sure, "the extrapolation or leap from one chemical to another must be reasonable and scientifically valid." Moore v. Ashland Chem. Inc., 151 F.3d 269, 279 (5th Cir. 1998), cert. denied, 526 U.S. 1064, 119 S. Ct. 1454, 143 L. Ed.2d 541 (1999); see also Basko v. Sterling Drug, Inc., 416 F.2d 417, 426-27 (2d Cir. 1969) (finding that the evidence fairly established drugs producing the same idiosyncratic side effect). Case law has applied these extrapolation principles to Accutane and other Vitamin A derivatives. Golod v. Hoffman La Roche, 964 F. Supp. 841, 856 (S.D.N.Y. 1997) (noting that Vitamin A derivatives, including Tegison and Accutane, have similar side effects); Newton v. Roche Labs., Inc., 243 F. Supp.2d 672, 678 n.4 (W.D. Tex. 2002) (noting that Vitamin A and Accutane are retinoids, and thus research on retinoids is relevant to causation).

There was ample evidence before the trial court to enable plaintiff to advocate to the jury that Accutane and Vesanoid are similar drugs, and they produced similar side effects. As we have noted, Accutane is chemically isotretinoin, Vesanoid is tretinoin, and both drugs are retinoids. Accutane metabolizes into tretinoin and 4-oxo-isotretinoin. Dr. Sachar asserted that because Accutane (isotretinoin) metabolizes into Vesanoid (tretinoin), it was not only "reasonable," but

"mandatory" within the scientific community to study the side effects of tretinoin. We are satisfied that Dr. Sachar's review of the Vesanoid data reasonably constituted part of a sufficiently sound and admissible scientific methodology.

Dr. Sachar specifically reviewed the information provided to physicians on the Vesanoid label. The label indicated that thirty-four percent of the patients reporting adverse effects suffered from gastrointestinal hemorrhage. The Vesanoid label also stated that this adverse effect was common in patients suffering from APL. Dr. Sachar testified that these results noted on the label were significant, because such a high percentage of gastrointestinal hemorrhages would not be expected, even for patients suffering from APL. The fact that Dr. Sachar reviewed the Vesanoid label, and not the underlying clinical study that formed the basis for the label's warning, fairly goes to the weight, but not the admissibility, of his testimony on that subject.

F. Biological Plausibility

Roche next argues that Dr. Sachar's testimony should have been excluded because he improperly relied on a hypothesis about how Accutane might cause IBD. The trial judge rejected that argument, and so do we.

In determining whether an association between a drug and a disease is causal, scientists review various factors, including whether there exists a biologically plausible mechanism by which the drug could cause the disease. Magistrini, supra, 180 F. Supp. 2d at 592-93. If the association between a drug and a disease makes sense in terms of known biological mechanisms, it becomes more plausible as a cause-and-effect relationship. Landrigan, supra, 127 N.J. at 416.

Here, as the trial judge found, the reliability of Dr. Sachar's opinions on causation were

strengthened because he presented a biologically plausible explanation for how Accutane causes IBD. Dr. Sachar explained that although the exact mechanism of how Accutane works is unknown, it has been reported in peer-reviewed medical journals (such as the Reddy study), that the drug affects epithelial cells by inhibiting cell growth. The intestines are lined and protected by a mucosal lining of epithelial cells. Therefore, it is biologically plausible that Accutane, which has a toxic effect on epithelial cells, similarly disrupts the mucosal lining of the intestines, causing damage. The lining of the walls of the intestines become inflamed as a result of this damage, and in some individuals that immune reaction becomes chronic, resulting in IBD. That theory is plausibly supported by scientifically authoritative sources. The judge did not abuse her discretion in permitting such testimony.

G. The Federal MDL Litigation

In advocating that Dr. Sachar's expert testimony should have been declared inadmissible under New Jersey law, Roche urges us to adopt the reasoning of the federal MDL judge in Florida, who found the plaintiff's causation expert's testimony in another Accutane IBD case inadmissible under F.R.E. 702. See In re Accutane Prod. Liab., supra, 511 F. Supp 2d at 1288, aff'd, Rand v. Hoffman-LaRoche, 291 Fed. Appx. 249 (11th Cir. 2008). The district judge's ruling was affirmed by the Eleventh Circuit Court of Appeals, under an abuse-of-discretion standard of review. Id., 291 Fed. Appx. at 251.

We decline to follow the federal court's decision in Rand because (1) the causation expert in the Florida case was not Dr. Sachar, and that particular expert's methodology was not as demonstrably sound as that of Dr. Sachar; (2) the standards for expert admissibility under N.J. R.E. 702 are not identical to F.R.E. 702; and (3) the testimonial record in this case, having proceeded to trial, was more developed than it was in the Florida case on a pretrial motion, lending greater confidence to our conclusion to sustain the trial judge's decision to admit Dr.

Sachar's testimony.

The causation expert retained by plaintiffs in Rand was Dr. Ronald Fogel, a practicing gastroenterologist and the author of several articles on gastroenterology. Rand, 511 F. Supp. 2d at 1290. The federal opinion does not reflect that Dr. Fogel, although he was found by the court to be "a well-qualified gastroenterologist," ibid., possesses Dr. Sachar's depth of experience in specializing in IBD, as evidenced by the latter's extensive publications about IBD and related diseases and his chairmanship of the FDA advisory committee on gastroenterology.

Dr. Fogel apparently did not examine all of the data studies, and literature considered by Dr. Sachar. Dr. Fogel also clearly did not possess Dr. Sachar's expertise and familiarity with causality assessments. The federal judge sharply criticized Dr. Fogel on that score, faulting him for not making "any independent inquiry" as to the methodology used by Roche in creating the assessments. Id. at 1297. As the judge noted, Dr. Fogel "had no idea how they were created, why they were created, or in what context the words were used in the documents." Ibid. "He merely accepted them at face value because they refer to 'causality.'" Ibid. The judge found that Dr. Fogel's "willingness to reach conclusions based on documents that he does not understand indicates a bias of wanting to reach a particular conclusion." Ibid.

The federal judge also faulted Dr. Fogel's reliance on certain rat studies, which were not part of Dr. Sachar's analysis here. Id. at 1294. Although he consulted the Reddy study, Dr. Fogel did not consider the breadth of other scientific literature considered by Dr. Sachar. Nor did Dr. Fogel adequately take into account dose levels. Instead, he adopted an extreme view that "Accutane causes IBD no matter what the dose, no matter how long it has been since the individual last took Accutane, and, seemingly, no matter what other background factors are

present." Id. at 1302. Apparently, Dr. Fogel also did not rule out, as directly or as explicitly as Dr. Sachar, other potential causes of the plaintiff's IBD.

Apart from the distinguishing features of these two experts and the different steps in their reasoning, we also note that, as a matter of law, we are not bound by the federal court's assessment of an expert's admissibility. To date, our Supreme Court has declined to adopt the specific criteria of Daubert, supra, the admissibility standard applied in federal courts under F. R.E. 702, although our case law does look to considerations of reliability. See Hisenaj, supra, 194 N.J. at 15.

Moreover, the text and legislature history of N.J.R.E. 702 differs from F.R.E. 702, which was amended in 2000 to incorporate the Daubert factors. Given the differing federal and New Jersey admissibility standards, we are not bound by the federal MDL court's ruling, apart from the substantially distinguishable two experts involved. See Dewey v. R.J. Reynolds Tobacco Co., 121 N.J. 69, 80 (1990).

Lastly, we note that the federal court's analysis in Rand did not have the benefit of the expansive trial testimony that the trial judge had in this case. Here, the trial judge had the opportunity to consider not only the scientific reliability of Dr. Sachar's opinions based upon pre-trial discovery, but she had a second opportunity to reflect upon his methodology at the time of Roche's post-trial motion to set aside the verdict. At that point, the judge had heard Dr. Sachar's trial testimony on direct and cross-examination, the competing testimony of Roche's own causation experts, Dr. Davies and Dr. Scherl, and the advocacy of counsel informed by a complete trial record. The judge reaffirmed her original decision to admit Dr. Sachar's testimony, having had a plenary opportunity to reconsider her decision.

We do not suggest that a trial judge's important gatekeeper function for expert proof should

be tempered by a "wait and see" approach. Even so, we do find significant that the judge in this case, unlike her federal counterpart in Rand, likely had a fuller opportunity to assess the reliability of Dr. Sachar's methodology when she was presented with the issue a second time on motions following this trial.

In sum, we do not find controlling the federal MDL court's determination of non-admissibility in Rand, a case involving a different expert, somewhat different data, and a different legal standard of admissibility. Nor do we find the federal court's rejection of Dr. Fogel's testimony a persuasive basis to exclude Dr. Sachar's testimony in the present case under New Jersey law.

H. Conclusion

Taking each of Roche's criticisms into account, we are satisfied that the trial court did not abuse its discretion in allowing Dr. Sachar to testify. His opinion that Accutane caused plaintiff's IBD was reasonably consistent with sound scientific principles and methodology. The methodology involved data and information of the type that may be reasonably relied on by experts in the scientific field, including animal studies, human clinical studies, dechallenge/ rechallenge reports, class effects, causality assessments, published scientific literature, plaintiff's medical history and biological plausibility. The trial court's decision to admit Dr. Sachar was not erroneous and was definitely not so "wide off the mark" to comprise "a manifest denial of justice." Brenman, supra, 191 N.J. at 31. For these many reasons, we affirm the trial court's rejection of Roche's motion in limine to bar Dr. Sachar under Rule 702, and the court's subsequent denial of a new trial on that evidentiary issue.

III.

Apart from its attacks upon the scientific foundation for Dr. Sachar's causation opinions, Roche

argues that the trial court erred in allowing Dr. Sachar to comment, at various times, about the company's conduct and motives.

The testimony at issue arose in this fashion. Dr. Sachar testified that Roche had not performed any post-approval epidemiological or clinical studies to test the relationship between Accutane and IBD. In an answer to a question as to how Roche should have responded to the IBD reports, Dr. Sachar said, "at a minimum" the company "must pay special attention and invest special concern." After reviewing extensive documents and transcripts of sworn testimony, Dr. Sachar "formed the opinion that rather than pay[ing] special attention to this problem, this company, as a matter of policy, chose to minimize and downplay this risk and, as a matter of policy, deliberately inhibited the dissemination of this concern to the profession and the public." The trial court overruled defense counsel's objection to this testimony.

Later, Dr. Sachar repeated, without objection, that Roche had sought to "downplay or minimize the implications" of the adverse event reports. Dr. Sachar also testified that instead of a systematic evaluation of the reports, Roche engaged in "systematic dismissal and downplaying and suppression." In discussing Roche's 2002 causality assessments, Dr. Sachar testified, again without objection, that he was not "surprised" that Roche had found causality in cases of IBD, because he had come to the "same conclusion." Dr. Sachar added that "[t]he only thing that surprises [him] is that they denied causality." Also, in describing the Naranjo scale, Dr. Sachar, this time over objection, testified that the purpose of the scale was to "eliminate bias," explaining that

> it might be in the interests of a pharmaceutical company, for its own reasons, to try and minimize the likelihood of causality. It might be, hypothetically, in the interests of a plaintiff in litigation to try and overemphasize causality. This [Naranjo scale] is the medical community's best effort at trial to achieve some kind of objective measurement, free of bias.

When she denied Roche's motion for a new trial based, in part, upon the claim that the jury had been impermissibly tainted by Dr. Sachar's views of the company's conduct, the judge found:

> It should be clear that the best type of studies on causation were lacking in this case. The "gold standard" that is considered the most scientifically reliable study is a controlled randomized clinical trial. None have been done to examine the causal relationship of Accutane and IBD. The lack of the best evidence is really the foundation of the defense attack on plaintiff's proof in this case. When Dr. Sachar was attacked on the lack of this type of study as a basis for his opinion, he responded in his deposition by attacking Roche saying it was 'criminal' the defendant did not do clinical trials in light of their own causality assessments. The Court in a motion in limine barred any reference to his belief the failure to test was "criminal." However, the fact that there were no trial[s] done was admissible. Usually it is the manufacturer who tests its product and organizes clinical trials on safety issues. There is something disturbing about defendants' attacking plaintiff's proof because they were unable to produce stronger evidence like clinical trials when the fact is it is the manufacturer who is ordinarily expected to do them but chose not to.

On appeal, Roche argues that Dr. Sachar's testimony as to its alleged motives and conduct amounted to an inadmissible net opinion. It emphasizes that an expert's opinion must be based upon "facts or data." N.J.R.E. 703. It is well settled that an expert's bare conclusion unsupported by factual evidence is inadmissible as a net opinion. Creanga v. Jardal, 185 N.J. 345, 360 (2005). The expert must present the "why and wherefore" supporting his conclusion. Beadling v. William Bowman Assocs., 358 N.J. Super. 70, 87 (App. Div. 2002).

Measured by these well-known standards, we are satisfied that Dr. Sachar's opinions about Roche's conduct were not net opinion. His opinions were based on Roche's receipt, over time, of numerous reports of patients who developed IBD, and its decision not to test Accutane clinically for such a causal relationship.

Roche further argues that even if Dr. Sachar had a basis for his conduct-related opinions, they were improperly admitted. Roche cites to several out-of-state cases in support of that

argument. Those cases, which are not binding on this court, excluded certain expert testimony on business ethics. Here, as the trial court found, Dr. Sachar's testimony regarding the company's lack of testing was presented in response to Roche's attack on his methodology. The testimony was reasonably found relevant and admissible by the trial judge. N.J.R.E. 401.

Even if the conduct-related opinions, most of which were not contemporaneously objected to by defense counsel, were excludable under N.J.R.E. 403, we defer to the trial judge's assessment that they did not warrant a new trial or other relief. Although Dr. Sachar's testimony sharply criticized Roche, his criticisms did not rise to such an inflammatory level that would cause us to find an abuse of discretion by the trial court. See N.J.R.E. 403 (affording discretion to trial judges in excluding testimony claimed to be unduly prejudicial); Green v. N. J. Mfrs. Ins. Co., 160 N.J. 480, 492 (1999) (applying an abuse-of-discretion standard of review to rulings implicating N.J.R.E. 403).

Roche maintains that the trial court, in admitting Dr. Sachar's testimony and denying Roche a new trial, impermissibly "reverse[d] the burden of proof by blaming Roche for not performing more studies." We disagree. The jury was properly instructed in the court's charge about the appropriate burdens of proof and legal elements under products liability law, thereby ameliorating any potential juror confusion about the legal burdens that could have been suggested by Dr. Sachar's criticisms.

Finally, Roche argues that Dr. Sachar's opinions about the company's conduct were improper because they were not specifically disclosed in his expert report. In overruling Roche's objection on this basis below, the trial court found that Dr. Sachar "stated very clearly in [his] deposition that he thought there should have been clinical trials. It is not a surprise to you. That's part of his testimony." The court did not err in allowing similar testimony to be

presented at trial, and in finding that defense counsel was not unfairly surprised.

IV.

We turn to what has been described as the "numbers" issue. The issue refers to the fact that the trial court allowed plaintiff's witnesses and counsel to refer, on repeated occasions, to the number of adverse incidents reported from Accutane users or from other sources while, at the same time, the court restricted Roche's attempt at trial to place those adverse numbers into a larger quantitative context.

Specifically, the judge precluded Roche witnesses from more fully informing the jury about the large number of persons who had taken Accutane before it was prescribed to plaintiff in 1995, and the comparative significance of those figures. Although this issue presents a close and difficult question, we ultimately conclude that it was unfair to Roche for the trial court to have precluded such "numbers" counter-proof and that the court misapplied its discretion.

A central theme of plaintiff's case was that, by 1995, Roche had become sufficiently aware through case reports, causality assessments, animal studies and other sources and research to appreciate a significant cause-effect relationship between Accutane use and IBD. This company knowledge, according to plaintiff, obligated Roche to change its label before 1995 and make more clear and prominent to doctors and patients that Accutane could cause them to suffer IBD, even after they ceased to use the drug.

In support of this theory, plaintiff was allowed at trial to tell and to remind the jury, in numerical fashion, about a host of adverse incidents in which Accutane users contracted or manifested symptoms associated with IBD. During opening arguments, plaintiff's counsel noted that Roche had added the IBD warning to the Accutane label in 1984 as a result of

receiving 13 ADR reports. Counsel asserted that after 1984, Roche continued to receive ADR reports of IBD, but made no further changes to the label. Counsel specifically cited to the 33 cases of colitis referred to in the February 24, 1994 internal report by Dr. Lefrancq.

Thereafter, during the evidentiary phases of the trial, plaintiff's counsel and witnesses continued to stress the numbers of these adverse post-usage events. For example, Dr. Sachar testified that from 1984 to 1995, Roche had received "hundreds of cases" of gastrointestinal complaints. On that same theme, plaintiff's counsel asked Dr. Bess of Roche on cross-examination whether "literally hundreds" of people had reported suffering from diarrhea after taking Accutane, although Dr. Bess responded that he could not recall.

Plaintiff also moved into evidence several exhibits containing figures about gastrointestinal maladies suffered by Accutane users. These exhibits included, for example, Dr. Schifferdecker's memorandum of August 17, 1988, recounting that from January 1 to June 30, 1988, Roche had received 38 ADR reports from patients experiencing colitis in association with the use of Roaccutane. In another exhibit, Roche stated that up to January 6, 1994, 104 colitis and related syndromes, including Crohn's disease, had been reported in Accutane users, of which 33 were given a "possible" or "probable" causality rating. Another Roche document placed in evidence by plaintiff, dated December 17, 2002, set forth that there were 159 reports of adverse events from exposure to Accutane received from worldwide sources, and of those patients, 64 had Crohn's disease.

Quantitative proof about the ADR reports was also presented to the jury through Dr. Sachar's extensive testimony about the various scientific journals. The extensively-cited Reddy article reported that between 1997 and 2002, the FDA had received 85 reports of IBD following isotretinoin use. Reddy article, supra, 10 Am. J. Gastroenterology at 1570. Another article cited by Dr. Sachar reported that there were "more than 200 reports to the Food and Drug

Administration of gastrointestinal pathology in patients treated with isotretinoin, and a large number of unreported cases have been cited through an Internet news group." See Reniers & Howard article, supra, 35 Annuals Pharmacology at 1215.

In discussing these peer-reviewed articles, Dr. Sachar stated that adverse events are often under-reported, estimating that only about 1% of serious adverse events are actually reported. Plaintiff's counsel asked Dr. Sachar if, using that analysis, and given that there were 85 adverse reports of IBD from 1997 to 2002 (as reported in the Reddy article), whether the actual number of patients suffering an adverse event would be close to 8,500. Dr. Sachar agreed, responding, "[i]f you applied that analysis."

Similarly, Dr. Blume, plaintiff's expert in drug development and testing, testified that "it's been estimated that the reports we receive only represent maybe 1 to 10 percent, that's it, of the total number of events appearing out there, because people just don't either know to report them or they don't take the time to call them in." (Emphasis added). Dr. Blume also testified that most companies receive "only 10 percent of the adverse events that are occurring in the public."

With regard to rechallenge reports, Dr. Sachar testified that he reviewed between 12 and 14 MedWatch case reports that contained positive challenge/dechallenge/ rechallenge events. Dr. Sachar stated that these reports are taken "very seriously," and are "very important" in determining whether there is a causal relationship between a drug and an adverse event. Plaintiff's counsel specifically asked Dr. Sachar what it means "[w]hen you see this kind of number," referring to the twelve to fourteen positive MedWatch reports (emphasis added). Dr. Sachar replied that "[i]t means that there's something you have to pay attention to."

In a similar vein, Dr. Blume underscored that from 1984 to 1995, Roche received several ADR

reports relating to IBD, including 4 MedWatch reports of positive rechallenges and 1 positive rechallenge report in a recognized medical journal. These reports constituted, according to Dr. Blume, "critically important" information in evaluating the relationship between a drug and an adverse effect. She opined that it was "unusual" for a pharmaceutical company not to change its label after receipt of 5 such positive rechallenges.

Plaintiff's counsel again highlighted these figures in closing arguments. He reminded the jurors that Roche had received "several" positive challenge/dechallenge/rechallenge reports, and that Dr. Huber of Roche had acknowledged in his testimony that just one dechallenge report can be "significant in terms of assessing causation." With regard to Roche's internal causality assessments, counsel repeated to the jury that out of "a total of 104" reported cases, Roche designated "33 cases [as receiving a] possible or probable causality rating." (Emphasis added). He also noted that the Reddy article authors scored 5 cases as "highly probable," 58 cases as "probable," and 23 cases as "possible."

The jurors were not allowed, however, to hear certain competing figures and expert testimony that Roche had proffered, in an effort to put the adverse numbers stressed by plaintiff in a better light. Prior to trial, plaintiff objected to potential expert testimony from Dr. J. Paul Waymack, a physician and a former FDA medical officer retained by Roche. Among other things, Dr. Waymack had asserted in his expert report that

> [i]n light of the background rate on inflammatory bowel disease, one would anticipate that well in excess of 5,000 patients receiving Accutane would have developed IBD. This number is in excess of an order of magnitude greater than the number of spontaneous event reports. To that end, the spontaneous event reports do not suggest that there is an association between Accutane use and the development of inflammatory bowel disease.
>
> [(Emphasis added).]

The trial judge ruled that, unless further hearing on the subject persuaded her otherwise, she would bar Dr. Waymack from testifying that "adverse event reports, compared to background reports, prove Accutane is not causally related to IBD . . . ."

Having been guided by the court's pre-trial directive limiting Dr. Waymack's testimony, Roche did not call him as an expert witness at trial. However, as the numbers of adverse events repeatedly emerged in plaintiff's case-in-chief, Roche attempted to elicit countervailing factual testimony to try to put those numbers into a more favorable context.

In that regard, Dr. Cunningham, Roche's former director of medical affairs, stated in the defense case that by 1983 about 300,000 patients had taken Accutane, and of these patients only seven or eight had reported symptoms of IBD. Likewise, Dr. Scherl, the defense expert gastroenterologist, testified that IBD is a prevalent disease in North America, affecting a range of 26 to 200 people, per 200,000.

Unfortunately, the defense was blocked in its attempt to develop this numerical context any further. In particular, the defense attempted to have background usage data presented through Dr. Huber, the lead clinical physician for Roche from 1996 to 1999, and the company's head of drug safety from 1999 to 2005. Dr. Huber testified that when he became head of drug safety, he reviewed all the past drug records for Accutane to determine whether there had been a change in the number of reported incidents sufficient to warrant a change in labeling.

Defense counsel then asked Dr. Huber, "what was Roche's estimate on the number of people who had been treated with Accutane since its approval in 1982?" Plaintiff's counsel objected, on the basis that the court had already precluded Roche from eliciting any testimony as to the number of adverse incidents compared with the number of total patients to prove causation. Counsel further argued that the defense could not have presented this evidence through Dr.

Huber. Counsel asserted that such data should instead have been elicited, if from anyone, from Dr. Bess, who was employed at Roche during the relevant time, and who would have been able "to draw that correlation to what happened in 1995."

In response to the objection, defense counsel responded that she was not "suggesting calculations, through the facts she was trying to elicit from Dr. Huber." Rather, defense counsel sought to admit this evidence to show the reasonableness of Roche's conduct, and represented that she "can make it clear it has to do with detecting a safety signal."

More specifically, defense counsel proffered that Dr. Huber would testify that from 1982 to 1995 (when plaintiff began treatment), five million people had been treated with Accutane, and from 1982 to 2005 (when Dr. Huber left the company), twelve to fourteen million people had been treated. As of 1995, there were approximately 130 to 140 ADR reports of Crohn's disease and ulcerative colitis. Defense counsel further represented that Dr. Huber would testify that from 1984 to 1995, Roche had monitored the amount of ADR reports "coming in on a yearly basis," and thus the proffered usage numbers were relevant to "notice and how they detect signals."

The judge sustained the plaintiff's objection to this line of questioning, finding that "[t]o suggest that a reasonable company doesn't explore a rare risk is an unfair suggestion to the jury." Later, during the charge conference, the judge elaborated that "[t]here's only one purpose to bring in [the total number of Accutane users], and that's to show that the number [of ADR and rechallenge reports] is not significant compared to the population, and that's not a fair reason to bring it in." The judge ruled "that it does not matter if the drug is sold to 10 million people or 5 million people or 1,000 people, because if you have a serious risk, it is significant."

Consequently, Roche was not permitted to introduce, among other things, evidence that from 1982 to 1995, five million people had taken Accutane. Roche was confined, in effect, to only its numerical proof from Dr. Cunningham that 300,000 patients had taken Accutane by 1983, and out of that group only about seven or eight patients had reported symptoms of IBD.

With all due deference to the trial judge, whose overall studious and even-handed management of this complex case was exemplary, she erred in forbidding Roche from placing into evidence statistics about Accutane usage that could have made Roche's conduct and labeling decisions appear far more reasonable to the jury. For instance, the "five million users" statistic proffered by Dr. Huber could have given the jurors very relevant contextual background, and possibly led the jury to be more indulgent of Roche's delay in upgrading the risk information on Accutane's label and package insert.

Even accepting, for the sake of argument, Dr. Sachar's contention that adverse events are heavily under-reported, the quantity of actual users of a drug logically is a significant part of the numerical landscape. At a minimum, the actual usage data for Accutane would go to "safety signaling" concerns, i.e., whether Roche had received sufficiently frequent adverse "signals" to take corrective action.

Whether or not the excluded proof would ultimately have altered the jurors' thinking about the reasonableness of the company's conduct, we are persuaded that the trial court unduly impeded Roche from offering this context-supplying evidence. Although the jury did learn from Dr. Cunningham that there were 300, 000 Accutane users by 1983, it would have been far more powerful to the defense presentation if Dr. Huber had been allowed to inform the jury that five million people had taken Accutane by 1995, when plaintiff began his own treatment. Five million is a far cry from three hundred thousand.

Had Roche been allowed to present the statistics showing five million Accutane users and other related counter-proofs, the jury would have had a fuller and more balanced picture of the data bearing upon the company's delay in changing its label. Principles of completeness and fairness warranted the presentation of this contextual information to the fact-finder. See N. J.R.E. 106 (requiring, by analogy, with respect to documentary proof, the introduction of writings or recorded statements "which in fairness ought to be considered contemporaneously"). The judge also should not have precluded Dr. Waymack's comparative expert testimony on this subject, which the jury may have found persuasive in disproving association and causation.

On this discrete and important issue, we do find instructive the federal district judge's observations in Rand about the significance of the Accutane background usage data. The district judge, there in the course of explaining why he had stricken plaintiff's causation expert, observed that:

> Since Accutane's approval in 1982 through 2000, nearly 20 million prescriptions of Accutane for approximately 12 million people worldwide were written. Given the incidence of IBD in the general population which, according to [the expert], is 16-20 per 100,000 persons, one would expect an incidence of IBD occurring in 1,920 to 2,400 persons in an average population of 12 million. Twenty-five percent of IBD cases are diagnosed before patients are twenty years of age. Since Accutane users tend to be adolescents and young adults, one would expect the incidence to be even higher for a group of Accutane users even if Accutane were not a cause of IBD. Moreover, given the episodic nature of IBD, one would expect some of those cases to occur coincidentally after Accutane is given and the disease to subside when Accutane is withdrawn.
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> [Rand, 511 F. Supp. 2d at 1301 (footnotes omitted).]

Although we disagree with the federal MDL judge that plaintiff's expert was obligated to consider such comparative frequencies, we are persuaded that the trial court in the present case should not have barred Roche from presenting additional proofs in its defense that would

have invited such relevant comparisons. Roche should have been permitted to divulge these figures to the jury.

We also are persuaded that the court's error was not harmless, given how much plaintiff's counsel and witnesses repeatedly emphasized the numbers of adverse events in his own case. The court's preclusionary rulings could have easily and prejudicially affected the jury's analysis of the causation issues, as well as its evaluation of the reasonableness of Roche's actions and inactions. Although we do not suggest that the "numbers proofs" should dominate the trial, the defense was entitled to have the jury at least consider this additional contextual evidence.

In sum, we hold that the trial court erred in unduly restricting Roche's effort to provide relevant background statistics and other related proofs about Accutane usage to the jury. The consequence of that restriction was, unfortunately, an imbalanced presentation that had the capacity to produce an unjust outcome. This error is of such a pivotal nature that the judgment in favor of plaintiff must be vacated, and a new trial conducted.

V.

Having concluded that the judgment must be vacated on other grounds, we only briefly address the remainder of Roche's arguments.

A. Statute of Limitations

Roche contends that the trial judge should have dismissed plaintiff's lawsuit as time-barred. It asserts that the judge erred in applying New Jersey law rather than Alabama law in finding the complaint was filed within the statute of limitations. Roche also argues that even if New Jersey law properly controls this issue, plaintiff's complaint was still untimely. We discern no error in the judge's analysis.

Although both states have a two-year statute of limitations for most tort matters, see N.J.S.A. 2A:14-2 and Ala. Code • 6-2-38(i) (2008), New Jersey follows the "equitable discovery" rule for all categories of tort claims. Smith, supra, 400 N.J. Super. at 543. At the time of Roche's motion for summary judgment, April 2007, Alabama applied the discovery rule only to fraud claims, and thus, under Alabama law, plaintiff's claim would be time-barred. Ibid.

After balancing the competing policy interests at stake, the trial judge concluded in a detailed written opinion that New Jersey's statute-of-limitations law applies to this case. The judge recognized that New Jersey has "strong contacts" to defendants, who are both corporations of this State and who manufacture Accutane here, while Alabama, the State where plaintiff resides, has "very little articulated interest" in applying its limitations statute to this lawsuit venued in New Jersey. We believe the judge's reasoning on this point was sound, and was consistent with our supervening decision in Smith v. Alza Corp., 400 N.J. Super. 529, 543 (App. Div. 2008) (applying New Jersey's statute of limitations law to a case filed by an Alabama resident against a New Jersey drug packager).

We also agree that the judge had ample factual grounds to find that our State's two-year limitation period should be equitably tolled to accommodate plaintiff's lawsuit. Plaintiff took Accutane in 1995 and was diagnosed with IBD in 1996. Although plaintiff did not file the instant lawsuit until 2002, the court deemed credible his testimony that he did not know of the association between Accutane and IBD until his grandmother showed him, many years after his IBD diagnosis, an advertisement for a law firm pursuing Accutane cases. The judge did not misapply her authority in applying equitable tolling principles to this setting. R.A.C. v. P.J.S., Jr., 192 N.J. 81, 98-104 (2007); Lopez v. Swyer, 62 N.J. 267, 273-76 (1973).

B. Adequacy-of-Warning Laws

Roche separately argues that it was entitled to judgment as a matter of law because its labeling of Accutane as of 1995 was adequate under applicable state law. We are satisfied that state law does not compel such a conclusion and, moreover, that the jury's contrary finding that the label was inadequate has reasonable factual support.

On this discrete question, the trial judge reached a different outcome in her choice-of-law analysis than she did regarding the statute of limitations. The judge found that Alabama products liability law, see Atkins v. Am. Motors Corp., 335 So.2d 134, 137 (Ala. 1976) (detailing that State's products liability law under the Alabama Extended Manufacturer's Liability Doctrine), rather than New Jersey's Products Liability Act, N.J.S.A. 2A:586-1 to -7, governs plaintiff's substantive products claims. A principal difference between those two State laws is that New Jersey's PLA recognizes a rebuttal presumption that a drug warning is adequate if it was approved by the FDA. N.J.S.A. 2A:58C-4.

The proofs admitted at trial were ample to reasonably support the jury's finding that Accutane's labeling in 1995 was inadequate, whether Alabama products law or New Jersey products law governs that issue. Plaintiff's labeling expert, Dr. Blume, offered several rational grounds for considering Accutane's labeling, as it existed in 1995, insufficient and misleading, including the "temporally associated" terminology that had the asserted capacity of downplaying the long-term risks involved.

Dr. Gerald, plaintiff's dermatologist, specifically testified that she had relied on the Accutane label and that if Accutane caused permanent IBD the label should have said so. Since plaintiff had no prior history of bowel problems, Dr. Gerald was not discouraged by Accutane's label from prescribing the drug for him. On the other hand, Roche had learned by 1995 about numerous instances of patients developing IBD after taking Accutane. Given these and other

proofs, a rational fact-finder could have concluded that Roche's label failed to communicate the risks at stake in an adequate manner.

Although we have concluded in Part IV, supra, that Roche should have been afforded a fuller opportunity to present usage statistics that would have cast the company's labeling decisions in a better light, we are satisfied that at least a triable issue exists here on the adequacy of the label, either under Alabama law or New Jersey law. Brill v. Guardian Life Ins. Co. of Am., 142 N.J. 520, 540 (1995) (requiring the court, on a motion for summary judgment, to view the proofs in a manner that accords all reasonable inferences to the non-moving parties). We also find that the trial judge reasonably applied Alabama products liability law substantively to this matter, and that the trial court may continue to do so in the remand proceedings.

C. Federal Preemption

Lastly, we briefly address Roche's argument that plaintiff's failure-to-warn claims are preempted by federal law because the FDA approved the wording of the Accutane label that was in use when plaintiff was prescribed the drug in 1995. At the time of trial, based on long-standing New Jersey law, see Feldman v. Lederle Labs., 125 N.J. 117, 157 (1991), cert. denied, 505 U.S. 1219, 112 S. Ct. 3027, 120 L. Ed.2d 898 (1992), plaintiff's claim was manifestly not preempted by the federal labeling regulations.

Following oral argument on this appeal, the United States Supreme Court issued its decision in Wyeth v. Levine, 555 U.S. ___, ___ S. Ct. ___, ___ L. Ed.2d ___, No. 06-1249 (March 4, 2009). Reviewing a plaintiff's verdict from a Vermont state court against the manufacturer of an antinausea drug, the Court held that FDA approvals of the drug's label did not preempt the state-law claim for failure to warn.

The Court in Wyeth specifically rejected the defendant's argument that plaintiff's state law claims were preempted because it was allegedly impossible for the company to comply with both the state law duties underlying those claims and federal labeling requirements. (slip op. at 15). The Court explained that the FDA's pre-market approval of a new drug application includes the approval of the exact text in the proposed label, and, generally, that a manufacturer may only change a drug label after the FDA approves a supplemental application. (slip op. at 11). However, the FDA's so-called "changes being effected" ("CBE") regulation, 21 CFR • 314.70 permits a manufacturer to make changes to its label before receiving the FDA's approval, to "add or strengthen a contraindication, warning, precaution, or adverse reaction" or to "add or strengthen an instruction about dosage and administration that is intended to increase the safe use of the drug product." The Court found that when the risk of an adverse reaction from a certain type of injection of the drug became apparent, the manufacturer Wyeth had "a duty to provide a warning that adequately described that risk, and the CBE regulation permitted it to provide such a warning before receiving the FDA's approval." (slip op. at 15).

The Court in Wyeth identified a limited exception to these principles. As the majority opinion noted:

> Of course, the FDA retains authority to reject labeling changes made pursuant to the CBE regulation in its review of the manufacturer's supplemental application, just as it retains such authority in reviewing all supplemental applications. But absent clear evidence that the FDA would not have approved a change to Phenergan's label, we will not conclude that it was impossible for Wyeth to comply with both federal and state requirements.
>
> [(slip op. at 15) (emphasis added).]

The Court determined that Wyeth had offered no such evidence, and had not "attempted to give the kind of warning required by the Vermont jury but was prohibited from doing so by the

FDA." (slip op. at 15).

Applying Wyeth here, plaintiff's state law products liability claims for failure to provide an adequate warning would not be preempted, unless Roche can show by "clear evidence" that the FDA would not have approved a change to the Accutane label. In its brief on appeal Roche argues that "[t]he FDA explicitly considered the potential risk of IBD both in 1983-84 and again in 2000 - both times declining to adopt a warning like the causation warning advocated by [p]laintiff." Roche does not, however, establish whether it advocated such a stronger warning, or whether the FDA would not have approved a stronger warning, both requirements for application of the Wyeth exception.

The incomplete record supplied to us about the chronology of the FDA's review of Accutane's labeling is insufficient for us to evaluate, at least in the first instance, the preemption issues implicated by Wyeth. In fact, the trial court, unaware of what rule of law the Supreme Court would ultimately adopt in Wyeth, excluded certain portions of Roche's proffered evidence about the labeling process. In order to address the potential applicability of the Wyeth exception, the record will need to be further developed on these discrete issues.

Given that we are remanding this matter on other grounds because of independent trial errors, we also remand the preemption issues to the trial court, for further development of the record and evaluation in light of Wyeth. The trial court is free to permit additional discovery, motion practice and other proceedings as may be necessary to rule on these issues prior to any new trial.

D. Other Issues

We have fully considered the balance of Roche's arguments and subsidiary points on appeal

and have concluded that those additional contentions lack sufficient merit to warrant discussion in this opinion. R. 2:11-3(e)(1)(E).

VI.

The trial court's decision to admit the testimony of plaintiff's causation expert, Dr. Sachar, is affirmed. The court's exclusion of the Accutane usage data and related evidence proffered by Roche is reversed. The judgment is accordingly vacated and the case remanded for reconsideration of the preemption issues in light of Wyeth, supra, and, subject to the court's preemption ruling, for a new trial. We affirm the trial court on all other issues raised on this appeal.

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Affirmed in part, reversed in part, and remanded for further proceedings. We do not retain jurisdiction.

These pre-clinical results drew the early attention of the FDA. In a memorandum dated May 3, 1978, M.J. Schiffrin, a Roche employee, reported a telephone call that he had received from Dr. Manfred M. Hein, a pharmacologist with the FDA. In that call, Dr. Hein expressed concern to Schiffrin about the gastrointestinal bleeding that had been observed in the animal studies.

The FDA subsequently approved a label change for Accutane in 2000, removing the word "temporally," and warning that the symptoms of IBD "have been reported to persist after Accutane treatment has stopped." The new label was excluded from evidence at trial. See N.J. R.E. 407 (the subsequent remedial measure rule).

See A.C. Naranjo et al., A Method for Estimating the Probability of Adverse Drug Reactions, 30 Clinical-Pharmacology & Therapeutics 239 (1981).

By way of illustration, an IBD report would receive a "probable" rating totaling 6 points if there were previous conclusive reports on the adverse reactions (question one) (1 point); the adverse event occurred after drug use (question two) (2 points); there were no alternative causes identified (question five) (2 points); and the adverse event was confirmed by objective evidence (question ten) (1 point).

Dr. Lefrancq's first name is not identified in the record.

The recommended dose was between .05 mg/kg/day to 2g/kg/day for fifteen to twenty weeks.

Our factual recitation discusses Dr. Sachar's expert testimony substantially more than the other testifying experts, because the admissibility of his opinions and methodology under N.J.R. E. 702 is specifically challenged by Roche on appeal. Moreover, Roche's appellate briefs do not elaborate upon the testimony of the other experts.

Roche argues that these and similar criticisms of its conduct were beyond the scope of Dr. Sachar's expertise and were improperly admitted. We address this argument within Part III of this opinion, infra.

Despite what is shown on Roche's table, the actual total for this column is twenty-four, not twenty-three.

The Reddy article did note, however, that these results "should be interpreted with caution." Id. at 1571. "Although the temporal relationship between Isotretinoin use and onset of IBD is convincing in many of the reported cases, it is impossible to be certain that this is not coincidence. In addition, patients may have had sub-clinical symptoms of IBD prior to the use of isotretinoin, but sought medical care only after becoming aware of an association between the two." Ibid.

Even though we are vacating the judgment on other grounds, see Part III, infra, we examine this issue in detail to provide guidance on a re-trial and other pending Accutane cases. We were advised at oral argument that over 400 such cases are pending in the Law Division.

We recognize that the "sounder practice" often is to conduct such a live hearing, Kemp, supra, 174 N.J. at 432. Even so, we discern no abuse of discretion by the judge in choosing to forego an evidentiary hearing in this case, given the extensive materials before her. Indeed, Roche does not claim that such a hearing was required.

The New Jersey version of Rule 702 largely tracks the original version of Federal Rule of Evidence 702, but it does not incorporate the further language added to the federal rule in 2000, which inserted the condition that such an expert may testify only "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 methods reliably to the facts of the case." This additional text placed in the amended federal rule was an effort to codify the principles of Daubert v. Merrell Dow Pharm., Inc., 509 U.S. 579, 113 S. Ct. 2786, 125 L. Ed.2d 469 (1993) (outlining the federal requirements for scientific expert testimony).

See also West's Reference Manual on Scientific Evidence 345-47 (2d. ed. 2000) (noting that animal studies "may be used to determine toxicity in humans," and that such studies "often provide useful information about pathological mechanisms and play a complementary role to epidemiology in assisting researchers in framing hypothesis and in developing study designs"). The Manual also recognizes, on the other hand, the disadvantages of such studies and the need for careful assessment of, among other things, "the quality of the toxicologic studies and the questions of interspecies extrapolation." Ibid.

In the study Roche cites, the dogs were given 3 mg/kg/day of isotretinoin. Side effects were recorded by the dogs' owners, and laboratory tests, including blood samples and skin biopsies. No gastrointestinal side effects were listed. However, no stool samples were taken and the dogs were not autopsied. By comparison, at this same low dose, the dogs in the fifty-five-week study relied on by Dr. Sachar revealed gastrointestinal inflammation only at autopsy. Thus, the dogs in the low-dose study cited by Roche may have suffered gastrointestinal inflammation, but no such effects were recorded due to the nature of the study itself.

Although none of the patients in these studies were diagnosed with IBD, it does not appear that any monitoring, such as stool samples, was done to assess IBD symptoms, with the exception of one study which asked the participants if they had suffered from watery diarrhea. For example, in the study on patients suffering from terminal malignant intracranial tumors, monitoring was performed with an emphasis on skin, liver, lipid, muscle, and joint toxicity, not gastrointestinal side effects.

The recommended dose for humans was from .05 mg/kg/day to 2 mg/kg/day.

Moreover, lower-dose dogs in the fifty-five-week study did suffer gastrointestinal effects. Although there was no visible blood in the stools of the dogs in the low-dose group, gross anatomical lesions suggestive of gastrointestinal irritation were found on autopsy in four of the eighteen dogs in the mid-dose group, two of the eighteen dogs in the low-dose group, and only one dog in the control group. The study report concluded that these observations suggested the administration of Accutane was "associated with a slight dose-related gastrointestinal toxicity due to local irritation." This finding is not inconsistent with Dr. Sachar's theory.

See, e.g., Allison v. McGhan Med. Corp., 184 F.3d 1300, 1316 (11th Cir. 1999); Caraker v. Sandoz Pharms. Corp., 188 F. Supp.2d 1026, 1035 (S.D. Ill. 2001) (excluding plaintiffs' experts' opinions that relied on dechallenge/rechallenge reports); Glastetter v. Novartis Pharms. Corp., 107 F. Supp.2d 1015, 1030 (E.D. Mo. 2000) (declaring case report not to be scientifically-valid proof of causation), aff'd, 252 F.3d 986 (8th Cir. 2001); Hollander v. Sandoz Pharms., Inc., 95 F. Supp.2d 1230, 1237 (W.D. Okla. 2000) (deeming three dechallenge/ rechallenge reports too few to constitute reliable evidence of causation), aff'd in part, remanded in part, 289 F.3d 1193 (10th Cir.), cert. denied, 537 U.S. 1088, 123 S. Ct. 697, 154 L. Ed.2d 632 (2002); Wade-Greaux v. Whitehall Lab., 874 F. Supp. 1441, 1483 (D.V.I. 1994) (finding that anecdotal reports are not the type of data reasonably relied on by experts in field of teratology).

See, e.g., In re Phenylpropanolamine Prods. Liab. Litig., 289 F. Supp.2d 1230, 1248 (W.D. Wash. 2003) (allowing case and ADR reports, textbooks, treatises, and testimony from other experts and scientists); Glaser v. Thompson Med. Co., 32 F.3d 969, 972 (6th Cir. 1994) (holding that published studies, published articles, case reports, and the expert's own clinical and research experience constituted sufficient reliable scientific data upon which an expert may base conclusion).

However, we did recognize in Smith that the context of that criminal case, involving the defendant's state of mind in biting the victim, did not require the State expert's opinions to be cast in terms of "reasonable medical causative certainty." Id. at 520.

We find the case at bar distinguishable from other cases concluding that an expert had improperly relied upon causality assessments. See, e.g., Soldo v. Sandoz Pharms. Corp., 244 F. Supp.2d 434, 465 (W.D. Pa. 2003) (wherein plaintiff did not show, or even argue, that the regulatory "causality assessment" methodology is accepted in medical or scientific fields for establishing medical causation); Glastetter, supra, 107 F. Supp. 2d at 1037 (wherein a causality assessment involving only one individual was held insufficient to establish causation).

In a similar fashion, we reject Roche's related contention that it was unfairly prejudiced by plaintiff's counsel in the manner in which they questioned witnesses about the causality assessments and in the manner in which they described them in closing arguments. Roche presented its own competing proofs and arguments about the limited significance of causality assessments. The jury heard competing experts on the causation issues as a whole. Given the context, we do not think that plaintiff's attorneys exceeded the bounds of fair advocacy.

Although Roche's brief characterizes Dr. Lefrancq's internal company memorandum as "unauthenticated," it raises no argument under N.J.R.E. 901 that the contents of that memorandum should have been excluded from the jury's consideration on that basis. Nor does Roche raise any claims of a violation of the rule of completeness under N.J.R.E. 106. Roche faults plaintiff for not deposing Dr. Lefrancq, but it does not establish that he was inaccessible to the company's own attorneys, or that his memorandum fails the requirements for a business record admissible under N.J.R.E. 803(c)(8).

"Physicians do not usually require a specific understanding of the underlying mechanism of a . . . disease before assessing causation." David Egilman, M.D., et al., Proving Causation: The Use and Abuse of Medical and Scientific Evidence Inside the Courtroom--An Epidemiologist's Critique of the Judicial Interpretation of the Daubert Ruling, 58 Food & Drug L.J. 223, 245 (2003).

See In re Baycol Prods. Litig., 532 F. Supp.2d 1029, 1053 (D. Minn. 2007) (observing that "[p]ersonal views on corporate ethics and morality are not expert opinions"); In re Rezulin Prods. Liab. Litig., 309 F. Supp.2d 531, 546 (S.D.N.Y. 2004) (holding that the objected-to opinions of expert witnesses on intent, motives, or state of mind of a corporation had no basis in any relevant body of knowledge or expertise).

Roche refers to an article posted on an Internet site reporting that a juror in this case had allegedly stated, "We'd like to send a message to Roche to clearly do further testing and evaluations." There is no indication whether this reported comment is accurate. As the trial judge found, no separate failure-to-test claim was presented to the jury, and Dr. Sachar's testimony was justifiably presented in response to an attack on his methodology. The Internet posting does not alter our confidence in the judge's ruling.

Such "calculations" presumably would have violated the judge's pre-trial ruling in connection with Dr. Waymack.

We also reject plaintiff's separate contention that Dr. Huber was not qualified to testify about those figures from the company's records, simply because he had not been employed by Roche in 1995. We believe that an adequate foundation could have been laid through Dr. Huber to satisfy the elements of business records admissible under N.J.R.E. 803(c)(6), and his

work-related knowledge of their contents under N.J.R.E. 602.

For instance, if the jury had learned about the twelve or more million persons who have used Accutane to date (as represented by Roche) it might have regarded the twelve-to-fourteen MedWatch rechallenge incidents as only representing a "one-in-a-million" risk, depending on the jury's assessment of Dr. Sachar's claim that adverse events are highly under-reported. Although we do not necessarily adopt that comparison, it was the kind of counter-advocacy that the jury was entitled to consider.

After the judge rendered her decision in this case, the Alabama Supreme Court adopted a discovery rule for toxic tort cases, to be applied in that particular case and prospectively. Griffin v. Unocal Corp., 990 So.2d 291 (Ala. 2008).

We make this observation mindful that Roche was not permitted to present fully its background "numbers" evidence to the jury.

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March 12, 2009
