Case No. 07-13883-BB, etc.

IN THE UNITED STATES COURT OF APPEALS FOR THE ELEVENTH CIRCUIT

JUSTIN RAND, *et al.*,
Plaintiffs-Appellants,

v.

HOFFMAN-LA ROCHE, INC., *et al.*, Defendants-Appellees.

On Appeal From The United States District Court For The Middle District of Florida, Tampa Division

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BRIEF FOR APPELLEES

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Case No. 07-13883-BB

JUSTIN RAND

Plaintiff-Appellant,

v.

HOFFMAN-LA ROCHE, INC., et al.

Defendants-Appellees.

Case No. 07-13884-BB

CALEB ROBERT MCCLAIN, et al.

Plaintiff-Appellant,

v.

HOFFMAN-LA ROCHE, INC., et al.

Defendants-Appellees.

Case No. 07-13885-BB

MARY E. FARR, et al.

Plaintiff-Appellant,

v.

HOFFMAN-LA ROCHE, INC., et al.

Defendants-Appellees.

Case No. 07-13886-BB

KENNETH CANNADY

Plaintiff-Appellant,

v.

HOFFMAN-LA ROCHE, INC., et al.

Defendants-Appellees.

Case No. 07-13887-BB

DIANE REED, Trustee for the
Estate of Andrew Dean Messick

Plaintiff-Appellant,

v.

HOFFMAN-LA ROCHE, INC., et al.

Defendants-Appellees.

Case No. 07-13888-BB

DARRELL W. TEMPLE

Plaintiff-Appellant,

v.

HOFFMAN-LA ROCHE, INC., et al.

Defendants-Appellees.

Case No. 07-13889-BB

JARED STEVENS

Plaintiff-Appellant,

v.

HOFFMAN-LA ROCHE, INC., et al.

Defendants-Appellees.

Case No. 07-13890-BB

RICHARD PECHER

Plaintiff-Appellant,

v.

HOFFMAN-LA ROCHE, INC., et al.

Defendants-Appellees.

Case No. 07-13891-BB

BRITT MARIE WRIGHT

Plaintiff-Appellant,

v.

HOFFMAN-LA ROCHE, INC., et al.

Defendants-Appellees.

07-13883-BB, etc. Rand v.
Hoffman-La Roche, Inc.

CERTIFICATE OF INTERESTED PERSONS AND CORPORATE DISCLOSURE STATEMENT

The certificate contained in Appellants' Initial Brief is complete to the best of Appellees' knowledge, except the following related entity should be added:

Novartis AG
(NVS)

STATEMENT ON ORAL ARGUMENT

Although Appellees stand ready to argue the issues in this case, Appellees submit that oral argument is unnecessary because the dispositive issues are

squarely controlled by this Court's prior decisions in *McClain v. Metabolife International, Inc.*, 401 F.3d 1233 (11th Cir. 2005) and *Rider v. Sandoz Pharm. Corp.*, 295 F.3d 1194 (11th Cir. 2002).

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Sandoz Pharm. Corp., 295 F.3d 1194 (11th Cir. 2002) and find that the District Court abused its discretion in excluding an expert causation opinion that was based on selective animal studies, case reports, and causality assessments.

2. Whether this Court should affirm the District Court's evidentiary ruling excluding causality assessments.

3. Whether this Court should affirm the District Court's grant of summary judgment for Defendants on the alternative basis (not reached by the Court below) that the Accutane IBD warnings were adequate as a matter of law.

Statement of the Case

A. Course of the Proceedings Below

On August 13, 2003, Justin Rand filed a complaint against Appellees/Defendants Hoffmann-La Roche Inc. and Roche Laboratories Inc. ("Roche") in the Middle District of Florida. He alleged that Accutane®, a prescription acne medication produced by Roche, caused his inflammatory bowel disease ("IBD").

A number of additional Accutane cases were filed in other federal

jurisdictions. On November 1, 2004, these federal cases were consolidated with Mr. Rand's case into a multidistrict litigation ("MDL") in the Middle District of

Florida. (Doc 1.) This appeal concerns those plaintiffs who allege that Accutane caused them to develop IBD and who designated Ronald Fogel as their only general causation expert (the "IBD plaintiffs").[1]

A threshold element of each of the IBD plaintiffs' claims is general causation – that Accutane is capable of causing IBD. In addition, the IBD plaintiffs must each prove that Accutane specifically caused their IBD (specific causation) and that Roche failed to warn their physicians adequately of the risks of IBD
(adequacy).

The IBD plaintiffs proffered Ronald Fogel as their sole expert on both general and specific causation. (Doc 444 - Ex. 1.) After deposing Dr. Fogel, Roche filed three motions regarding his testimony on March 22, 2007: a motion to exclude the causality assessments upon which he partly relied (Doc 408); a *Daubert* motion to exclude his general causation testimony (Doc 411); and a *Daubert* motion challenging his specific causation opinions (Doc 420).

[1] Specifically, the nine cases on appeal are: Justin Rand, district court case no. 8:03-cv-1729-T-30TMB; Caleb McCain and Kathleen McClain-Rosario, 8:04-cv-2614-T-30TBM; Kenneth Cannady, 8:04-cv-2642-T-30TBM; Mary E. Farr, and Beth Parker, Administrator (Locke), and James Studensky, Trustee (Fechner), 8:04-cv-2641-T-30TBM; Diane Reed, Trustee (Messick), 8:04-cv-2643-T-30TBM; Jared Stevens, 8:05-cv-1478-T-30TBM; Britt Marie Wright, 8:06-cv-1546-T-30TBM; Richard Pecher, 8:06-cv-1063-T-30TBM; and Darrell Temple, 8:05-cv-370-T-30TBM. In addition to suing Roche, some of these plaintiffs also sued Roche's Swiss affiliates.

The District Court granted Roche's motion to exclude causality assessments on May 2, 2007. (Doc 506.) After rejecting the IBD plaintiffs' arguments that this evidence was relevant, the court ruled that any conceivable probative value of these assessments was outweighed by their substantial danger of unfair prejudice. (Doc 506.) The Court also specifically excluded Dr. Fogel's reliance on them, holding that his "opinion regarding causality assessments [was] speculative and conclusory and lack[ed] the indicia of reliability necessary under *Daubert*." (Doc 506 - Pgs 11-12.)

With respect to the *Daubert* motions, the District Court scheduled a *Daubert*

hearing for April 19, 2007. (Doc 366.) In advance of this hearing, the IBD plaintiffs told the District Court on several occasions that they did not see the need for live testimony from Dr. Fogel at the hearing. (Doc 435; Doc 436; Doc 467.) In the IBD plaintiffs' own words, "the case law in the United States Eleventh Circuit Court of Appeals and throughout the country is clear that *Daubert* evidentiary hearings, involving live testimony, are not necessary or compelled. Further, in light of the substantial record expected to be adduced by the [Plaintiffs' Steering Committee], the Court may consider these pending motions based upon record and through oral argument alone on April 19, 2007." (Doc 435 - Pg 1.)

The District Court granted the IBD plaintiffs' wish to avoid live testimony from Dr. Fogel and, on April 19, held a several-hour *Daubert* hearing without live

testimony. (Doc 481; Doc 493.) On June 15, 2007, the court excluded Dr. Fogel's general causation testimony under *Daubert.* (Doc 580.) As Dr. Fogel was the IBD plaintiffs' sole general causation expert, the court gave them twenty days to show why summary judgment should not be granted in favor of Roche. (Doc 580).[2]

On June 29, 2007, the IBD plaintiffs filed a motion for reconsideration and

rehearing that included dozens of new exhibits. (Doc 604.) The IBD plaintiffs offered no explanation for their late submission of these exhibits, nor did they even attempt to tie them to Dr. Fogel's testimony through an affidavit or otherwise. Among these new exhibits are several that the IBD plaintiffs now criticize Judge Moody for not having addressed in his opinion pre-dating the submission of the exhibits. *See, e.g.*, Appellants' Brief ("Br.") at 25 (criticizing the Court for "cit[ing] only one dog study," when the IBD plaintiffs only submitted the additional dog study after the Court's ruling); *id*. at 33-36 (criticizing the Court for "ignoring other such [rechallenge] reports," when the three additional reports were not provided to the Court before its ruling). Also among these new exhibits were many that appear in counsel's legal briefing but were not specifically referenced or otherwise discussed in Dr. Fogel's report, including one that the IBD plaintiffs continue to rely upon even though their counsel admitted at the *Daubert* hearing

[2] Because the general causation ruling terminated these cases, the Court subsequently denied as moot Roche's specific causation *Daubert* motion.

that it was not a basis for Dr. Fogel's testimony. (Doc 604 - Ex. 18; Doc 493 (tr. 46:13 – 47:15).)

On July 20, 2007, the District Court denied the IBD plaintiffs' motion for reconsideration, granted summary judgment for Roche in all the IBD cases in which Dr. Fogel was the named general causation expert (which encompassed all IBD cases before the Court in which the plaintiffs had reached the expert disclosure deadline), and stayed pending this appeal the remaining IBD cases in which the plaintiffs had not yet reached the point of expert disclosures. (Doc 615; Doc 616; Doc 620.)

The IBD plaintiffs subsequently filed this consolidated appeal. After it was initially dismissed for failure to follow Eleventh Circuit Rules, the appeal was reinstated on November 23, 2007.

B. Statement of Facts

Accutane (generically, isotretinoin) is a prescription acne medication that is uniquely effective in treating severe recalcitrant nodular acne. (Doc 411 - Ex. A.) More than 12 million patients worldwide have been prescribed Accutane since its

approval in 1982. (Doc 411 - Ex. A.)

IBD primarily refers to two diseases characterized by inflammation of the gastrointestinal tract: ulcerative colitis and Crohn's disease. Both are permanent conditions in which gastrointestinal symptoms wax and wane over time. Although

it can occur at any age, IBD is most commonly diagnosed in late adolescence or early adulthood, the same time period in which many Accutane patients need the medication. (Doc 411 - Ex. B.) It is estimated that as many as 1.4 million people in the U.S. and Canada have IBD, and that as many as 90,000 new cases are diagnosed each year. (Doc 411 - Ex. B.)

The scientific consensus, including as stated by the American Gastroenterological Association, is that the causes of IBD are unknown. (Doc 411 - Exs. C-D.) However, IBD has been actively studied and, as Dr. Fogel himself recognizes, the scientific literature has identified several factors associated with a statistically significant increased rate of IBD, including family history, prior infections, smoking, oral contraceptives, and antibiotics.[3] (Doc 411 - Ex. E2 - Pgs 7-14.) By contrast, there is no evidence that Accutane — which has been used by

millions of patients in the past quarter-century and has been the subject of numerous clinical studies — is associated with a statistically significant increased risk of IBD.

The IBD plaintiffs proffered Dr. Ronald Fogel as their only expert to testify that Accutane causes IBD. Dr. Fogel does not rely on any clinical or

[3] Many of these potential risk factors are highly prevalent in the Accutane population. For example, every woman who uses Accutane is directed to use contraceptives to avoid the teratenogetic risks from Accutane. Similarly, the labeling for Accutane indicates that physicians should first try to treat a patient's acne with systemic antibiotics.

epidemiological studies establishing such a link. Nor does he rely on his own clinical experience, as he testified that he has only seen one IBD patient in his practice whom he knew had used Accutane. (Doc 411 - Ex. E1 - Pgs 26-27 (tr. 85:7 - 86:2).) He does not even rely on many of the sources plaintiff experts typically turn to, including tested mechanisms by which the drug might cause the disease; data showing that IBD increases with the dose or length of Accutane use

(so-called dose response); any systematic analysis of reported IBD cases that have arisen in connection with Accutane use; or a thorough review of animal studies, including to determine whether they can be analogized to human IBD.

Instead, lacking data that Accutane users suffer IBD at a higher rate than the general population, Dr. Fogel turned to three piecemeal data sources:

1. Selected animal data – 2 dog studies and unspecified rat studies, (Doc 580);
2. Anecdotal case reports, including rechallenge reports, that he did not systematically analyze, (Doc 580); and
3. Risk assessment devices known as causality assessments, (Doc 580).

In the end, even Dr. Fogel admits that there is no scientific evidence indicating an increased risk of IBD among patients who have taken Accutane:

> Q. . . . Doctor, as you sit here today, you cannot tell me that there is a statistically significant increased risk of IBD among patients who have taken Accutane, can you? . . .
>
> A. The data is not available to conclude what the risk is.

(Doc 411 - Ex. E2 - Pg 25 (tr. 185:8-21) (hyperlink).)[4] Nevertheless, Dr. Fogel concluded for the first time after his retention as an expert in these cases that

Accutane can cause IBD and, in fact, did so for each plaintiff.

C. Standard of Review

***Daubert* Ruling:** This Court reviews a district court's *Daubert* rulings for an abuse of discretion. *See, e.g.*, *Corwin v. Walt Disney Co.*, 475 F.3d 1239, 1250 (11th Cir. 2007). The *Daubert* line of cases "dictate[] that district courts . . . have 'considerable leeway' when deciding [whether] to admit or exclude expert testimony." *Hall v. United Ins. Co. of Am.*, 367 F.3d 1255, 1261 (11th Cir. 2004)). This Court has recognized that, "when employing an abuse-of-discretion standard, we must affirm unless we find that the district court has made a clear error of judgment, or has applied the wrong legal standard." *United States v. Frazier*, 387 F.3d 1244, 1259 (11th Cir. 2004)).

Exclusion of Causality Assessments: The District Court's exclusion of causality assessments was an evidentiary ruling. '"All evidentiary decisions are reviewed under an abuse-of-discretion standard.'" *United States v. Brown*, 415

[4] In addition to uploading this brief to the court's website and filing a paper copy, Roche is submitting this brief in CD-ROM format pending a ruling on Roche's

motion to file a CD-ROM version of the brief with hyperlinks to videotaped testimony from Dr. Fogel. These videotaped clips (which correspond to testimony cited in the brief) represent the only difference between the CD-ROM version of the brief and the uploaded and paper versions that have been filed in the customary manner.

F.3d 1257, 1264-65 (11th Cir. 2005) (citation omitted), *cert. denied,* 547 U.S. 1023 (2006). **Adequacy:** As discussed below, summary judgment should also be affirmed on an additional basis not reached by the District Court — the Accutane warnings were adequate as a matter of law. This is a question of law that this Court should address *de novo*. *Osborne v. Terry*, 466 F.3d 1298, 1304-05 (11th Cir. 2006) ("This court . . . reviews *de novo* both questions of law and mixed questions of law and fact."), *cert. denied,* 128 S. Ct. 84 (2007).

SUMMARY OF THE ARGUMENT

The District Court did not abuse its discretion by excluding Dr. Fogel's unreliable testimony; rather, it properly applied controlling Eleventh Circuit

precedent in *McClain* and *Rider*, as well as the principles outlined in *Daubert* and its progeny.

Rather than grappling with the purpose of *Daubert* and this Court's on-point holdings in *McClain* and *Rider*, the IBD plaintiffs attempt to divert attention from the shortcomings of Dr. Fogel's analysis with blanket assertions that the District Court somehow invaded the province of the jury by fulfilling its gatekeeping duties. This contention fundamentally misunderstands the critical gatekeeping function assigned to the District Court under *Daubert*.

The IBD plaintiffs criticize the District Court for its searching review of the selected pieces of support Dr. Fogel cites in support of his causation opinion. Each line of evidence advanced by Dr. Fogel, though, has been rejected both by scientists in the field and by courts as a reliable basis for reaching conclusions on medical causation. After carefully examining these lines of evidence, the District Court properly held that Dr. Fogel's methodology falls far short of the standard required by *Daubert*. In the end, Dr. Fogel cannot manufacture a reliable causation

opinion by cobbling together a hodge-podge of individually unreliable and insufficient lines of evidence.

Additionally, judgment for Roche is appropriate for a reason not reached by the District Court: because Roche expressly warned about the risk of IBD.

ARGUMENT

I. THE DISTRICT COURT PROPERLY EXCLUDED DR. FOGEL'S CAUSATION OPINION.

A. The District Court Properly Met Its Gatekeeping Obligation.

Close to half of the IBD plaintiffs' appellate Argument is an extended criticism of the District Court for meeting its gatekeeping responsibilities. *See* Br. Part V.A-D, G-H. The plaintiffs open this argument not with a citation to *Daubert* case law, but with a quote from an amicus brief that preceded the *Daubert* decision. They cite the brief to support their running argument that the District Court erred in carefully examining each basis for Dr. Fogel's opinion and finding

each lacking, rather than simply accepting Dr. Fogel's attempt to add a series of unreliable lines of evidence into causation. Br. at 12.

Setting aside quotes from amicus briefs, *Daubert* itself was clear: district courts must perform an essential gatekeeping function to ensure that expert testimony is reliable. *Daubert v. Merrell Dow Pharm., Inc.*, 509 U.S. 579, 589-93, 597, 113 S. Ct. 2786, 2794-97, 2798-99 (1993). As this Court has consistently held
:

> As a gatekeeper the court must do "a preliminary assessment of whether the reasoning or methodology underlying the testimony is scientifically valid and of whether that reasoning or methodology properly can be applied to the facts in issue." . . . The proposed testimony must derive from the scientific method; good grounds and appropriate validation must support it. "In short, the requirement that an expert's testimony pertain to 'scientific knowledge' establishes a standard of evidentiary reliability."

McClain, 401 F.3d at 1237-38 (*Daubert* citations omitted).

At bottom, the IBD plaintiffs' complaint is less a challenge to the District Court's ruling than it is a challenge to the propriety of *Daubert* itself. Accepting their repeated refrain that it was inappropriate for Judge Moody to conduct a searching gatekeeping inquiry – when in the plaintiffs' view all questions regarding reliability should have slipped through to the jury – would effectively eliminate *Daubert* review. As this Court has stated, the IBD plaintiffs' "jury

question" approach would inappropriately result in courts "dumping a barrage of scientific evidence on a jury, who would likely be less equipped than the judge to

make reliability and relevance determinations." *Rider*, 295 F.3d at 1197; *see also McClain*, 401 F.3d at 1238 (reversing decision that left reliability questions to jury).

The District Court properly fulfilled its gatekeeping duty: the Court's exclusion Order reflects a thorough and careful consideration of each aspect of Dr. Fogel's methodology. Rather than weighing the evidence, it properly found the evidence faulty just as this Court and courts around the country have consistently done when faced with similar evidence.

B. Dr. Fogel's Lines of Evidence Do Not Withstand Daubert Scrutiny.

The District Court addressed Dr. Fogel's lines of evidence as he laid them out. On appeal, the IBD plaintiffs have reordered Dr. Fogel's lines of evidence and abandoned some of his specific opinions, such as his independent reliance on a hypothetical mechanism of action by which Accutane might cause IBD.[5]

[5] Even Dr. Fogel admitted that these mechanisms were entirely speculative and untested: "many biological plausibilities exist" and "[a]t present, the exact mechanisms of these conditions is unknown." (Doc 411 - Ex. H - Pgs 5-6; *see also* Doc 411 - Ex. E2 - Pg 25 (tr. 186:17-21) (increased permeability of intestinal mucosa theory: "That is correct, it has not been tested."); Doc 411 - Ex. E3 - Pg 4 (tr. 210:1-8) (apoptosis hypothesis "remains to be proven": "That is correct.").) This speculation cannot form a reliable basis for a causation opinion: "'Subjective speculation that masquerades as scientific knowledge' does not provide good grounds for the admissibility of expert opinions." *McClain*, 401 F.3d at 1245(citation omitted); *see also Sanderson v. Int'l Flavors & Fragrances. Inc.*, 950 F. (continued...)

Supp. 981, 996 (C.D. Cal. 1996) ("Plausibility does not equal reliability; only

Specifically, plaintiffs' counsel now cites three lines of evidence on which Dr. Fogel relied: (1) animal studies, Br. Part V.E.1; (2) case reports, including rechallenge case reports, Br. Part V.E.2, V.E.3; and (3) causality assessments, Br. Part V.F.[6] This appellate reshuffling does not change the fact that each of these lines of evidence was closely reviewed by the District Court and properly found to be lacking.

These lines of evidence closely parallel those found unreliable in *McClain* and *Rider*. In *Rider*, this Court affirmed a court's exclusion of five experts who – despite their "impressive credentials" – improperly relied like Dr. Fogel did upon animal data, case reports (including rechallenge reports), and a purported class effect. *Rider*, 295 F.3d at 1198. In *McClain*, this Court went farther, holding that it was an abuse of discretion to allow two experts to offer opinions similar to Dr.

'objective, independent validation' equals reliability."); *Black v. Food Lion, Inc.*, 171 F.3d 308, 314 (5th Cir. 1999) ("In this case, neither [the expert] nor medical science knows the exact process that results in [the disease] or the factors that trigger the process. Absent these critical scientific predicates, for which there is no proof in the record, no scientifically reliable conclusions on causation can be drawn."). [6] At times in their brief, the IBD plaintiffs vaguely allude to a larger

universe of data upon which Dr. Fogel purportedly relied: "cell culture studies, clinical trials, scientific literature, and a comparison of Accutane and drugs in its same class." *See*, *e.g.*, Br. at 19. The IBD plaintiffs do not offer more than a glancing reference to these types of evidence because they are in fact subsumed by the three lines of evidence the IBD plaintiffs otherwise addressed on appeal, and should be rejected as the basis of a causation conclusion even if these vague allegations put them properly before the Court.

Fogel's that were premised on case reports, rechallenge reports, hypothetical mechanisms of action, and purported class effects. *McClain*, 401 F.3d at 1244-55.

The IBD plaintiffs' brief is largely an exercise in avoiding these two controlling cases. The IBD plaintiffs cite over a dozen other sources on *Daubert*, largely from district court opinions and secondary sources, before even mentioning the existence of *McClain.* And it is not until page 44 of their 50-page brief that they reveal the *Rider* case — in a string cite and without even begrudging acknowledgement that the Court affirmed the exclusion of experts functionally identical to Dr. Fogel.

The IBD plaintiffs' failure to confront the controlling Eleventh Circuit

precedent betrays their inability to defend Dr. Fogel's methodology under the governing legal standards. If anything, Dr. Fogel's opinion is more objectionable than those in *McClain* and *Rider*, as Dr. Fogel has proven particularly willing to discard scientific inquiry in favor of litigation advocacy. *See Daubert (II) v. Merrell Dow Pharm., Inc.*, 43 F.3d 1311, 1317 (9th Cir. 1995) (questioning reliability of causation experts who simply present lawyer-crafted opinions rather than testifying "about matters growing naturally and directly out of research they have conducted independent of the litigation"); *EEOC v. Rockwell Int'l Corp.*, 60 F. Supp. 2d 791, 797 (N.D. Ill. 1999) ("A proffered expert must 'bring to the jury

more than the lawyers can offer in argument.'") (citation omitted), *aff'd,* 243 F.3d 1012 (7th Cir. 2001). For example:

- he made no effort to account for the background rate of IBD or to show that Accutane increased that rate;[7]
- he failed to account for dose response or consider whether there was a necessary threshold dose;[8]

- he relied upon evidence he admittedly did not understand;[9]
- he ruled out what he admitted were other possible causes of IBD without understanding the scientific literature regarding these alternative causes,

[7] *Compare McClain*, 401 F.3d at 1243-44 ("A reliable methodology should take into account the background risk. . . . O'Donnell offered no evidence of additional risk.") *with* (Doc 411 - Ex. E2 - Pg 25 (tr. 185:8-21) (hyperlink) ("The data is not available to conclude what the risk is.")). [8] *Compare McClain*, 401 F.3d at 1241-42 ("O'Donnell could not provide any opinions about the general dose-response levels for Metabolife's toxicity . . . . The expert who avoids or neglects this principle of toxic torts without justification casts suspicion on the reliability of his methodology."); *with* (Doc 411 - Ex. E3 - Pg 16 (tr. 258:16-21) (hyperlink) ("Q. You haven't done any analysis that deals with whether or not there's a threshold dose that's required to trigger that event, true? A. I did not do that analysis, no, but that information wasn't available to even consider doing such an analysis."). [9] *Compare Soldo v. Sandoz Pharmaceuticals Corp.*, 244 F. Supp. 2d 434, 545 (W.D.

Pa. 2003) ("Where the methodology is unknown, the opinion is inadmissible.") *with* (Doc 411 - Ex. E3 - Pgs 14-15 (tr. 255:4 - 255:19) (hyperlink) ("I have no information about the Roche methodology.").

essentially admitting that he only needed to see that a patient took Accutane in order to attribute causation to Accutane;[10]

- he picked and chose amongst the data, rather than integrating it all;[11] and
- he "infer[red] conclusions from studies and reports that the papers do not authorize."[12]

These errors, as they appear in each of Dr. Fogel's lines of evidence, are discussed further below. Through these errors, though, Dr. Fogel proved his opinion to be

[10] Q. Okay. With that in mind, would you agree then that essentially when you got the file in Ms. Farr's case, once you determined that she took Accutane and got Crohn's, that at that point it's your opinion that the most likely cause of her Crohn's is Accutane?

A. Correct. (Doc 580 - Pg 27; *see also* Doc 420 - Ex. D - Pg 27 (tr. 94:22 - 95:21) (hyperlink). *Compare with Miller v. Pfizer*, 196 F. Supp. 2d 1062, 1086-87

(D. Kan. 2002), *aff'd,* 356 F.3d 1326 (10th Cir. 2004) (reliance on pre-selected evidence from interested parties, to exclusion of other relevant, reliable evidence, is inconsistent with reliable methodology). (*See also* Doc 411 - Ex. W1 - Pg 13 (tr. 41:3-17) (hyperlink) ("Q. So that [smoking literature] is not literature that you reviewed for the purpose of forming your opinions in this case; is that fair? A. I did not review – I did not review that literature."); *id.* - Pg 14 (tr. 46:3 - 47:7) (hyperlink) ("I did not review the medical literature regarding antibiotics for this case, no."); (Doc 411 - Ex. E2 - Pg 12 (tr. 134:5-15) (hyperlink) ("I have not reviewed those [antibiotic] studies, but I have seen them mentioned in review articles."); *id.* - Pg 11 (tr. 129:14-20) (hyperlink) ("Q. Have you reviewed the literature – have you made a systematic review of the literature regarding oral contraceptive use in inflammatory bowel disease? A. I have not."); *id.* - Pg 13 (tr. 138:22 - 139:5) (hyperlink) ("I have not reviewed that [NSAID] literature specifically . . . .").) [11] *Compare Caraker v. Sandoz Pharm. Corp.*, 172 F. Supp. 2d 1046, 1051 (S.D. Ill. 2001) (ignoring data adverse to one's hypothesis is indicative of unreliable methodology); *with* (Doc 411 - Ex. H - Pg 6) (relying on two dog studies but ignoring other animal studies). [12] *McClain*, 401 F.3d at 1240. *Compare with* (Doc 411 - Ex. F) (study showing that causality assessments – which Dr. Fogel relies upon to show ***causation*** – show only "a ***possible association***") (emphasis added).

nothing more than speculation, and "subjective speculation that masquerades as scientific knowledge does not provide good grounds for the admissibility of expert opinions." *McClain*, 401 F.3d at 1245 (quotation marks and citations omitted).

1. Animal Studies

The District Court properly found that Dr. Fogel's reliance on carefully selected – and highly limited – animal data could not support a reliable causation opinion.[13]

Dr. Fogel relied upon two dog studies. The first study (the "Dog Metabolite Study") involved 4-oxo-isotretinoin, an Accutane metabolite: in the first phase of this study, 4 beagles were given very high doses of the metabolite; in the second phase, 9 beagles were given doses ranging from near-human doses to much higher doses. (Doc 444 - Ex. 4.) Some of the higher-dose dogs showed reversible injuries to their intestinal linings. (Doc 444 - Ex. 4 - Pg 6.) The lower-dose dogs showed no notable effects. (Doc 444 - Ex. 4 - Pg 7.)

Dr. Fogel's second dog study (the "1979 Dog Study") was a 55-week study conducted in 1979. Reflecting the paucity of their data, the IBD plaintiffs actually

[13] The IBD plaintiffs have abandoned Dr. Fogel's reliance below on two cell culture studies. As the District Court properly noted, these two cell culture studies were unreliable because: (1) they involved Vitamin A, not Accutane; (2) they involved cancer cells, not normal intestinal cells, and Dr. Fogel admitted that he had no basis to analogize from one type of cell to the other, (Doc 411 - Ex. E3 - Pg 12 (tr. 241:8-15)); and (3) as even the cell culture study authors stated, one cannot automatically assume that test tube results will apply in the body.

suggest that this single study was in fact two studies: they first discuss a 30-week interim report that arose from this study, Br. at 25-26, and they then falsely refer to the final report from this study as "another of the dog studies," *id.* at 26.

In this 1979 Dog Study, dogs were given Accutane in doses ranging from near-human doses to doses up to 60 times the maximum recommended human dose. (Doc 604 - Ex. 9.) At the end of this study, 14 of the 36 higher-dose dogs showed non-profound and reversible gastrointestinal injuries, and the higher-dose dogs also experienced reversible gastrointestinal bleeding. (Doc 604 - Ex. 9 - Pg 13 (RDR021730) ("The gastrointestinal changes associated with [Accutane] are

neither profound nor irreversible."); *id.* at 41-42 (RDR021758-59) (injuries); *id.* at 28-29 (RDR021745-46 (bleeding).) No notable differences were seen between the close-to-human-dose group and the control groups — the frequency of bleeding or other gastrointestinal injuries in the low-dose dogs did not distinguish them from the control groups. (*Id*. at 14-15 (RDR021731-32); *id.* at 41-42 (RDR021758-59) (injuries); *id.* at 28-29 (RDR021745-46 (bleeding).)

The IBD plaintiffs also state that Dr. Fogel relied on studies involving rats and Vitamin A, a substance that is related to but chemically distinct from Accutane. The IBD plaintiffs did not introduce these rat studies into the record below or before this Court, and Dr. Fogel did not specifically identify them in his report, (Doc 411 - Ex. H - Pg 6), nor was he able to identify them during his

deposition, (Doc 411 - Ex. E2 - Pg 25 (tr. 187:25 - 188:21)). However, Roche submitted to the District Court the rat studies which Dr. Fogel seemed to be citing, (Doc 411 - Exs. Q, R), and like his two dog studies, these rat studies involved super-toxic dosing levels.

In sum, Dr. Fogel selected data from two studies involving less than 100

dogs and from unspecified Vitamin A rat studies, ignoring all other human and animal studies in the more than thirty-year history of Accutane research. While animal studies might in appropriate circumstances provide support for a causation opinion, Dr. Fogel's parsing of the data to find the handful of dogs and the unspecified Vitamin A rats that purportedly support his opinion was improper for at least five reasons:

1. Dr. Fogel admittedly lacked the knowledge to extrapolate from these animals to humans.
2. Dr. Fogel failed to account for contrary data from other animal studies and from humans.
3. Even within his carefully selected studies, Dr. Fogel improperly ignored data from human-comparable doses and focused only on high-dose data.
4. Dr. Fogel failed to explain how the reversible gastrointestinal conditions these animals experienced translated to permanent IBD in humans.
5. Only one of these studies even involved Accutane.

a) Dr. Fogel's Inability to Analogize from Animals to Humans.

Dr. Fogel admitted that: "drugs may have different activity and effect in humans than they do in . . . animals"; you "do not assume you'll see the same effect in humans"; and "even between animal species you will see differences in drug activity and effect." (Doc 411 - Ex. E3 - Pg 12 (tr. 242:18-21; 242:22-24; 243:9-14).) Yet he admitted that he had no idea how dog or rat gastrointestinal data related to human gastrointestinal data. (Doc 411 - Ex. E3 - Pg 12 (tr. 244:13-17) (dogs: "I have not undertaken any systematic studies"); (Doc 411 - Ex. E3 - Pg 12 (tr. 244:25 – 244:4)) (rats: "I have not").) Courts have consistently rejected such unsubstantiated reliance on animal data. *See Raynor* v. *Merrell Pharm., Inc.*, 104 F.3d 1371, 1375 (D.C. Cir. 1997); *see also Lynch v. Merrell-National Labs*., 830 F.2d 1190, 1194 (1st Cir. 1987) (animal studies not capable of proving human causation absent epidemiological data); *Allen v. Pennsylvania Eng'g Corp*., 102 F.3d 194, 197 (5th Cir. 1996) (animal studies are of limited usefulness); *Soldo*, 244 F. Supp. 2d at 546 ("To ensure that the expert's conclusion based on animal studies is reliable, there must be 'a scientifically valid link' – such as supporting human data – 'between the sources or studies consulted and the conclusion reached.'")

(citation omitted).

b) Impermissibly Ignoring Adverse Studies.

Dr. Fogel parsed out a scant selection of animal data from the much larger body of animal and human data. Accutane has been studied in numerous animal studies involving a number of species as well as in numerous human studies. (*See, e.g.*, Doc. 411 - Exs. S, U.) Dr. Fogel privileged his small selection of animal data — the dog studies he depends most heavily on involve only a little over 100 dogs combined, and showed observable gastrointestinal injuries in only roughly 25 of those dogs — over the much larger universe of animal and human data without providing any analysis that meshes the limited findings he depends upon with this larger universe of data. Courts have recognized that such biased data selection is the hallmark of an unreliable methodology. *See Miller*, 196 F. Supp. 2d at 1086-87 (reliance on pre-selected evidence from interested parties, to exclusion of other reliable evidence, is inconsistent with reliable methodology); *Caraker*, 172 F.

Supp. 2d at 1051 (same).

c) Impermissibly Ignoring Doses Equivalent to Human Doses

.

The maximum recommended human dose of Accutane is 2 milligrams of Accutane per human kilogram per day (2 mg/kg/day). The two dog studies on which Dr. Fogel relied involved super-toxic doses far in excess of normal human doses, ranging from 20 mg/kg/day to 120 mg/kg/day. In fact, when the 1979 Dog Study used doses close to (but still higher than) human doses – 3 mg/kg/day – no

notable effects were seen. Although Dr. Fogel admitted that he did not know how to compare animal to human dosing (Doc 411 - Ex. E2 - Pg 26 (tr. 190:16-191:9)), he gave no explanation for his decision to ignore the no-effect findings from the human-comparable doses and focus only on the super-toxic dosing effects. This unexplained parsing of the data deviated from reliable scientific inquiry.

Dr. Fogel's failure to analyze the relevance of dosing levels in this data is indicative of his larger disregard for the dose-response relationship. In *McClain*, this Court identified the dose-response relationship as "the basic methodology that

scientists use to determine causation." 401 F.3d at 1242; *see id.* at 1241 ("When analyzing an expert's methodology in toxic tort cases, the court should pay careful attention to the expert's testimony about the dose-response relationship."). "The expert who avoids or neglects this principle of toxic torts without justification casts suspicion on the reliability of his methodology." *Id.* at 1242.

Dr. Fogel failed to conduct any analysis of whether there was a threshold dose of Accutane that is necessary to cause IBD in humans.

> Q. You haven't done any analysis that deals with whether or not there is a threshold dose that's required to trigger that event, true?
>
> A. I did not do that analysis, no, but that information wasn't available to even consider doing such an analysis."

(Doc 508 - Pg 9-10; *see also* Doc 411 - Ex. E3 - Pg 16 (tr. 258:16-21) (hyperlink).) Like the expert in *McClain*, who "could not provide any opinions about the general

dose-response levels for Metabolife's toxicity, [*i.e.,*] the dose or level of exposure at which it causes harm," 401 F.3d at 1241, Dr. Fogel is willing to opine that even "one pill" of Accutane can cause a lifelong disease. The District Court wrote:

> Dr. Fogel is of the opinion 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. He states that he might find Accutane as the cause of IBD even if it was used for only one or two days or perhaps even if only 'one pill' were used.

(Doc 508 - Pg 25; *see also* Doc 420 - Ex. G - Pg 24 (tr. at 74:8-19) (hyperlink).)

The District Court did not abuse its discretion in excluding Dr. Fogel's opinion by applying the analysis set forth by this Court in *McClain*.

d) Failure to Relate Reversible Animal Effects with Permanent Human Effects.

As the District Court noted, Dr. Fogel's animal data involved effects that were "***temporary, not permanent***." (Doc 580 - Pg 9 (emphasis added); Doc 604 - Ex 9 - Pg 13 (RDR021730) (1979 Dog Study) ("The gastrointestinal changes associated with [Accutane] are neither profound nor irreversible."); Doc 444 - Ex 4 - Pg 2 (Dog Metabolite Study).) IBD, of course, is a permanent disease. Dr. Fogel's failure to explain how temporary effects in animals are equivalent to a permanent human disease provides yet another basis for rejecting his animal testimony

.

e) Failure to Link Data Involving Other Chemicals to Accutane.

Of Dr. Fogel's animal data, only the 1979 Dog Study involved Accutane: the Dog Metabolite Study and the rat studies involve Vitamin A or other retinoids, chemicals that are part of the same class as Accutane but which are chemically distinct from Accutane. Dr. Fogel provided no basis for analogizing other retinoids to Accutane, perhaps because, as he conceded, he is "not an expert in retinoid chemistry or pharmacology." (Doc 580 - Pg 11.)

To properly analogize from other retinoids to Accutane, Dr. Fogel had to show both (1) that the other retinoid actually causes IBD, and (2) that Accutane is sufficiently similar so as to have the same effect.[14] Dr. Fogel made neither showing, instead simply assuming a class effect.

[14] To support Dr. Fogel's use of inapplicable retinoid data, the IBD plaintiffs continue to rely on evidence that ***Dr. Fogel never considered***, including the

Vesanoid label, which the IBD plaintiffs' counsel was forced at argument to concede was not relied upon by Dr. Fogel:

> "MR. O'BRIEN: . . . . We've attached the Vesanoid label to our brief, I believe – excuse me, we have not attached the Vesanoid label.
>
> THE COURT: Well, nowhere in his report does it say he relied on some Vesanoid studies to support his position on Accutane or why he thinks they're similar.
>
> MR. O'BRIEN: In the absence of the Vesanoid studies, he did, I believe, cite the Vitamin A class effect, the retinoid class effect at pages 4 to 6. Maybe that's what my learned co-counsel was referring to in my executive summary that he gave me." (Doc 613 - Ex. A - Pg 5 (tr. 47:3-13).)

This Court, like others around the country, has rejected this type of unexamined assumption: '"[e]ven small differences in chemical structure can sometimes make very large differences in the type of toxic response that is produced.'" *McClain*, 401 F.3d at 1246 (unsupported assumptions of chemical relatedness simply "do not make for reliable opinions") (citation omitted).[15] Indeed, a significant body of the case law rejecting "chemical guilt by association"

has grown up in the Accutane context.[16]

[15] *See also Soldo*, 244 F. Supp. 2d at 564 (rejecting "'guilt by association' inference"); *Caraker*, 172 F. Supp. 2d at 1051-52 (same); *Siharath v. Sandoz Pharm. Corp*, 131 F. Supp. 2d 1347, 1363-64 (N.D. Ga. 2001) (same), *aff'd sub nom., Rider v. Sandoz Pharm. Corp.,* 295 F.3d 1194 (11th Cir. 2002). [16] *See Newton v. Roche Labs., Inc.*, 243 F. Supp. 2d 672, 680 (W.D. Tex. 2002) ("[T]he human body reacts to Accutane and Vitamin A in different ways."); *Thomas v. Hoffman-LaRoche, Inc.*, 949 F.2d 806, 814 n.36 (5th Cir. 1992) ("[L]isting the actual side effects reported by Accutane patients provides a much better indication of the risks associated with Accutane [ ] than would a list of the side effects of Vitamin A . . . ."); *Grimes v. Hoffmann-LaRoche Inc.*, 907 F. Supp. 33, 38 (D.N.H. 1995) (excluding expert who "failed to identify any scientifically reliable basis for concluding that Accutane causes cataracts simply because other

photosensitive drugs cause cataracts").

2. Case Reports, Including Rechallenge Reports

Dr. Fogel relied upon two types of case report evidence: case reports generally; and a specific type of case report called a rechallenge report.

A case report involves a single patient who reports an adverse event after having used a medication. The report may be made to the pharmaceutical company or to the FDA by a patient, physician, or even a plaintiff lawyer, or it may be published as a case study in a journal.

A rechallenge report is a specific type of case report in which a patient experiences a symptom when they begin using a medication (challenge), they have the symptom stop when the medication stops (dechallenge), and the symptom returns when the medication returns (rechallenge).

Courts, including the Eleventh Circuit, have repeatedly found both types of evidence insufficient to support causation opinions. Moreover, the manner in which Dr. Fogel relied on case reports and rechallenge reports was particularly

unreliable

.

a) Case Reports

The plaintiffs offer only a token defense of Dr. Fogel's general reliance on case reports. *See* Br. at 36-37. This may spring from the fact that this Court and courts around the country have repeatedly found anecdotal case reports to be unreliable evidence of causation. *See*, *e.g.*, *McClain*, 401 F.3d at 1250

("Uncontrolled anecdotal information offers one of the least reliable sources to justify opinions about both general and individual causation").[17] As one court explained:

> Case reports are an "account of a particular patient's reaction to a drug or other stimulus" and "make little attempt to screen out alternative causes for a patient's condition," and "frequently lack analysis." . . . Case reports are not controlled studies, and they cannot be verified through peer review. Case reports often do not include information about the patient's medical history, family medical history, use of other medications or drugs, or other information that would be necessary to determine . . . causation . . . can be established. ***Case reports are not scientific proof of causation.***

Dunn v. Sandoz Pharms. Corp., 275 F. Supp. 2d 672, 682 (M.D.N.C. 2003)

(citations omitted and emphasis added).

These fundamental shortcomings led this Court to reject causation testimony based on case reports in both *McClain* and *Rider*. *McClain*, 401 F.3d at 1240

[17] *See Rider*, 295 F.3d at 1199 (rejecting reliance on case reports); *Glastetter v. Novartis Pharm. Corp.*, 252 F.3d 986, 990 (8th Cir. 2001) (same), *aff'g.* 107 F. Supp. 2d 1015, 1030 (E.D. Mo. 2000) (same); *Black*, 171 F.3d at 313 n.2 (same); *Dunn v. Sandoz Pharm. Corp.*, 275 F. Supp. 2d 672, 682 (M.D.N.C. 2003) (same); *Cloud v. Pfizer*, 198 F. Supp. 2d 1118, 1133 (D. Ariz. 2001) (same); *Castellow v. Chevron USA*, 97 F. Supp. 2d 780, 787 (S.D. Tex. 2000) (same); *Brumbaugh v. Sandoz Pharm. Corp.,* 77 F. Supp. 2d 1153, 1156 (D. Mont. 1999) (same); *In re Breast Implant Litig.*, 11 F. Supp. 2d 1217, 1231 (D. Colo. 1998) (same); *Willert v. Ortho Pharm. Corp.,* 995 F. Supp. 979, 981 (D. Minn. 1998) (same); *Haggerty v. Upjohn Co.*, 950 F. Supp. 1160, 1165 (S.D. Fla. 1996) (same), *aff'd*, 158 F.3d 588 (11th Cir. 1998); *Hall v. Baxter Healthcare Corp.*, 947 F. Supp. 1387, 1411 (D. Or. 1996) (same); *Casey v. Ohio Med. Prods.*, 877 F. Supp. 1380, 1385 (N.D. Cal. 1995) (same); *Wade-Greaux v. Whitehall Labs. Inc.,* 874 F. Supp. 1441, 1453 (D.V.I.) (same), *aff'd*, 46 F.3d 1120 (3d Cir. 1994); *Heckstall v. Pincus*, 797 N.Y.S.2d 445, 447 (N.Y. App. Div. 2005) (same); *Newton v. Roche Labs. Inc.*, 243

F. Supp. 2d 672, 680 (W.D. Tex. 2002) (disqualifying expert who relied on case reports to prove that Accutane causes psychiatric conditions).

(expert "unjustifiably relies on . . . consumer complaints to establish medical causation"); *Rider v. Sandoz Pharm. Corp.*, 295 F.3d 1194, 1199 (11th Cir. 2002) ("[C]ase reports alone ordinarily cannot prove causation."). As the Court held, "case reports raise questions; they do not answer them." *McClain*, 401 F.3d at 1254.

b) Rechallenge Reports

Dr. Fogel placed special reliance on a handful of case reports that involved "rechallenge." (*See* Doc 411 - Ex. E3 - Pg 5 (tr. 215:11-12) ("The evidence that I found most compelling was the challenge-dechallenge-rechallenge.").) While these "rechallenge" reports have superficial appeal, they are no more reliable than other case reports because they remain uncontrolled and unconfirmed data. For this reason, this Court and others reject causation opinions based on rechallenge reports, particularly when there is no analysis to show that the rechallenge incidents occurred more often than would be expected by chance. *See McClain*, 401 F.3d at 1254-55 ("'[Challenge-dechallenge-rechallenge] tests are still case reports and do not purport to offer definitive conclusions as to causation.'") (quoting *Rider*, 295 F.3d at 1200).[18]

[18] (same); F.3d studies methodology (continued...) *See* 1326 *also*, to *Miller* test (10th *e.g.*, . a *v.* . hypothesis . *Rider*, Cir. *Pfizer*, ."); 2004) *Soldo*, 295 196 is ("Use F.3d 244 F. inadequate Supp. F. at of 1200 Supp. a 2d small (same); and 1062, 2d number at not 541 1077 *Soldo*, generally ("The of (D. challenge-dechallenge 244 Kan. accepted F. 2002), Supp. *aff'd,* 2d at 541

Rechallenge reports are particularly unreliable in the IBD context. IBD follows a cyclical course, with symptoms coming and going over time. Moreover, millions of patients have taken Accutane in the last twenty-five years. These facts mean that some rechallenge reports will arise wholly by chance – some patients among the millions who have used Accutane will have their IBD wax and wane by chance as they stop and start courses of Accutane. It is especially unreliable to premise a causation opinion on this type of data without reliable evidence that accounts for these chance rechallenge reports. Dr. Fogel has no such evidence.

c) Dr. Fogel's Reliance on This Evidence Was Especially Unreliable.

Even aside from the general questions about whether an expert may premise a causation opinion on case reports, Dr. Fogel's handling of the case reports was particularly unreliable.

Dr. Fogel admittedly made no effort to conduct any quantitative analysis to see whether these reports arose by chance or due to something else, nor did he even delve into the basic details of the case reports. Thus, for example, he was forced to admit that he did not even know whether some of the case reports upon

which he relied involved correct diagnoses of IBD. (*See* Doc 411 - Ex. E3 - Pg 8

'dechallenge/rechallenge' reports relied upon by plaintiff's experts lack controls, involve injuries other than ICH, are too scant in number, and 'do not contain a testable and systematic inquiry into the mechanism of causation.'") (quoting *Caraker,* 172 F. Supp. 2d at 1050).

(tr. 226:3-14) (admitting that alleged IBD reports he relied upon did not actually support IBD diagnosis: "Q. . . . And so you would not, as you previously testified here today, make a diagnosis of inflammatory bowel disease on the presence of rectal bleeding alone, true? A. True.").)[19]

The closest that the IBD plaintiffs have to an actual analysis of case reports was conducted not by Dr. Fogel, but rather by the authors of the Reddy study, who performed causality assessments on all case reports submitted to the FDA from 1997 and 2002. (Doc 411 - Ex. F.) Yet while the Reddy authors surveyed case reports and other available data and found only a "possible association," (Doc 411 - Ex. F - Pg 5), Dr. Fogel claims that their study establishes causation. To borrow from *McClain's* criticism of similar expert practice, while "[t]he authors of

the article[] limit the application of their stud[y] consistent with the principles of good science; [Fogel] expands the application beyond good science." *McClain*,

[19] Indeed, the IBD plaintiffs cite three alleged IBD rechallenge reports and criticize the District Court for not considering these reports in its ruling. Br. at 33- 36 (citing Doc 604 - Exs. 33, 36, 38). This criticism rings hollow given that they did not even submit these reports to the District Court until *after* its ruling. Moreover, none of these three reports, which plaintiffs trumpet to support "clear scientific proof of causation," appear to even reflect reports of IBD -- a permanent, chronic condition about which Dr. Fogel now seeks to offer his causation opinion: Ex. 33 ("NO SUGGESTION OF CHRONICITY"; "RECTAL BIOPSY: SIX MONTHS AFTER STOPPING ACCUTANE. NORMAL."); Ex. 36 ("DURING A 24-MONTH FOLLOW-UP PERIOD WITH NO FURTHER INTRODUCTION OF ROACCUTANE, THE PATIENT DID NOT HAVE ANY PAINFUL ABDOMINAL ATTACKS OR DIARRHOEA."); Ex. 38 ("AT THE TIME OF THIS REPORT, THE EVENT HAD RESOLVED.").

401 F.3d at 1247; *see also id.* at 1245 ("[T]he plain reading of the HSP article does

not authorize O'Donnell's conclusions."); *id.* at 1248 ("But this shows again O'Donnell's lack of scientific rigor in that he draws unauthorized conclusions from limited data – conclusions the authors of the study do not make."). Moreover, Dr. Fogel went beyond good science without even having reviewed the data underlying the article. As the District Court noted, Dr. Fogel did what the Reddy authors were unwilling to do, citing their study as proof of causation "without having done the intensive review performed by" them. (Doc 580 - Pg 25.)

But it was in his treatment of the rechallenge reports that Dr. Fogel showed an especially notable disregard for basic analytical inquiry. Rather than analyzing whether rechallenge occurred at a rate higher than chance, or whether *positive* rechallenge happened more frequently than *negative* rechallenge (when a patient restarts Accutane but *does not* experience IBD), Dr. Fogel instead glibly suggested that three rechallenge reports are always sufficient to prove causation: "One or two challenge-dechallenge-rechallenge occurrences may be coincidental. If there are at least three of those reported events, strong and compelling evidence of causation becomes apparent." (Doc 411 - Ex. H - Pg 8.)

Dr. Fogel's "magic number three" theory illustrates the unscientific nature of

his "methodology." While he would apparently be uncertain about causation if faced with two rechallenge reports among a small patient population, his

phrenological willingness to find causation automatically from three rechallenge reports among the more than 12 million people who have used Accutane is strikingly unreliable and falls fundamentally short of a valid analytical or statistical analysis. For these reasons, even setting aside the distaste that plaintiffs may have for this Circuit's case law rejecting causation opinions founded on case reports, Dr. Fogel's specific use of this evidence does not allow him to present a reliable causation opinion.

3. Causality Assessments

Dr. Fogel's final line of evidence was causality assessments. Causality assessments are ratings that companies generate for each case report based on simple checklists (*e.g.*, did the event follow drug use, *etc.*)[20] or other guidelines. The ratings – which are required by European but not American regulators – are used by companies in their risk assessment efforts, to sort out case reports which

are less likely to be drug-related from those which merit closer review. No

[20] An example of how these ratings are calculated is contained in the Reddy article, which used the Naranjo checklist to generate causality assessments. (Doc 411 - Ex. F.) Under that checklist – as with other causality assessments – the questions are skewed towards generating a higher rating. For example, if a case report involves a patient who developed IBD following Accutane use, had the IBD medically confirmed, and has no other known cause for the IBD (because IBD has no known cause), the patient will automatically receive a "probable" rating, even though no scientist would claim based simply on that evidence that the Accutane probably caused the IBD.

company, regulator, or scientist uses these checklist ratings to determine actual causal relationships.

The District Court issued two rulings regarding causality assessments. It first found the assessments irrelevant and unduly prejudicial. It then specifically found that Dr. Fogel's reliance on the assessments failed *Daubert* standards. Both

rulings were correct.

a) The District Court Properly Excluded Causality Assessments.

The plaintiffs sought to use causality assessments as proof of causation, arguing that they represented actual admissions by Defendants that Accutane caused specific instances of IBD.[21] As Judge Moody ruled, such a suggestion fundamentally misunderstands the nature of causality assessments.

Because causality assessments are based entirely on individual case reports, they necessarily suffer the same defects discussed above for proving causation from case reports. Moreover, causality assessments are used for risk assessment

[21] Plaintiffs separately argued below that causality assessments were proof that Roche was on notice of case reports, but Defendants have never contested that they were on notice that there were reports of IBD following Accutane use – in fact, that notice is the reason why Defendants have expressly warned physicians of the risk of IBD for more than twenty years. The District Court explicitly rejected this notice argument, including in its ruling excluding this evidence in the psychiatric cases. (Doc 636 - Pgs 2-3 ("Notice is not really an issue in the case. Roche acknowledges that it has received notice and as a result has included warnings on

its label. And, if notice were an issue, notice would come from the case reports, not the causality assessments.").)

purposes only – to separate case reports that require further evaluation from those where there is little possibility of a drug relationship. They are thus heavily skewed in favor of finding a potential relationship so that heightened signal detection may be conducted.

Dr. Martin Huber, the former Global Head of Drug Safety at Roche, explained Roche's causality assessments as follows:

> The [causality] assessment of probable in a comment field in a database is not the same as saying this is a case that is causally related to the drug. What these approaches do . . . is you are on an individual case basis making some assessment of the degree of data supporting some association. . . . . The assessment . . . of a probable relationship . . . does not indicate that the product specialist has concluded that the event is caused by the drug in that case.

(Doc 408 - Ex. L - Pgs 9-10 (tr. 717:18 - 718:1; 722:7-11).) Plaintiffs can point to no contrary evidence, other than their alluring title, that these individual case assessments are ever understood to represent findings of actual causation.[22]

[22] The IBD plaintiffs attempt to soundbite other witnesses in order to suggest that "the name 'causality assessments' clearly reflects their purpose," but these witnesses' complete testimony rejects the plaintiff assertion that causality assessments are scientific assessments of causality. For instance, they cite testimony from Dr. Daniel Reshef as to the extensive efforts Roche makes in following up on and evaluating adverse event reports, but they omit in their discussion the central component of his testimony about causality assessments: "everything we refer to as causality in this discussion ***really means relatedness***." (Doc 506 - Pg. 6 (emphasis by the District Court).)

From a risk assessment standpoint, there is good reason for liberal causality assessment procedures like those Roche uses. But adopting procedures that are so heavily biased in favor of finding relatedness renders causality assessments particularly meaningless as evidence of scientific causation. For these reasons, every federal court to have spoken on this issue has concluded that causality assessments are not reliable evidence of causation.[23] *See Soldo v. Sandoz Pharm.*

Corp., 244 F. Supp. 2d 434, 465 (W.D. Pa. 2003) (causality assessments are undertaken "'primarily to determine which reports of suspected adverse reactions contribute to the total evidence, which do not, and which deserve further consideration. However, these useful scales have *no objective reliability* which would render them useful in a wider environment.'") (citation omitted); *In re Meridia Prods. Liab. Litig.*, 328 F. Supp. 2d 791, 809-10 (N.D. Ohio 2004) (rejecting evidence of internal "probable" company causality assessments as sufficient proof of causation), *aff'd*, 447 F.3d 861 (6th Cir. 2006).

This Court's own jurisprudence has rejected analogous risk assessment evidence. In the *Rider* case, the five plaintiff experts attempted to hinge their causation opinions on the fact that the FDA had taken the dramatic step of withdrawing Parlodel from the market based on the FDA's risk assessment for that

[23] Two state courts have allowed causality assessments into evidence, without published opinions, in Accutane trials.

drug.[24] *Rider*, 295 F.3d at 1201. This Court rejected this dramatic risk assessment

as causation evidence because the "risk-utility analysis involves a much lower standard than that which is demanded by a court of law." *Id.* The *McClain* decision elaborated on this reasoning in rejecting similar risk assessment determinations as evidence of causation. Quoting the *Reference Manual on Scientific Evidence*, the Court stated that: "[p]roof of risk and proof of causation entail somewhat different questions because risk assessment frequently calls for a cost-benefit analysis." *McClain*, 401 F.3d at 1249. The same reasoning applies here: causality assessments used to assess potential risk signals may not be perverted into the proof of causation that the plaintiffs claim them to be.

Given that causality assessments are not probative of causation, any use of them for this purpose would be highly prejudicial. And the plaintiffs made clear below that they intended to use causality assessments for exactly that purpose. The District Court properly rejected that use under Rule 403:

> [I]t is likely that a lay juror would have difficulty distinguishing that the term 'causality assessment,' as the term relates to safety surveillance, is not the same as causation. "[T]he procedures commonly used in [safety surveillance] for the purpose of establishing public health guidelines . . . are often . . . of marginal relevance to estimating causation in an individual." *McClain*, 401 F.3d at 1249 (citations omitted). In fact, it is highly probable that a juror would

[24] Accutane, with its 25-year history unmarked by a single study linking the product to IBD, stands as a stark contrast to this example.

> perceive the company's "yes" response in the causality assessment field as an admission by Defendants' physicians that Accutane did in fact cause the adverse events reported. Therefore, the potential prejudice outweighs the probative value of the reports.

(Doc 506 - Pg 11-12.)[25]

b) The District Court Properly Rejected Dr. Fogel's Specific Reliance on Causality Assessments.

Setting aside the broader question of whether causality assessments are admissible, the District Court properly excluded Dr. Fogel's reliance on them on a separate and independent basis: Dr. Fogel had no idea what they meant. Dr. Fogel frankly acknowledged that he has no idea how Roche's causality assessments are generated: "I have no information about the Roche methodology." (Doc 411 - Ex. E3 - Pgs 14-15 (tr. 255:4 - 255:19) (hyperlink).) Instead, rather than acting as an independent scientist would in the field, he simply followed the direction of Plaintiffs' counsel and assumed that the term "causality assessments" meant there

was a scientific analysis of causation: "if somebody says something is causally related then it's causally related." *Id*. Based on Dr. Fogel's confession of ignorance, the District Court found that Dr. Fogel "had no idea how they were

[25] The district court subsequently reaffirmed this ruling in the psychiatric cases, after having the benefit of seeing how plaintiffs' counsel used these cases in a state court trial in which they were allowed into evidence: "they are highly prejudicial and excludable under Rule 403, Federal Rules of Civil Procedure. The McCarr[e]ll trial in state court in New Jersey is a perfect example of that. (See specific examples in Roche's Reply Brief, Dkt. #584.)" (Doc 636 - Pgs 2-3; Doc 584).

created, why they were created, or in what context the words were used in the documents. . . . He merely accepted them at face value because they refer to 'causality.'" (Doc 580 - Pg 15.) Given his utter lack of understanding about these causality assessments, the District Court correctly determined that Dr. Fogel is not competent to testify about them: "[i]t is disconcerting, and perhaps telling, that Dr. Fogel did not make any independent inquiry as to the methodology used by

Hoffman-LaRoche in creating the assessments." *Id.*; *see also Soldo*, 244 F. Supp. 2d at 545 ("Where the methodology [for making causality assessments] is unknown, the opinion is inadmissible.").

* * * * * * *

As the discussion above illustrates, Dr. Fogel's opinions do not meet the requirements of *Daubert* using the guidelines set forth in *Daubert* itself:

1. Dr. Fogel has conducted no study to ***test*** his theory regarding Accutane and IBD, and no study has ever found even a statistically significant association between Accutane and IBD;
2. Dr. Fogel has never subjected his speculative theories to ***peer review*** – to the contrary, he reached these opinions for the first time in this litigation;
3. Dr. Fogel's reliance on anecdotal evidence and speculation creates a significant ***expected rate of error***, as illustrated by his admission that he does not even know what the risk of IBD from Accutane, (Doc 411 - Ex.

E2 - Pg 25 (tr. 185:8-21) (hyperlink)), combined with his fantastical willingness to speculate that 10% of the more than 12 million Accutane

users have developed IBD, (Doc 411 - Ex. G2 - Pg 1 (tr. 90:15-18) (hyperlink));[26] and

4. Dr. Fogel's methods — relying on selected animal data, anecdotal case reports, and causality assessments — are ***not generally accepted*** methods in the scientific community for reaching causation determinations.

See McClain, 401 F.3d at 1251 (citing *Daubert*, 509 U.S. at 593-94, 113 S. Ct. at 2797). As discussed above, each specific type of evidence offered by Dr. Fogel cannot survive individual scrutiny. As this Court and courts around the country have recognized, Dr. Fogel may not overcome these individual deficiencies by somehow packaging these various unreliable sources together into a causation opinion. *See Rider*, 295 F.3d at 1201 (rejecting similar effort to create causation from series of unreliable factors); *McClain*, 401 F.3d at 1250-52 (same); *Ealy v. Richardson-Merrell, Inc.*, 897 F.2d 1159, 1160 (D.C. Cir. 1990) (same).

[26] Dr. Fogel's "10%" estimate would mean that roughly 500,000 people in the United States have Accutane-induced IBD. (*See* Doc 411 - Ex. A.) Stated differently, even though Dr. Fogel has only met a single IBD patient whom he

knew took Accutane, his opinion is that half of the one million IBD patients in the United States developed that disease directly as a result of Accutane. (*See* Doc 411 - Ex. E2 - p. 22 (tr. 174:2-3).) Dr. Fogel appears to be the only scientist to have detected this startling epidemic during the 25-year history of Accutane, and only after being hired to testify in these cases.

Ultimately, "in law as in mathematics zero plus zero equals zero." *Henderson v. Kennedy*, 253 F.3d 12, 19 (D.C. Cir. 2001).

C. Lawyer Arguments Cannot Rehabilitate Dr. Fogel's Opinion.

The IBD plaintiffs attempt to prop up Dr. Fogel's opinions with several after-the-fact lawyer arguments that bear little relationship with his actual methodology, none of which survive scrutiny.

Most notably, the IBD plaintiffs try to shoehorn Dr. Fogel's methodology into the Bradford Hill criteria that are sometimes used to assess whether a demonstrated statistical association between a substance and an effect might be considered to be a causal relationship. Br. at 31 - 32. In none of his expert reports or his multiple depositions, however, did Dr. Fogel once even mention "Bradford

Hill," let alone attempt to apply the criteria in any systematic way. Nor could he, because the evidence of Accutane's relationship to IBD fails all of the Bradford Hill factors.

But more fundamentally, the Bradford Hill criteria simply do not apply here. These criteria serve to evaluate the likelihood that ***an identified statistically significant association*** reflects a cause-and-effect relationship. *See* Austin Bradford Hill, "The Environment and Disease: Association or Causation?," 58 *Proceedings of the Royal Society of Medicine*, 295-300 (1965). Where, as here, there is no evidence of a statistically significant association, the Bradford Hill

criteria never even come into play, as many courts have recognized.[27] Dr. Fogel freely admits that there are no clinical or epidemiologic studies showing a statistically significant association between Accutane use and IBD. Consequently, the Bradford Hill criteria are simply irrelevant here, and his sponsoring counsel cannot rescue his defective methodology by mere invocation of "Bradford Hill" in legal argument.

The IBD plaintiffs offer various other after-the-fact arguments to bolster Dr. Fogel's testimony that similarly crumble upon examination. For example:

- The IBD plaintiffs suggest that a Roche doctor was considering the relationship between Accutane and IBD when they quote him as saying, "a possible causative role for ROACCUTAN seems only reasonable." Br. at 41. In truth, the author was speaking not of IBD, but of elevated

[27] *See, e.g., Dunn v. Sandoz Pharm. Corp*., 275 F. Supp. 2d 672, 679 (M.D.N.C. 2003) ("*The first step* in the causation analysis pursuant to Bradford Hill *is an epidemiological study that has identified an association between two variables*.") (emphases added) (quoting *Reference Manual on Scientific Evidence* 336-37 (2d ed. 2000)); *Amorgianos v. Nat'l R.R. Passenger Corp.*, 137 F. Supp. 2d 147, 168 (E.D.N.Y. 2001) ("Even when an appropriately designed study yields evidence of a *statistical association* between a given substance and a given health outcome, epidemiologists . . . . generally look to several *additional* criteria to determine *whether a statistical association is indeed causal*. These criteria are sometimes referred to as the Bradford Hill criteria . . . ."") (emphases added, internal quotation marks and citations omitted), *aff'd* 303 F.3d 256 (2d Cir. 2002); *In re Breast Implant Litig.*, 11 F. Supp. 2d 1217, 1223-1234 n.5 (D. Colo. 1998) ("The

Bradford-Hill criteria *start with an association demonstrated by epidemiology and then apply such criteria* as the temporal sequence of events, the strength of the association, the consistency of the observed association, the dose-response relationship, and the biologic plausibility of the observed association.") (emphasis added).

triglycerides (a known effect of Accutane), as the entire sentence selectively quoted from the document makes clear: "A possible causative role for ROACCUTAN seems only reasonable, however, for increased triglycerides." (Doc 604 - Ex. 27 - Pg 4.)

- The IBD plaintiffs cite the labeling for another retinoid (Vesanoid), even though Plaintiffs' counsel was forced to admit at the *Daubert* hearing that Dr. Fogel had not relied on Vesanoid. *See* note 14.
- The IBD plaintiffs cite two different reports from the ***same*** study (an interim report and a final report), improperly suggesting that the two reports represent separate studies. Br. at 25-26.
- The IBD plaintiffs conclusively assert "There is no doubt that the evidence

of a dose-response is strong with regard to Accutane and IBD," yet Dr. Fogel disavowed any knowledge of this purported dose response.[28]

[28] (Doc 411 - Ex. E3 - Pg 16 (tr. 258:24-259-10) (hyperlink) (agreeing he "didn't do any analysis that pertains to" "dose response in humans with respect to inflammatory bowel disease" and hasn't "made any review of any individual case report to ascertain whether or not the events in any individual case report were, in fact, dose response related").) The IBD plaintiffs' other experts likewise acknowledge the absence of any dose relationship. (Doc. 407 - Ex. A - Pg 61 (tr. 449:21-450:2) ("I have no independent evidence" that would "suggest that inflammatory bowel disease is in any way dose related to Accutane"); Doc 406 - Ex. E1 - Pgs 17-18 (tr. 209:22-210:2) ("Q: Have you ever seen any evidence that IBD specifically is dose-related, or rather, is a dose- related side effect of Accutane? A: As I – um, I don't think that I note anything, one way or the other, regarding dose response.").)

- The IBD plaintiffs accuse the District Court of not examining the record fully, pointing to the 1979 Dog Study which they did not introduce into the

record until ***after*** the District Court had issued the ruling they criticize. *See* Br. at 2.

- The IBD plaintiffs criticize the District Court for not considering three alleged IBD rechallenge case reports when they had not provided them to the District Court until ***after*** its ruling and which in fact do not reflect permanent inflammatory bowel disease. *See* note 19.

The IBD plaintiffs' resort to lawyer argument tethered neither to the stated grounds of Dr. Fogel's opinion nor to the actual factual record betrays the deficiencies in Dr. Fogel's methodology they now struggle to defend.

II. Accutane's Express IBD Warnings Provide An Independent Basis for Affirmance.

Because the District Court granted summary judgment on causation, it did not reach Roche's separate motion seeking summary judgment based on the adequacy of Accutane's physician warnings about the risk of IBD. These express warnings provide an independent basis to affirm the Court's grant of summary judgment on the IBD plaintiffs' claims, all of which are premised on Roche's failure to warn about Accutane's IBD risks. Accordingly, this Court may also

affirm Judge Moody's grant of summary judgment on this alternative ground as well. *See, e.g., Gholston v. Housing Authority of the City of Montgomery*, 818

F.2d 776, 780 n.3 (11th Cir. 1987) (appellee "is entitled to raise any argument on appeal that supports the judgment of the district court").[29]

A. Accutane's Physician Label Expressly Warned of the Risk of IBD.

Beginning in 1984, Roche expressly warned about the risk of IBD in the WARNINGS section of the Accutane physician package insert. That warning stated:

> *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.

(Doc 477 - Ex. C.) Beginning in May 2000, this express warning was slightly modified to read:

> *Inflammatory Bowel Disease*: Accutane has been associated with inflammatory bowel disease (including regional ileitis) in patients without a prior history of intestinal disorders. In some instances, symptoms have been reported to persist after Accutane treatment has been stopped. Patients experiencing abdominal pain, rectal bleeding or severe diarrhea should discontinue Accutane immediately (see

ADVERSE REACTIONS: *Gastrointestinal*).

(Doc 477 - Ex. F.)[30] To assist physicians in discussing Accutane's risks with their patients, Roche further provided physicians with patient brochures (the substance

[29] Affirming dismissal on this alternative ground would provide finality to the remaining IBD cases stayed by Judge Moody pending the outcome of this appeal.

[30] All of the IBD plaintiffs in the MDL took Accutane after 1984, and at least Plaintiff Justin Rand took Accutane after May 2000.

of which was reprinted on the actual Accutane blister packaging) which warned that Accutane "may cause" "severe stomach pain, diarrhea, rectal bleeding" – the three principal symptoms of IBD. (*See, e.g.*, Doc 477 - Ex. G (1994 patient brochure); Doc 477 - Ex. H (1993 blister packaging)).

B. The Accutane IBD Warnings Are Adequate As a Matter of Law.

Like almost every state, Florida, Texas, and Indiana[31] recognize that prescription medications fall into the special category of "unavoidably unsafe" products – products that provide a net societal benefit but which cannot be made perfectly safe. Because these medicines will cause some harm to some users, the

law provides that manufacturers will not be held liable for such injuries if they provide an adequate warning of the known risks of the medication. *Ziliak v. Astra Zeneca L.P.*, 324 F.3d 518, 521 (7th Cir. 2003) (Indiana law); *Hacket v. G.D. Searle & Co.*, 246 F. Supp. 2d 591, 595 (W.D. Tex. 2002) (Texas law); *Felix v. Hoffmann-La Roche, Inc.*, 540 So. 2d 102, 103,105 (Fla. 1989).

In the prescription medication context, the adequacy of a warning is gauged by the effect upon trained physicians who by law are the only ones able to prescribe the medicine. This "learned intermediary" doctrine provides that courts

[31] Although there are no material differences, the laws of the IBD plaintiffs' home states presumptively govern: Texas for Plaintiffs Cannady, Farr, Fechner, Locke, Messick, and Stevens; Indiana for McClain; and Florida for Rand. *See, e.g.*, *Dunseth v. Eli Lilly & Co.*, 404 F. Supp. 2d 97, 102 (D.D.C. 2005) (applying law of state where plaintiff "was prescribed, bought, and ingested" medicine).

will "rely on the expertise of the physician intermediary" when evaluating the adequacy of a medication's prescribing information. *See Toole v. Baxter*

Healthcare Corp., 235 F.3d 1307, 1314 (11th Cir. 2000). As long as the warning to the physician provides an "accurate, clear and unambiguous" statement of possible risks of the drug, it is adequate as a matter of law. *Felix*, 540 So. 2d at 105. As with any inquiry into the adequacy of a product's warnings, "the warning need only be one that is ***reasonable*** under the circumstances and it need not be the best possible warning." *Reynolds v. Bridgestone/Firestone, Inc.*, 989 F.2d 465, 471 (11th Cir. 1993) (emphasis added and citation omitted).

Applying these principles, courts throughout the country – including in Texas, Florida, Indiana, and various multidistrict litigations – have held that physician warnings are adequate as a matter of law when they clearly and accurately inform doctors of the specific adverse event suffered by the plaintiff:

Glaucoma "rare instances of glaucoma, increased intraocular pressure, and cataracts have been reported"

"If a pharmaceutical manufacturer warns doctors that specific adverse side effects are associated with the use of a drug, then a

ısal relationship between use of the drug
l development of potential side effects is
ɔlicit in the warning." *Ziliak*, 324 F.3d at
l (Indiana law).

Birth defects

Severe bleeding requiring hysterec- tomy

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een

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"It is inconceivable that reasonable persons could disagree as to the adequacy of the warnings in conveying to physicians that the prescription drug, Accutane, is dangerous to pregnant women . . . ." *Felix*, 540 So. 2d at 103,105 (Florida law).

"It is inconceivable that reasonable persons could disagree as to the adequacy of the warnings in conveying to physicians that the prescription drug, Accutane, is dangerous to pregnant women . . . ." *Felix*, 540 So. 2d at 103,105 (Florida law).

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heart attack and stroke

Stevens-Johnson syndrom e

a

ıe law does not mandate that ırmaceutical manufacturers and rketers provide such specific instructions t they leave little room for doctors' sonable medical judgment." *Meridia*, 3 F. Supp. 2d at 810-15.

as

"In the present case, the warning clearly included the reaction suffered by Rolen." *Rolen v. Burroughs Wellcome Co.,* 856 S.W.2d 607, 609 (Tex. App. – Waco 1993).

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"In the present case, the warning clearly included the reaction suffered by Rolen." *Rolen v. Burroughs Wellcome Co.,* 856 S.W.2d 607, 609 (Tex. App. – Waco 1993).

Risk of

	Dizziness , headache, and other effects.	26 side effects	
he		۸]ny competent healthcare provider uld have been aware of the 26 dverse Reactions' listed in the Norplant /sician labeling . . . ." *In re Norplant ntraceptive Prods. Liab. Litig.*, 215 F. op. 2d 795, 825-29 (E.D. Tex. 2002).	
	"[T]he Rezulin information . . . specifically warned that the injuries claimed by the plaintiffs . . . were possible side effects. . . ." *In re Rezulin Prods. Liab. Litig.*, 331 F. Supp. 2d 196, 199-02 (S.D.N.Y. 2004).	۸]ny competent healthcare provider uld have been aware of the 26 dverse Reactions' listed in the Norplant /sician labeling . . . ." *In re Norplant ntraceptive Prods. Liab. Litig.*, 215 F. op. 2d 795, 825-29 (E.D. Tex. 2002).	
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As the table above shows, courts routinely hold that warnings are adequate as a matter of law even when they are far less prominent and descriptive than the Accutane IBD warning. In many of these cases, the warning described only antecedent conditions to the more serious effect ultimately experienced by the plaintiff. *See, e.g., Upjohn; Meridia*. The same is not true of Accutane, where the warning expressly referenced "inflammatory bowel disease," a serious and permanent disease. In fact, the Accutane warning highlighted this risk, identifying

the common symptoms of IBD and highlighting that even Accutane patients without a prior gastrointestinal history had developed IBD, thereby emphasizing that anyone is at risk.

Similarly, many of the cases above find warnings adequate as a matter of law where the Adverse Reaction section of the physician package insert passingly

referenced the relevant condition in a chart or line listing. *See, e.g., Upjohn; Rezulin; Norplant*. Again, the same may not be said about the Accutane physician package insert, which prominently warned about IBD in the WARNINGS section of the package insert. By virtue of its position in the WARNINGS section, the Accutane label alerted Plaintiffs' physicians that IBD was one of the most significant risks associated with Accutane use. *See* 21 C.F.R. § 201.57(e) (2005) ("Under this section heading, the labeling shall describe serious adverse reactions and potential safety hazards, limitations in use imposed by them, and steps that should be taken if they occur."); *Martin v. Hacker*, 628 N.E.2d 1308, 1312 (N.Y. 1993) ("[T]he Warnings section deals with side effects of graver consequence than the Adverse Reactions section.").

It would be incongruous indeed if Accutane's IBD warning could be held adequate as a matter of law if the term "Inflammatory Bowel Disease" appeared as a simple line item in the Adverse Reaction section – as was the case in *Norplant* and *Rezulin* – but not if the IBD warning was elevated to the WARNINGS section and more detailed risk information conveyed. Yet, that is precisely the perverse situation facing Roche. A prior appellate court has already ruled that the pre-1984 IBD labeling – which simply listed IBD as a possible adverse event in the "Adverse Reactions" section – was adequate as a matter of law. *See Mikell v. Hoffman-LaRoche, Inc.*, 649 So. 2d 75, 76-77, 78 (La. Ct. App. 1994). The *Mikell*

Court had no trouble concluding that this predecessor labeling clearly warned "of the possible side effect of inflammatory bowel disease associated with the use of Accutane." *Id.* at 80.[32]

Faced with this record, the IBD plaintiffs were left to argue below that the express IBD warnings in Accutane's package insert could have been a little clearer in articulating the plaintiffs' view that Accutane causes IBD.[33] But the case law uniformly rejects the legalistic argument that a warning is inadequate simply

because it does not have the word "cause" in it. *See, e.g.*, *Ziliak*, 324 F.3d at 521 ("If a pharmaceutical manufacturer warns doctors that specific adverse side effects are associated with the use of a drug, then a causal relationship between use of the drug and development of potential side effects is implicit in the warning."). Moreover, if the *Daubert* discussion above demonstrates anything, it is that the causation evidence even to this date is so preliminary that no express causation warning was ever merited. *See, e.g.,* 44 Fed. Reg. 37,434, 37,435 (June 26, 1979) ("The [FDCA] permits labeling statements with respect to safety *only if they are*

[32] Two state trial courts in 2007 have permitted plaintiffs' IBD warnings claims to proceed to trial, and both decisions are facing first-level appellate review. [33] Plaintiffs employed so-called labeling experts to espouse these views for them, but courts are quick to cast aside such *ipse dixit* opinions that conflict with the plain language of the applicable warnings. *See, e.g., Ames v. Apothecon, Inc.*, 431 F. Supp. 2d 566, 570-73 (D. Md. 2006) (finding manufacturers' amoxicillin warnings adequate after rejecting opinion of Dr. Blume – the IBD plaintiffs' primary labeling expert here – that the warnings should have contained additional information about the risk of toxic epidermal necrolysis).

supported by scientific evidence and are not false or misleading in any particular.")

(emphasis added).

* * * * * * *

For these reasons, the specific warning provided in the Accutane label regarding IBD is adequate as a matter of law.

CONCLUSION

For the reasons stated above, Roche respectfully asks the Court to affirm the judgment of the District Court.

Dated: December 21, 2007 Respectfully submitted,

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CERTIFICATE OF COMPLIANCE

I certify that this brief complies with the type-volume limitation set forth in FRAP 32(a)(7)(B). This brief contains 12,987 words excluding the portions exempted by FRAP. 32(a)(7)(B)(iii).

I certify that this brief complies with the typeface requirements of FRAP 32(a)(5) and the type style requirements of FRAP 32(a)(6) because it has been prepared in a proportionally spaced typeface using Microsoft Word 2003 in 14 point Times New Roman font.

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