

IN THE UNITED STATES DISTRICT COURT  
MIDDLE DISTRICT OF FLORIDA  
TAMPA DIVISION

IN RE: ACCUTANE PRODUCTS  
LIABILITY LITIGATION

CASE NO. 8:04-MD-2523-T-30TBM  
MDL 1626 – PSYCHIATRIC TRACK

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**PLAINTIFFS’ STEERING COMMITTEE’S RESPONSE TO DEFENDANTS’  
MOTION TO EXCLUDE TESTIMONY OF J. DOUGLAS BREMNER, M.D.**

**I. INTRODUCTION**

Roche’s challenges to the admissibility of Dr. Bremner’s testimony are not sustainable. First, Dr. Bremner is eminently well qualified to testify in the field of psychiatry and neuroscience. He is one of the leading experts on psychiatry and neuroimaging. Second, the fact that Roche’s experts and lawyers may disagree with the conclusions in applying his methodology or that there may be an alternative methodology does not make the testimony excludable. These factual disagreements go to the weight the jury will give the evidence, not its admissibility. Third, whatever the history of Dr. Bremner’s research, the recalculations eliminate any complained of prior errors as a basis for exclusion. If anything, the study results are stronger and more convincing today than they were a year ago. Fourth, Roche’s own expert concedes the Emory Study is a reproducible study whose methodology was sufficiently stated such that others could attempt to replicate the study if they so chose. See

Exhibit 20 Mintun, 5/3/07 pp. 187-195. Based upon these and other reasons stated herein, this Court should deny Roche's motion in its entirety.<sup>1</sup>

**II. DR. BREMNER IS WELL QUALIFIED BY KNOWLEDGE, EXPERIENCE, TRAINING, AND EDUCATION TO TESTIFY IN THIS CASE.**

Dr. Bremner has been a co-author on over one hundred thirty (130) peer reviewed articles, including over twenty (20) specifically in the area of brain functioning and neuroimaging; over thirty (30) book chapters involving the brain, brain functioning, and neuroimaging; and four (4) books involving the brain. Dr. Bremner's CV demonstrates robust experience in brain-imaging and psychiatry. See Exhibit 1. As a Yale trained scientist, Dr. Bremner is board certified in Psychiatry and Neurology and holds a separate Board Certification in Nuclear Medicine. Roche's expert, Dr. Mintun, is not double-boarded in any two specialties of medicine.

Therefore, it is not surprising that in 2005, when Roche was considering collaborating with a leading PET Center for their Global Imaging Initiative involving Central Nervous System functioning, Roche's head of the program contacted Dr. Bremner directly to see if he would be interested in a long term collaboration with Roche. See Exhibit 3; 5/24/06 Tr. at pp. 48-50.<sup>2</sup> The message (sent within days of the publication of the Emory PET scan study

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<sup>1</sup> In perhaps one of the most over-stated positions taken, Defendants argue that "litigation opinions" are in and of themselves unreliable because these opinions have been rendered in litigation. As the court in Daubert v. Merrell Dow Pharms. Inc., 43 F.3d 1311, 1317 (9<sup>th</sup> Cir. 1995) stated: "That an expert testifies for money does not necessarily cast doubt on the reliability of his testimony, as few experts appear in court merely as an eleemosynary gesture." The cases cited by Defendants simply hold that the fact that an expert testifies based on research he has conducted independent of the litigation is evidence of reliability; it is by no means a required element of the Daubert analysis or in any aspect of admissibility that an opposite conclusion is mandated where such research is performed after litigation has begun.

<sup>2</sup> Since Defendants cannot attack Dr. Bremner's impeccable credentials, Roche points to prior reprimand involving an entirely unrelated issue. Plaintiffs object to the admissibility of this reprimand, which was to remain confidential. In short, the Department of Health and Human Services Office of Research Integrity has closed the book on this investigation. On November 22, 2005, the ORI issued a letter:

involving Isotretinoin) proves Roche was aggressively attempting to establish a long-term collaboration with Dr. Bremner for their global imaging program. Common sense commands the reason Roche wanted to collaborate with Dr. Bremner was because Dr. Bremner is one of the leading PET scan and neuroimaging specialists in the world.<sup>3</sup>

### III. LEGAL STANDARD

Rule 702 of the Federal Rules of Evidence provides:

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

“For scientific expert testimony to be admissible, the expert must first be qualified to testify competently regarding the matters he intends to address.” Allison v. McGhan Medical Corp., 184 F.3d 1300, 1309 (11<sup>th</sup> Cir. 1999). After determining whether a witness is qualified, the court must continue to perform its “gatekeeping” role to ensure the expert’s testimony is both reliable and relevant. See Daubert v. Merrell Dow Pharmaceuticals, 509 U.S. 579, 589 (1993). Scientific evidence is reliable if it is based on an assertion that is grounded in

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ORI concurred with the institution’s determination that there was insufficient evidence to warrant an investigation. Consistent with Federal law and ORI policy, inquiries that result in a recommendation that no investigation is warranted remain confidential for ORI. We ask that you respect this policy.

See Exhibit 2. No evidence to even warrant an investigation! In short, these allegations and the (confidential) record adduced in support by Roche is not competent, relevant, or admissible evidence for the Court’s consideration and should be ignored and stricken from the record.

<sup>3</sup> In a astonishingly blatant misrepresentation and falsity to this Court, the Defendants state in footnote 9 that James O’Donnell preceded Dr. Bremner as a “plaintiffs’ expert”. None of the plaintiffs’ counsel were involved in that case or even aware of the status of that case and had not retained this other “expert”. Newton v. Roche Laboratories, 243 F. Supp. 2d 672, 678 (W.D. Texas 2002). The Newton case can best be read as concluding Mr. O’Donnell (who was not a medical doctor) was not qualified to render the opinions those plaintiffs put him forward on the topics clearly outside his expertise. See, e.g., Newton, 243 F.Supp. 672, 677, fn2; fn3. To compare Dr. Bremner to Mr. O’Donnell an example of the Defendants overstating their position.

methods of science. Daubert, 509 U.S. at 590. **The focus is on principles and methodology, not conclusions.** Id. at 596. For the causation expert, a sound methodology looks to certain factors such as those identified by Sir Austin Bradford Hill in 1965. Reference Manual on Scientific Evidence, at 376 (2d ed. Federal Judicial Center 2000)

These factors include: (1) strength of association (i.e., whether the association is strong and statistically significant); (2) temporal relationship (i.e., whether the timing of the exposure and the onset of disease is consistent with the latency period of the disease); (3) consistency of the relationship (i.e., whether the results of multiple scientific studies are consistent); (4) biological plausibility (i.e., whether there exists a biologically plausible *mechanism* by which the agent *could* cause the disease); (5) consideration of alternative explanations (i.e., whether the association could be accounted for by other factors); (6) specificity (i.e., whether the *specific* chemical is associated with the *specific* disease at issue); and (7) dose-response relationship (i.e., whether an increase in exposure yields an increase in risk).”

Magistrini v. One Hour Martinizing Dry Cleaning, 180 F. Supp.2d 584, 592-593 (D.N.J. 2002) (emphasis in original). As has been aptly stated:

The assessment process, that is, the process of examining whether “good grounds” exist, focuses on the methodologies the witness used to reach the opinion he or she will express, not the scientific *correctness* of the opinion. It is not part of the trial judge's gatekeeping role to determine whether the proffered opinion is scientifically *correct* or *certain* in the way one might think of the law of gravity. The gatekeeping role is addressed to mere evidentiary admissibility; it is the role of the fact-finder (usually a jury) to determine whether the opinion is correct or worthy of credence. For the trial court to overreach in the gatekeeping function and determine whether the opinion evidence is correct or worthy of credence is to usurp the jury's right to decide the facts of the case. All the trial judge is asked to decide is whether the proffered evidence is based on “good grounds” tied to the scientific method.

Brasher v. Sandoz Pharmaceuticals Corp., 160 F. Supp.2d 1291, 1295 (N.D. Ala., 2001).

Consistent with these principles,

A key but sometimes forgotten principle of Rule 702 and Daubert is that Rule 702, both before and after Daubert, was intended to relax traditional barriers to admission of expert opinion testimony. See, e.g., Daubert, 509 U.S. at 588. Accordingly, courts are in agreement that Rule 702 mandates a liberal standard for the admissibility of expert testimony. [citation omitted]. As the Advisory Committee to the 200

amendments to Rule 702 noted with apparent approval, “[a] review of the case law after Daubert shows that the rejection of expert testimony is the exception rather than the rule.”

Cook v. Rockwell Int’l Corp., \_\_\_ F. Supp.3 \_\_\_, 2006 WL 3533049 at \*4 (D. Colo 2006), attached as Exhibit \_\_\_. See also 4 Jack B. Weinstein & Margaret A. Berger, Weinstein’s Federal Evidence, Section 702.02[2][c] (2d ed. 2005)(court should approach Daubert exclusion carefully and “should admit the testimony of there is any chance at all it will be beneficial to the finder of fact.”). It has also been observed:

Expert testimony must be based on a reliable methodology to be admissible. This does not mean, however, that the offering party must prove “that the expert is indisputably correct” for the expert evidence to be admissible. Rather, the party need only prove that “the method employed by the expert in reaching the conclusion is scientifically sound and that the opinion is based on facts which sufficiently satisfy Rule 702’s reliability requirements.” “The evidentiary requirement of reliability is lower than the merits standard of correctness,” and gaps or inconsistencies in an expert’s reasoning may go to the weight of the expert evidence, not its admissibility. As the Supreme Court acknowledged in Daubert, expert evidence can be “shaky” and yet still admissible and may be attacked through the traditional means of “[v]igorous cross-examination, presentation of contrary evidence, and careful instruction on the burden of proof.” Maintaining this distinction between the evidentiary requirement of reliability and the higher standard of whether the expert’s conclusions are correct or sufficient to prove the merits “is indeed significant as it preserves the fact finding role of the jury.

Cook, supra at \*6 (citations omitted).

**IV. PLAINTIFFS HAVE OFFERED SUFFICIENT EVIDENCE ON ALL THE FACTORS NECESSARY TO CONSIDER IN ESTABLISHING CAUSATION.**

Dr. Bremner considered the factors consistent with the Bradford Hill methodology followed by general causation experts. **Causation analysis using the Bradford Hill factors does not require a finding that all factors exist for there to be causation.** Instead, “[d]rawing causal inferences after finding an association and considering these factors

requires judgment and searching analysis, based on biology, of why a factor or factors may be absent despite a causal relationship, and vice-versa.” Reference Manual, at 375.

Defendants’ argue there is no current absolute scientific proof as to the cause of psychiatric side effects or an absolute certain causal link between Accutane and psychiatric side effects. However, the law rejects the need for this definitive scientific proof. In fact, Defendants’ position in seeking only the highest levels of proof to the exclusion of all other proof is unfounded and refuted by the very cases they cite. See e.g., Rider v. Sandoz Pharmaceuticals, 295 F.2d 1194, 1198-1199 (11<sup>th</sup> Cir. 2002) (“It is well-settled that while epidemiological studies may be powerful evidence of causation, the lack thereof is not fatal to a plaintiff’s case... This Court has long held that epidemiology is not required to prove causation in a toxic tort case”) (citations omitted); Benedi v. McNeil-P.P.C.U, Inc., 66 F.3d 1378, 1384 (4<sup>th</sup> Cir. 1995) (“expert testimony need not be based upon identical case studies or epidemiological data”).<sup>4</sup> As has been said:

*Daubert* does not require proof to a certainty, or even proof convincing to the trial judge. The trial judge is not required to find that the proffered opinion is scientifically correct, but only that it is trustworthy because it is tied to good scientific grounds. What *Daubert* does require is that the expert's opinion be based on sound methodologies of the type used by experts in the field in which the opinion is offered. **There can be little question that scientists routinely use animal studies, case reports, and pharmacological comparisons of similar classes of drugs to infer conclusions, which are expressed in peer-reviewed journals and textbooks.** Unquestionably, epidemiological studies provide the best proof of the general association of a particular substance with particular effects, but it is not the only scientific basis on which those effects can be predicted. In science, as in life, where

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<sup>4</sup> Defendants citation to Ealy v. Richardson-Merrell, Inc., 897 F. 2d 1159, 1160 (D.C. Cir. 1990) is unhelpful. In reaching its decision, the court noted that the body of published epidemiological opinions contradicting that of the plaintiff was “extensive, [and] indeed massive.” Id. at 1162. The evidence upon which Dr. Bremner relies is much more substantial than the evidence upon which the plaintiff relied in Ealy. Moreover, the type of evidence Dr. Bremner is relying upon is of the type that is cited throughout the scientific community, especially when valid epidemiological studies are scant or nonexistent.

there is smoke, fire can be inferred, subject to debate and further testing.

Brasher, 160 F. Supp.2d at 1296 (emphasis added).<sup>5</sup>

**A. Retinoids, Vitamin A and Class Effect all support biological plausibility and causation.**

The similarity of vitamin A and retinoid drugs is apparent in their chemical make-up:

|                         |                   |
|-------------------------|-------------------|
| (Vitamin A)             | $C_{20}H_{30}O$   |
| Accutane (isotretinoin) | $C_{20}H_{28}O_2$ |
| Vesanoid (tretinoin)    | $C_{20}H_{28}O_2$ |
| Soriatane (acitretin)   | $C_{21}H_{26}O_3$ |
| Tegison (etretinate)    | $C_{23}H_{30}O_3$ |

Defendants acknowledged in early Food and Drug Administration (“FDA”) submissions that “[s]ince the molecular structure of isotretinoin is very similar to the other vitamin A analogs (differing only in the cis configuration of the 13, 14 double bond), it would be expected that the oxidative behavior of this compound *would be quite similar to the vitamin A chemistry published in the literature.*” See Exhibit 4 (emphasis added).

Isotretinoin (or 13-Cis Retinoic Acid), the active ingredient in Accutane, is a stereoisomer of retinoic acid, “which is derived from vitamin A (retinol) by oxidation in the liver.” See Exhibit 5. Yet, therapeutic doses of retinoic acid cause hypervitaminosis A. The resulting adverse effects limit dosage and actually “prompted the search for derivatives with similar therapeutic activity, but lower toxicity than retinoic acid.” Id.

Vitamin A’s therapeutic value and early use in dermatology treatment is at the root of Accutane development. A Roche power point presentation highlighting “Milestones in Retinoid History” notes that treatment of acne with high doses of vitamin A dates back to

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<sup>5</sup> In fact, as was held in Brasher, even alternative explanations for the injury is not enough to exclude expert testimony. Brasher, 160 F. Supp.2d at 1299.

1943 and lead to the development of “new vitamin A derivatives (retinoids) with an improved therapeutic index.” See Exhibit 6. Research papers and other documents on Accutane and other retinoids also frequently discuss the relationship between the retinoid drugs and vitamin A. Many of these articles were written by Roche scientists. See Exhibit 7.

In other examples, a 1973 Investigational Drug Brochure on Accutane, Roche explores the toxicology and pharmacology of Vitamin A. See Exhibit 8. A September 1981 Roche manuscript on the Toxicology, Carcinogenicity and Teragenicity of Some Orally Administered Retinoids provides data on vitamin A “for purposes of comparison.” See Exhibit 9. Also, as noted in a 1984 Roche manuscript on the PreClinical Development of Retinoids, “[i]n contrast to vitamin A, published reports on the subchronic toxicity of other retinoids is relatively sparse.” See Exhibit 10. More specifically, with regard to Accutane’s active ingredient, isotretinoin, the same author noted “[i]n contrast to Vitamin A, tretinoin and etretinate, little has been published on the subchronic toxicity of isotretinoin . . .” Id.

The Accutane label also warns against taking vitamin A supplements while on Accutane “to avoid additive toxic effects.” See Exhibit 10. The side effects of Accutane are also said to closely resemble those described in patients who take very high doses of vitamin A (“hypervitaminosis A syndrome”). Id. Internally, Roche acknowledges the common side effects of vitamin A and retinoids, noting that “oral retinoid therapy is associated with an adverse event profile similar to the symptom complex of Hypervitaminosis A Syndrome.” See Exhibit 10. Roche documents and even the Accutane label acknowledge the similarities between Vitamin A and Accutane and their side effects. See Exhibit 11 at 3; see also Exhibit

12; Tr. 7/13/06 at p. 102-104 (literature discussing how retinoids effect neurotransmitters in brain).

As the multi-disciplinary scientific team from Emory stated:

- Istoretinoin is chemically similar to the retinoid Vitamin A, a fat soluble vitamin stored in high concentrations in the liver. Vitamin A is converted after oxidation to retinoic acid, when it has biological effects. Arctic explorers who fed on polar bear liver developed symptoms of confusion and psychosis;
- Large doses of vitamin A can have a number of other neurological and mental effects, including fatigue, decreased interest, headache, and diplopia (double vision);
- Published case reports of vitamin A toxicity include symptoms of aggression, personality changes, depression, poor concentration, tearfulness, psychotic symptoms, and guilty rumination that resolved with discontinuation of vitamin A;
- Retinoids have important effects on the developing brain in animal studies and use of isotretinoin during pregnancy has long been known to result in CNS defects in newborns;
- Retinoids modulate gene expression in the brain in a broad spectrum and have effects on several neurochemical systems, including the dopamine system, which has been hypothesized to play a role in dysregulation of mood and emotion;
- High levels of the enzyme involved in retinoid synthesis, aldehyde dehydrogenase are found in mesostriatal and mesolimbic dopamine pathways;
- Dopamine mesocortical pathways involve release of dopamine transmitter in the orbitofrontal cortex and other parts of the prefrontal cortex;
- Administration of retinoids causes changes in dopamine receptors, while genetic mutations of retinoid receptors are associated with deficits in dopamine receptors as well as mesolimbic dopamine functioning;
- Retinoids are associated with the inhibition of neurogenesis in the hippocampus, a brain area with connections to the prefrontal cortical areas, including the orbitofrontal.

See Exhibit 26 at pp. 983, 988. See also Exhibit 3, Tr. 5/24/06 at pp. 72-74.

In a 2003 letter to the Journal of American Academy of Dermatology, FDA scientists drew attention to an article on the issue of Hypervitaminosis A and psychiatric effects of retinoids. Silverman, AK, *Hypervitaminosis A Syndrome: A Paradigm of Retinoid Side Effects*, J Am Acad Dermatol 1987; 16:1027-39:

In 1987 Dr. Ellis coauthored an article entitled “*Hypervitaminosis A Syndrome: A Paradigm of Retinoid Side Effects.*” We are not aware of any reason to abandon the excellent advice offered by Dr. Ellis and his coauthors in this 1987 article: “Follow-up of any patient being treated chronically with retinoids should include close attention to neuropsychiatric symptoms. Neuropsychiatric abnormalities may elude detection because these are subtle change, often ignored or minimized by patients.”

See Exhibit 13.<sup>6</sup> See also Exhibit 14, Tr. 5/31/06 pp. 8-11; and Exhibit 3 Tr. 5/24/06 pp. 239-242.

Separately, as stated by the FDA in reviewing these matters:

Are any other retinoids associated with psychiatric disturbance? Yes, including the “natural” retinoid, Vitamin A when consumed in excessive amounts.

Are retinoid receptors and binding proteins found in the adult mammalian brain? Yes.

Have any well-conducted studies demonstrated a functional role for retinoids/receptors in the central nervous system of animals? Yes.

See Exhibit 14; Tr. 5/31/06 at pp. 15-23. See also Exhibit 12, Tr. 7/13/06 at pp. 99-101.

Drugs need not be identical in order for information relating to them to be relevant. See generally, Smith v. Ingersoll-Rand Co., 214 F.3d 1235, 1248 (10<sup>th</sup> Cir. 2000) (“The substantial similarity rule does not require identical products; nor does it require us to compare the products in their entirety”); see also Kennedy v. Collegen Corp., 161 F.3d 1226, 1228 (1998) (admitting expert testimony relying in part on evidence of similar drugs); see also Newton v. Roche Laboratories, Inc., 243 F. Supp.2d 672, 678, n. 4 (W.D. Tex. 2002) (despite finding unqualified and ill-prepared expert did not survive Daubert, court recognized comparison of Vitamin A and Accutane and research on retinoids as “potentially relevant to

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<sup>6</sup> In response, Dr. Ellis emphasized that the 1987 article on other retinoids and hypervitaminosis was not inconsistent with the issues involving Accutane (a retinoid), and agreed that patients should be monitored for psychiatric side effects since Accutane is a retinoid. See Exhibit 14; Tr. 5/31/06 pp. 8-11.

the causation issue in this case”); Golod v. Hoffman-La Roche, 964 F. Supp. 841 (S.D.N.Y. 1997) (other retinoid evidence admissible in Accutane case)

Despite the view of the scientific community, the FDA, and the content of Roche’s own documents, Defendants cite to a distinguishable case, Soldo v. Sandoz Pharmaceuticals Corp., 244 F. Supp. 2d 434, 564 (W.D. Pa. 2003) (problems with comparison was due to different mechanism of the comparator drugs). Kannankeril v. Terminix Intn’l, the Third Circuit Court of Appeals case cited in Soldo, is more analogous and more instructive. 128 F.3d 802 (3d Cir. 1997). The court noted that the toxic effects of organophosphates, the same class of drugs as the subject drug, on humans were well recognized by the scientific community. Kannankeril, 128 F. 3d at 809. Clearly, that is more akin to the issues in this case.<sup>7</sup>

In short, there is no valid basis for this Court to conclude anything other than Accutane is within the class of retinoids and Vitamin A and the side effects known to be caused within that class are supportive of the conclusions and opinions of Dr. Bremner.

**B. FDA has issued strong public statements in rebuttal to Roche’s public marketing strategy of undermining the scientific basis in support of the causal relationship between Accutane and psychiatric side effects.**

Frustrated by Roche’s strategy of sponsoring and publishing biased literature meant to undermine the causative link between Accutane and psychiatric side effects, senior members of the FDA team responsible for Accutane wrote a rebuttal letter to the Journal of the American Academy of Dermatology in 2003:

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<sup>7</sup> The Defendants’ citations to Caraker v. Sandoz Pharms Corp., 172 F. Supp. 2d 1046 and 188 F. Supp. 2d 1026 (S.D. Ill. 2001) and Siharath v. Sandoz Pharms. Corp., 131 F. Supp. 2d 1347 (11<sup>th</sup> Cir. 2002) both involve Parlodel, like Soldo, and are therefore distinguishable on the same grounds.

- In response to the suggestion by Dr. Jacobs, Roche's expert who Roche supported for the publication of an article, that clinical depression would not be expected to lift upon removal of the drug, the FDA senior scientist pointed out: "In fact, it is the prompt resolution of symptoms that suggests a substance-induced mood disorder instead of a primary (coincidental) psychiatric disorder."
- The FDA scientists address the issue of biological plausibility: "The authors do discuss research **clearly demonstrating an important role for retinoic acid in adult mammalian brain function.** We do not think that this research is nonsupportive of plausibility simply because isotretinoin must be isomerized to bind retinoid receptors and there is no direct evidence for such isomerization in the central nervous system. The article does not address whether direct evidence has yet been sought. Even if direct evidence had been adequately sought and found lacking, there is no reason to assume that all biologic actions of retinoids derive from engagement of retinoic acid or retinoid X nuclear receptors. In fact, studies conducted to date about isotretinoin and the brain have been largely confined to effects on central nervous systems development or treatment of brain tumors. **A complete discussion of biologic plausibility is beyond the scope of this letter, but we think it important to note that none of what is known about retinoids and the adult mammalian brain is inconsistent with a biologically plausible association between isotretinoin and psychiatric events.**" (emphasis added). See also Exhibit 12, Tr. 7/13/06 at pp. 8-9.
- In conclusion, the FDA scientists state: "We are not aware of any study, or combination of studies, adequate to support a conclusion that there is no causal association between isotretinoin and serious psychiatric events."

See Exhibit 15; Tr. 7/12/06 pp. 238-242. The FDA scientists also addressed evidence from the case reports as it relates to causation:

At the Dermatological Advisory Committee Meeting in September 2000, the Food and Drug Administration discussed 40 reports of patients who experienced psychiatric symptoms while taking Accutane, recovered after the Accutane stopped, and had recurrence of symptoms during a second course of Accutane (positive rechallenge). Of these patients, 75% had no reported psychiatric history before Accutane therapy. ... When the drug was restarted, the time to onset of psychiatric symptoms was on average shorter, and 10 patients reported persistent psychiatric symptoms after Accutane discontinuation or medical intervention.

Reports that document positive rechallenge do not prove a causal relationship for events such as depression that have a high background rate and chronic remitting natural history. Nonetheless, positive rechallenges are very important evidence in overall causality assessment of isotretinoin and psychiatric adverse events. ....Dr Jacobs [Roche's expert] and his colleagues do not address these rechallenge cases.

See Exhibit 13.

**C. Roche’s citation to “epidemiological” studies is misleading and each of the studies have been debunked by the FDA and experts.**

Astonishingly, Roche actually cites to work by Dr. Susan Jick that has been debunked by not just Plaintiffs’ experts, but by the FDA and Roche’s own consultants. See, e.g. Exhibit 28. The FDA, in criticizing the Jick paper, referenced the same shortcoming of another study put forth by Roche to the FDA, the UnitedHealth Care database study.

Could be considered a positive study using sensitive definition of depression; however, the investigators favored a definition of depression that gave no association of depression with Accutane dispensing.

When depression was defined by an antidepressant dispensing, the overall incidence of depression was nearly 1.5 times higher in the Accutane group than in the non-user group and this difference was highly statistically significant ( $p=.0005$ ) Table 11.

*When depression was defined by a depression diagnosis OR an antidepressant dispensing, the results were also statistically significantly higher in the Accutane group than in the non-user group ( $p=.0044$ ) Table 15.*

Plaintiffs’ Exhibit 11. (emphasis added); See also 5/31/06 Tr. at pp. 25-28. As a result, this study actually supports a causal relationship with Accutane and depression.<sup>8</sup>

Defendants do cite to two other papers: Ng (which Dr. Bremner testified was significant because 5 patients dropped out of the study due to psychiatric side effects the authors believed were caused by Accutane) and Chia, (where Dr. Bremner pointed out that the authors reported “convincing reports” of dechallenge/rechallenge). See Exhibit 12, Tr.

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<sup>8</sup> Roche suggests in their brief that Dr. Bremner cites to the Jick study as an example of good and meaningful epidemiology establishing no causal link between Accutane and psychiatric side effects. Roche’s Brief at 13. This assertion is absurd. Not only has the FDA and Roche consultants criticized Jick, but Dr. Bremner, like the FDA, has testified that the paper supports a causal relationship between Accutane and psychiatric side effects. See Exhibit 14, Tr. 5/31/06, p. 26-28.

7/13/06 p. 106-112. However, these suffer from such significant limitations (based on size and limited scientific evaluation) as to be unpersuasive in the face of the other evidence. More importantly, neither support the legal conclusion Dr. Bremner's opinion should be stricken.<sup>9</sup>

In short, Defendants cite to industry sponsored literature in the guise of "epidemiological" work and irrelevant articles that do not and cannot stand for the proposition that there is affirmative evidence that Accutane does not cause psychiatric side effects.<sup>10</sup> In fact, when examined closely, the FDA and Roche's own consultant, as well as Dr. Bremner, concluded one of the studies actually supported a causal relationship.

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<sup>9</sup> In Chia (See Exhibit 49, Chia, CY; *Isotretinoin Therapy and Mood Changes in Adolescents With Moderate to Severe Acne*, Arch Dermatol, 2005; 141:557-560), the sample size was small and had a nonrandomized subject selection. They also noted that the CES-D survey used to assess symptoms of depression is a screening tool only - it cannot diagnose major depressive disorders. Additionally, the authors noted that "[c]onvincing reports of positive dechallenge and rechallenge suggest an association between depression and isotretinoin use that this study cannot exclude." (p. 560). See also Tr. 7/13/06 at p. 128. Interestingly missing from the Defendants explanation of this article is the fact that epidemiologists consider this cohort study size so underpowered as a study as to be of little or no significance. See Exhibit 16, Strom p. 388 ('postmarketing surveillance cohort studies will not be able to detect rare drug effects reliably unless they include at least 1,000 exposed individuals'; Chia had 101 participants completing the study) See also, Exhibit 16, Strom, p. 22 (disadvantages of cohort study: possibly biased outcome data and done prospectively, may take years to complete). Finally, noticeably missing from the article is a financial disclosure.

The authors of the Ng article (See Exhibit 50, Ng, CH; *Prospective study of depressive symptoms and quality of life in acne vulgaris patients treated with isotretinoin compared to antibiotic and topical therapy*, Australasian Journal of Dermatology, 2002; 45:262-268) noted in the introduction to their article "There were 37 suicides, 110 hospitalized patients and 24 cases of recurring depression on drug rechallenge. Of concern is that isotretinoin is one of the top 10 drugs in the FDA's database with the most number of reports of depression and suicide attempts." See Exhibit 50. Furthermore, the authors note that five patients treated with isotretinoin complained of "worsening mood" and were withdrawn from the study. (p. 265). This is evidence supporting Dr. Bremner's opinions - where 5 people dropped out due to mood conditions caused by Accutane. Tr. 7/13/06 at pp. 105-107; 112-113. Finally, the article concludes that "[r]are cases of depression related to isotretinoin are known and these are strongly suggested by recurring depression on drug rechallenge or persistent depression that only resolves on drug discontinuation." (p. 267) In the end, the caption of this article is telling: Research Report.

<sup>10</sup> Defendants cite to distinguishable cases in support of this attack. For instance, in Caraker v. Sandoz Pharms. Corp., 172 F. Supp. 2d 1046 (S.D. Ill. 2001), plaintiffs' Parlodel experts attacked the epidemiological studies cited, but then selectively cited statistically insignificant numbers in support. However, importantly, the Caraker court also noted that it imposes no absolute epidemiology requirement or any other requirement except relevance and reliability on admissibility. Further, the case of Gen. Elec. Co. v. Joiner, 522 U.S. 136 (1997), really is better read as a case which debunked four epidemiological studies relied upon by plaintiff. The

**D. Clinical trials actually support a conclusion that there is an affirmative causal relationship between Accutane and psychiatric side effects.**

In a series of clinical trials involving seven hundred (700) patients, one (1) in one hundred (100) demonstrated clinically significant findings of depression. See Exhibit 29 (Scheinman, P, et al., *Acute Depression from Isotretinoin*, J. Am Acad. Derm. 1990, Volume 22, No. 6:112-114)<sup>11</sup> See also Exhibit 14; Tr. 5/31/06 at pp. 11-13. The clinical investigators, wrote:

A spectrum of central nervous system side effects, similar to that observed with the hypervitaminosis A syndrome induced by retinyl esters has been described with other natural and synthetic retinoids. For example, depressive symptoms, such as crying spells, malaise, and forgetfulness, have been noted in some patients receiving isotretinoin.

See Exhibit 29 at 1112. **The clinical investigators concluded that the observed clinical findings of major depressive episode in all seven patients “most likely” were caused by isotretinoin.** Id. at 1113.<sup>12</sup> Scientific literature continues to support Dr. Bremner’s opinions.

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statistical flaws in those studies were individual to the studies themselves, and are not relevant to this case. The remaining cases cited address statistical significance in the context of disparate impact cases and not scientific causation.

<sup>11</sup> The clinical investigators observed fatigue (increased sleep, loss of energy), irritability, decreased concentration, sadness, crying spells, loss of motivation, forgetfulness, suicidal ideation, anhedonia (the inability to gain pleasure from normally pleasurable experiences), abnormal dreams, fear of going insane. See Exhibit 29 at 1113.

<sup>12</sup> Roche relegates to a footnote (see fn. 6) a string cite reference to clinical trials Roche says supports its position that there is no association. However, these cited studies are utterly unresponsive and scientifically unreliable for the proposition cite by Roche:

*Khuri*: This study aimed at identifying the effectiveness of low dose Accutane at reducing rate of second primary tumors or death related thereto. Obviously, the dosing was different in so far as it was low dose over a three year period. In order to even be eligible patients had to have ongoing acute medical illnesses in addition to cancer and the mean age was 60 years old. More importantly, there is absolutely no information on any whether or how these patients were even monitored for depression or psychiatric side effects. Frankly, the citation to this article for the proposition that it is a clinical trial that establishes no causation relationship between Accutane and psychiatric side effects is frivolous.

*Wismeth*: The study participants were aged 18-70 years. (p. 80). The study contained only *cancer* 23 patients, only 12 of whom completed the "quality of life" questionnaire, which was the only survey done which is remotely related to psychological issues. (p. 82). It is difficult to see how anything relevant could be gleaned from this sample of patients (whose age range is not comparable to Accutane users for acne indication) or how the quality of life for a cancer patient post or pre treatment, translates to the issues involved in this case;

See, e.g., Exhibit 17 (Friedman, T; *Increased use of mental health services related to Isotretinoin treatment: A 5-year analysis*, European Neuropsychopharmacology, 2005);

**E. Animal models support the conclusion that Accutane affects the brain and causes behavioral changes.**

Animal models have also shown that Isotretinoin (a/k/a 13-cis-retinoic acid) causes significant changes in the brain. See, e.g., Crandall J, Sakai Y, Zhang J, et al. *13-cis-retinoic Acid Suppresses Hippocampal Cell Division and Hippocampal-dependent Learning in Mice*, Proc. Natl. Acad. Sci. USA, 2004; 101(14):5111-5116:

This report demonstrates that a clinical dose (1 mg/kg/day) of 13-*cis*-RA in mice significantly reduces cell proliferation in the hippocampus and the subventricular zone, suppresses hippocampal neurogenesis, and severely disrupts capacity to learn a spatial radial maze task. The results demonstrate that the regions of the adult brain where cell proliferation is ongoing are highly sensitive to disruption by a clinical dose of 13-*cis*-RA.

\* \* \*

Thus, daily exposure to clinical levels of 13-*cis*-RA can depress cell proliferation in both the hippocampus and SVZ.

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*Ayoub*: The study participants were, on average, in their fifties. (p. 3548). Again, in no way is this comparable to the age population for acne indications. Further, there is nothing in the materials and methods, and no evidence in the article, that any psychological review, surveys, testing, etc. were conducted. Roche cannot use a study to support a lack of connection between Accutane and depression that did not even gather any data on the study participants' mood;

*Levine*: The study participants were 21-85 years old. (p. 957). Again, the age range is not comparable to that for acne indications. There is nothing in the materials and methods, and no evidence in the article that any psychological review, surveys, testing, etc. was conducted. And, Roche cannot use a study to support a lack of connection between Accutane and depression that did not even gather any data on the study participants' mood;

*Tangrea* (Defense Exhibit 19 and the only one about which Roche questioned Dr. Bremner): The study participants were 40-75 years old. (p. 376). The article states that "all potential adverse effects" were documented, (p. 376), but there is no information in the article as to how any mood or psychological symptoms were tracked. While the authors did note that patients had reported depression as a clinical adverse effect, no details were given as to the number of patients, severity, resolution, or how depression was evaluated. (p. 377) See also Tr. 7/13/06 at pp. 114-117. The un rebutted testimony is that this type of study is not a study which can affirmatively cited in support of Roche's conclusion that depression is not associated with Accutane;

*Hong*: There is nothing in the materials and methods, and no evidence in the article that any psychological review, surveys, testing, etc. was conducted. Again, Roche cannot use a study to support a lack of connection between Accutane and depression that did not even gather any data on the study participants' mood.

See Exhibit 3, Tr. 5/24/06 at 216; See also Exhibit 14, Tr. 5/31/06 at pp. 120-124.<sup>13</sup> See also Exhibit 19 (O'Reilly KC; *Chronic administration of 13-cis-retinoic acid increases depression-related behavior in mice*, *Neuropsychopharmacology* 2006; 31:1919-1927).

In addition, Roche itself ran a study in 1982 that demonstrated behavioral and central nervous system effects in animals given isotretinoin. See Exhibit 60 and Exhibit 3, Tr. 5/24/06 at p. 230. This study was not given to the FDA until 2002.

Even recent animal modeling supports the conclusion that there are behavioral changes in animals. As testified to by Dr. Bremner regarding Ferguson authored studies, the modeling demonstrated changes in open field activity, a measure of central nervous system function. See Exhibits 3; Tr. 5/24/06 at pp. 219-230; Exhibit 14, Tr. 5/31/06 at pp. 126-130; and Exhibit 12, Tr. 7/13/06 at pp. 118-120. Further, in one of the versions of the Ferguson papers, the study showed changes in metabolites of dopamine (HVA) and serotonin (5-HIAA) in the striatum, but the authors then called it 'mild'. The changes demonstrated were, in fact, statistically significant. See Exhibit 65, Ferguson, S; *Chronic Oral Treatment with 13-cis-Retinoic Acid (Isotretinoin) or all-trans-Retinoic Acid Does Not Alter Depression-Like Behaviors in Rats*, *Toxicol Sciences*, 2005; 87(2):451-459. Both versions of the papers show changes in both brain and behavior with exposure to Isotretinoin. The conclusions of 'mild' change in brain and 'no severe depression' are erroneous. You either have changes in brain and behavior, or you do not.

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<sup>13</sup> There is robust body of literature involving neuroimaging and the brain supporting that the hippocampus is generally accepted as part of the brain circuitry in depression and mood/behavior dysfunction. See Exhibit 18. Roche's expert, Dr. Mintun, has even said of the hippocampus: "The hippocampus often is the key to interpreting things such as whether an experience is good or bad, whether a person is looking at me with a happy face or a sad face, whether a person is angry with me, those sort of things." See Exhibit 20, Transcript of Deposition of Mark Mintun, 5/3/07 p. 136-37.

As explained by Dr. Bremner, the initial author abstract of this article published and presented at the Society for Neuroscience Meeting (with whom Dr. Bremner actually discussed the findings), concluded that there were, in fact, statistically significant changes in behavior in rats tests which were designed to assess depression after administration of Accutane:

**In general, short immobility and long climb/struggle durations are indications of decreased depression (i.e., antidepressant treatment shortens immobility time). Thus, ACC doses which produce blood levels similar to humans cause behavioral alterations in a rodent assessment designed to assess depression.**

See Exhibit 60 (emphasis added).

**F. Adverse drug event reports are an important element in the scientific methodology of examining causation.**

In 1999, prior to running a purported rigorous study to test the association (which was never actually run) Roche wanted to determine if the causal association evident from the adverse events reported was real. In response, Roche's own scientist responsible for Accutane review sent an email:

An update of these work-ups is certainly possible, if needed, using the same selection criteria than before. **However, a re-review of the whole cases and issues will not provide the conclusion that there is no real association since a couple of cases can be found by any reviewer which are clear-cut. FDA will certainly pull them out. See e.g. positive rechallenges with depression. Therefore, from cases on the database it is not possible to show that there is no association.**

See Exhibit 51. (emphasis added). During that exchange, Hilal Kremers, one of Roche's employees in Switzerland and co-author of the Jick paper meant to convince practitioners that psychiatric side effects were not being caused by Accutane, wrote to an external expert who was being retained to provide the FDA a report:

As I mentioned you before, there are 1500+ cases of psychiatric disorders in Advent and I am sure you would agree with me that the review of such a huge number of cases needs some planning before you start. **Also be aware, there are lots of worrying cases in that pool and it may be difficult to be convinced that the association is not real.**

See Exhibit 51 (emphasis added).<sup>14</sup>

Dr. Marilyn Pitts, the safety evaluator in the Office of Postmarketing Drug Risk Assessment for the FDA, testified at the September 19, 2000 FDA Advisory Committee Meeting regarding the issue of causation and methodology for assessing causation.

Some reasons to suspect a drug/adverse event relationship include the temporal, or the time relationship between administering the drug and the development of symptoms, a dose response, or a mechanism of action or biological plausibility, or a class effect, or the absence of alternatives, and dechallenge, or the abatement of symptoms when the drug is discontinued, and rechallenge, the recurrence of symptoms when the drug is reintroduced. Again, dechallenge and rechallenge provide additional evidence of a relationship between a drug and an adverse event.

See Exhibit 22, pp. 107-008. Dr. Pitts also addressed the quality of dechallenge/rechallenge reports: “In evaluating spontaneous adverse events, positive dechallenge/rechallenge cases provide the best evidence to support a relationship between a drug and an observed event.”

See Exhibit 22, p. 105; See Exhibit 14, Tr. 5/31/06 at pp 23-24. After reviewing the Accutane adverse event reports, Dr. Pitts went on to testify in summary:

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<sup>14</sup> This discussion of adverse drug events is consistent with the basic principles of ADE analysis and epidemiological work: “...**a temporal relationship between medical product and adverse event, coupled with positive dechallenge and rechallenge, can make isolated reports conclusive as to a product-event association.**” See Exhibit 16, Strom's book p. 166 (citing Temple. RJ, Jones, JK, Crout JR, *Adverse Effects of Newly Marketed Drugs*. New. Engl. J. Med. 1979; 300; 1046-47. See Exhibit 21.) (emphasis added). The citation to the Temple and Jones article is even stronger when one reviews the supporting citation:

Reports from alert physicians are still the most important source of information on the adverse effects of a drug during the first few years of its marketing. The epidemiological value of these reports is enhanced when they are collected in a single place and trends are followed. **But even isolated reports can be definitive in associating a drug with an adverse effect if the drug and event are temporally related, the events disappears when the drug is stopped (dechallenge) and the event reappears when the drug is readministered (rechallenge).**

See Exhibit 21, p. 1047.

In summary, we have 41 Accutane associated dechallenge/rechallenge cases. 76 percent were without a reported psychiatric history. The median time to onset of symptoms during the first course of Accutane was 30 days, and a median recovery time of 4.5 days. During the second course, or the rechallenge course, the time to onset of symptoms was shorter in the cases that provided the information. Also, after the second course of Accutane, depression persisted in some patients after discontinuation of Accutane and/or medical intervention. There was a possible dose-response to Accutane observed in 6 patients.

In conclusion, dechallenge/rechallenge cases provide strong evidence to support a link between a drug and an observed adverse event. We have presented 41 cases of positive dechallenge/rechallenge which provide further evidence to support a relationship between Accutane and depressive symptoms.

See Exhibit 22, p. 114; See also Exhibit 14, Tr. 5/31/06 at pp. 23-24; See also Exhibit 12, Tr. 7/13/06 at pp. 130-131.

Diane Wysowski, Ph.D., who was a senior scientist at the FDA, noted regarding psychiatric adverse event reported. "Large number of serious reports, temporal association, positive dechallenges [most with psychiatric treatment], positive rechallenges, lack of psychiatric history and contributing factors in some individuals, similar case reports in literature." See Plaintiffs' Exhibit 13; Tr. 5/24/06 at pp 251-256.

Importantly, in the July 17, 2001 meeting discussed above, the FDA explained to Roche the FDA's evaluation of the spontaneous adverse event reports:

Provided the signal for an association between Accutane and depression. Factors that favor an association:  
Large number of reports of depression and suicide  
Large number of reports of depression and suicide compared to other drugs in the AERS database  
Large number of reports of depression compared with other adverse events for Accutane  
Temporal association of depression/suicide with use of Accutane  
Positive dechallenges  
Positive rechallenges

Possible biological plausibility

See Exhibit 23.

The FDA has also emphasized the importance of adverse event reporting and positive dechallenge/rechallenge data:

Spontaneous reports are of immense importance to drug safety surveillance, even if incomplete. It is signals from concerned reporters that form the bedrock for hypothesis generation and further investigation.

An accumulating subset of qualitatively rich reports suggests a pattern of temporal association between Accutane treatment and emergence of psychiatric symptoms. These reports describe patients, with no previous history of psychiatric illness and no identified concomitant risk factors, who developed significant psychiatric problems during the course of Accutane therapy. The problems resolved within a few days when the Accutane course was completed or discontinued (positive dechallenge). They recurred when Accutane was restarted (positive rechallenge). Resolution was again noted within a few days on subsequent discontinuation. Commonly reported signs and symptoms include mood swings/irritability, uncontrollable crying, aggressive personality changes, and frank depression.

See Exhibit 24, p. 2. After establishing the importance of the adverse event reporting for Accutane, the FDA scientist asked and answered the following questions based upon the adverse event reporting and the known neuroscience surrounding this class of drugs and Accutane:

These spontaneous reports prompted us to ask whether other information supports a possible causal relationship:

Does Accutane reach the target organ of the observed adverse event (the brain)? Yes.

Is Accutane associated with other central nervous system adverse events?

Yes. Of all the organ systems classified in the spontaneous reporting database, the central nervous system has the largest number of serious adverse event reports for Accutane.

In cases with positive dechallenge, is the average time to resolution of symptoms consistent with Accutane pharmacokinetics? Yes.

Are there published reports of psychiatric adverse events associated with Accutane that pre-date the publicity of the 1998 warning? Yes.

Are the temporal and clinical patterns in these reports similar to the patterns in the spontaneous reports? Yes.

Are any other retinoids associated with psychiatric disturbance? Yes, including the "natural" retinoid, Vitamin A when consumed in excessive amounts.

Are retinoid receptors and binding proteins found in adult mammalian brain? Yes.

Have any well-conducted studies demonstrated a functional role for retinoids/receptors in the central nervous system of animals? Yes.

Has a mechanism of action been established to account for the observed events? No. Delineation of the mechanism of action for drug side effects is often clinically useful, but the unknown is of no utility, especially when studies of possible mechanisms have yet to be conducted. Indeed, dermatologists have managed for many years the potentially serious psychiatric side effects of systemically administered corticosteroids without delineation of the mechanism.

See Exhibit 24, p. 3.<sup>15</sup> Importantly, Roche must concede that Accutane reaches the target organ – the brain – because Accutane is known to cross the blood-brain barrier. See Exhibit 52.

In February 1998, Dr. O'Connell wrote a memorandum and concluded: "**Given all the pieces of evidence available, it is difficult to avoid the conclusion that Accutane can adversely affect the adult human brain in clinically significant ways and that Accutane**

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<sup>15</sup> Interestingly, the FDA also published an article addressing the link between the reports of headache and development of depression in users of Accutane. See Exhibit 66; See also Exhibit 14, Tr. 5/31/06 at pp. 7-8; See also Exhibit 3, Tr. 5/24/06 at pp. 205-210. Utilizing the adverse event drug database, in May 2005 the FDA scientist who also testified before the Advisory Committee regarding Accutane, found a positive relationship between headache and depression and users of Accutane which was highly statistically significant. Id. This is not an incidental finding or a finding that occurred by chance but was rather an important finding significant enough to have the FDA issue a public statement on the topic. While there were limitations to the study, interestingly, Roche never published a response to the article or disputed the findings of the FDA publicly. Importantly, while depression ranked number 39 in the list of reported side effects for all drugs, it was the number 1 reported side effect for Accutane. See Exhibit 66.

**is associated with severe psychiatric disease in some patients."** See Exhibit 25. (emphasis added). See also Exhibit 14, Tr. 5/31/06 at p. 14.<sup>16</sup>

A temporal relationship between ingestion of a drug and the side effect, as seen through case reports, is a valid element of causation, albeit insufficient evidence standing alone to establish causation. That is exactly what Dr. Bremner said in his report. Case reports are among the lines of evidence typically relied upon in considering issues of causation. Reference Manual on Scientific Evidence, at 469. While case reports have limitations, they are recognized evidence "when considered in light of other information available." Id., at 475. See also Tyler v. Sterling Drug, Inc., 19 F. Supp. 1239, 1241 (N.D. Okl. 1998). Case reports may be useful support for causation opinions even as the view of a significant minority of experts in the field. See Kennedy v. Collagen Corp., 161 F.3d 1226 (9<sup>th</sup> Cir. 1998); Tyler, 19 F.Supp. at 1241. In Glastetter v. Novartis Pharms. Co., 252 F.3d 986, 990-991 (8<sup>th</sup> Cir. 2001), cited by Defendants, the court held:

[R]echallenge and dechallenge data are substantially more valuable than run-of-the-mill case reports because a patient's reactions are measured against his own prior reactions. Measuring the patient's reaction bears some similarity to a controlled experiment. Of course, rechallenge and dechallenge events usually involve individual patients only (rather than study groups) and are not often subject to routine testing controls. The district court discounted Glastetter's rechallenge and dechallenge data because the paucity of examples presented statistically insignificant results. Further, a portion of the rechallenge and dechallenge data involved artery spasm and heart attacks, conditions which are quite distinct from Glastetter's ICH. Although we believe that this evidence is more potent proof of causation than the district court believed it to be, we nevertheless conclude that the district court did not abuse its considerable discretion in rejecting rechallenge and dechallenge data as proof that Parlodel acts as a vasoconstrictor.

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<sup>16</sup> See Exhibit 67 (finding psychological changes in 25% of patients where dosing 3 times recommended range, based upon reports of the family even when patient denied changes). See also Exhibit 12, Tr. 7/13/06 at p. 132.

(emphasis added). See also Rider v. Sandoz, 295 F.3d at 1199.

In response, Defendants overstate the holdings since in much of the case law they cite the courts did not reject *per se* the use of case reports. See, e.g., McClain v. Metabolife International, 401 F.3d 1233 (11<sup>th</sup> Cir. 2005) (case reports could not “redeem” the otherwise faulty proof relied upon); Rider v. Sandoz, 295 F.3d 1194, 1199 (11<sup>th</sup> Cir. 2002) (holding that dechallenge and rechallenge data “which may be analogized to controlled studies with one subject, can be particularly useful in determining whether a causal relationship exists” but rejecting the plaintiffs’ data because none of the cases involved the same injury as the plaintiff experienced). Fairly told, the Eleventh Circuit in these cases noted only that the use of case reports alone is insufficient to prove causation.<sup>17</sup> Other cases cited by Defendants are similarly distinguishable.<sup>18</sup> .

It is also noteworthy that Brumbaugh v. Sandoz Pharm. Corp., 77 F.Supp. 1153 (D. Mont. 1999) and Hollander v. Sandoz Pharms. Corp., 95 F.Supp. 1153, 1156 (D.Mont. 1999), relied upon by Defendants, have been criticized for placing too high a burden on plaintiffs even under the Federal Daubert standard. “Science, like many other human endeavors, draws conclusions from circumstantial evidence when other, better forms of evidence is not available.” Globetti v. Sandoz Pharms. Corp., 111 F. Supp. 2d 1174, 1180 (N.D. Ala. 2000).

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<sup>17</sup> Obviously, the PSC is cognizant of the previous ruling by this Court in the IBD track. D.E. 506. However, the PSC will be seeking the Court to examine this ruling under the facts set forth in the PSC’s Opposition to Roche’s latest motion to exclude causality assessments.

<sup>18</sup> Hall v. Baxter Healthcare Corp., 947 F.Supp. 1387 (D.Or. 1996) (the excluded experts relied on mere abstracts of unpublished studies, not the actual case reports); Soldo v. Sandoz Pharmaceuticals Corp., 244 F. Supp. 434, 545 (W.D. Pa. 2003) (excluded expert relied on causality assessments related to a different side effect than that experienced by the plaintiff).

In short, Dr. Bremner utilized the appropriate methodology for assessing causation as demonstrated by the testimony and documents utilized by the FDA.<sup>19</sup>

**VI. ROCHE INTENTIONALLY MISCHARACATERIZES THE PURPOSE OF THE EMORY STUDY IN AN EFFORT TO MISLEAD THE COURT AS TO HOW THE PET STUDY CAN BE APPROPRIATELY UTILIZED.**

Roche attempts to cast the Emory Study as a study aimed at determining whether or not Accutane causes suicide or depression. That was not the purpose of the study nor is it being used in such a capacity. The Court need look no further than the face of the study to understand the purpose: “The purpose of this study was to assess the effects of isotretinoin on brain functioning in acne patients.” See Exhibit 26, p. 984. Even the title accurately states the purpose. “Functional Brain Imaging Alterations in Acne Patients Treated with Isotretinoin.” The Emory Study demonstrated overall a 16% decrease in brain activity in the Orbitofrontal cortex (OFC) for the Isotretinoin arm and a 1% increase in the antibiotic arm. This result was highly statistically significant.<sup>20</sup>

Also, Roche, like mischaracterizing the purpose of the study, takes a single sentence out of the study to mischaracterize the result. In conclusion, the authors did not conclude that

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<sup>19</sup> Roche also cites to literature six (6) years ago where Dr. Bremner, prior to the results of the Emory study and the review of the documents and literature supporting his report in this case, stated there was not a consensus on the causal link between Accutane and depression. As noted, since then Dr. Bremner has reviewed significantly more scientific literature, reviewed additional clinical trial and animal model publications, internal documents of the Roche, researched the topic further and performed the Emory study. See Exhibit 14, Tr. 5/31/06, p. 102-113. The later writings, including the 2005 literature review entitled *Isotretinoin and Depression: Is There a Causal Link*, Practical Dermatology 2005: 28-33 is exactly that – a literature review of then existing literature written prior to the accepted date of publication. Defendants may be free to cross examine Dr. Bremner on these prior writings, but historical information does not preclude the admissibility of his opinions based upon his 2006 and 2007 reports.

<sup>20</sup> Simply put, the idea and purpose was to follow two groups of people and have each imaged twice (in a serial fashion) – at the beginning and end of the Accutane treatment to see if there was any difference in their own PET scan ... not as compared to others. The fact that depression was not identified was predictable – since the purpose of the study was not to examine the generation of depressive symptoms.

Isotretinoin affects the brains of all people at all times. Instead, they reasonably concluded, in an appropriately scientific manner, that Isotretinoin may affect the brains of users – meaning the obvious – in some people. That is all general causation in a legal setting need conclude and the fact that the authors appropriately stated the scientific significance of the study as conditional, does not diminish the import of the study or transform the opinion of Dr. Bremner, when considering all the other evidence examined by Dr. Bremner, into an excludable inadmissible opinion.

**X. NOT ONLY HAS ROCHE BEEN AWARE OF THIS PET STUDY SINCE 1999, ROCHE MET WITH DR. BREMNER AND DECLINED TO FUND THE STUDY, BUT KEPT TABS ON THE STUDY, AND EVEN SURREPTITIOUSLY RETAINED ONE OF CLINICAL INVESTIGATORS WHEN ROCHE BECAME AWARE THE STUDY WAS UNDERWAY.**

Roche was aware of the effort to utilize PET to measure the effect of isotretinoin on the brain since before the Emory study began. In 1999, Roche representatives met with Dr. Bremner. See Exhibit 53. Dr. Bremner had testified that he met with someone from Roche and sought funding from Roche to perform the study. See Exhibit 27.<sup>21</sup> As with the other

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<sup>21</sup> Despite the impression left with Dr. Bremner, Roche did not send some low level employee to meet with Dr. Bremner. Instead, they sent Dr. John McLane, whose last job at Roche was Director of Early Strategic Planning. He left Roche in May 2002. See Exhibit 32, McLane p. 40. He has his Ph.D. in Biology from the University of Rhode Island. See Exhibit 32, McLane, pp. 17-18. He took post-doctoral course at Yale and had a junior faculty position at Yale. See Exhibit 32, McLane p. 31. He was in the Department of Dermatology at Yale. See Exhibit 32, McLane p. 31. He went directly from Yale to Hoffmann-La Roche in 1992. Dr. McLane's role at Roche was significant as a senior executive. He participated with Roche in the September 2000 Advisory Committee Meeting. See Exhibit 32, McLane p. 41. He was an Accutane team leader. See Exhibit 32, McLane p. 333. He is listed as a member of the medical team at Roche in exhibit 226 to his deposition. See Exhibit 33. He was also considered a "medical science leader". See Exhibit 34. In the Accutane Team Minutes of October 10, 2000, See Exhibit 35, he was described as a "science leader".

In addition, Dr. McLane was deeply involved in the science of Accutane and the issues surrounding the issue of psychiatric side effects. He was involved in epidemiological studies with Jick in connection with other Roche epidemiological projects concerning Accutane. See Exhibit 32, McLane p. 137. Interestingly, Dr. McLane was the individual at Roche responsible for the clinical trials of Accutane New Formulation. Affinito Cert., Ex. 73, McLane p. 346. He was the primary author of the enhancement to Dr. Schifferdecker's report in connection with supervising patients on Accutane for depression. See Exhibit 36.

science, Roche, however, did not want to participate in the scientific process. Roche declined any financial assistance for the study – but kept tabs on the progress.<sup>22</sup>

Interestingly, Dr. Suephy Chen was initially listed as one of the clinical investigators in the Emory Study. Unbeknownst to anyone but Roche and Dr. Chen, Roche set out to contact Dr. Chen regarding this study. See Exhibit 30. And, more troubling, then retained Dr. Chen to speak on behalf of Roche...before the study was actually completed. See Exhibit 31.<sup>23</sup>

In the end, rather than utilizing the expertise of Dr. Mintun (Roche's PET scan retained expert), Roche intentionally avoided asking Dr. Mintun to perform any research or PET studies. See Exhibit 38, Mintun 11/17/05 p. 63; see also Exhibit 20, Mintun 5/3/07, p. 190.<sup>24</sup> Instead, Roche simply sat back, co-opted one of the investigators, kept tabs on the research, and waited to see the results of the Emory study -- and then criticize.

**V. PET SCANNING IS A USEFUL, SCIENTIFICALLY ACCEPTABLE TOOL AS USED BY DR. BREMNER AND THE CO-AUTHORS OF THE EMORY STUDY.**

PET scan technology has been recognized as reliable and admissible evidence by the Courts around the country for over 10 years and a generally accepted tool to measure brain function and metabolic rate. See, e.g., People v. Weinstein, 156 Misc.2d 34, 591 N.Y.S. 2d

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Finally, he was the author of the "negotiation memo" See Exhibit 37 describing getting all issues on the table with the FDA so that Roche could attain a strategic advantage when negotiating with FDA in connection with the Accutane label. Affinito Cert., Ex. 78.

<sup>22</sup> Now of course, they complain that the fact that funding was obtained from other sources.

<sup>23</sup> Interestingly, this effort was not just relegated to a low level scientist at Roche, but as can be seen from Exhibit 31, in house counsel in charge of the psychiatric case litigation was cc'd as an interested individual at Roche.

<sup>24</sup> Dr. Mintun has even performed research into retinoid receptors and utilizing PET scans to measure receptor binding in the brain. See Exhibit 38, Mintun 11/17/05 p. 157. Yet, Roche never even discussed this issue with Dr. Mintun See Exhibit 38, Mintun 11/17/05 p. 157.

715 (N.Y. Sup. 1992). In the most oft-cited case involving PET scans and its admissibility, the 8th Circuit Court of Appeal announced that PET scans are generally accepted as a scientific procedure and is a relevant piece of evidence in the courtroom. Hose v. Chicago Northwestern Transportation Co., 70 F.3d 968 (8th Cir.1995).

In a series of cases involving the National Childhood Vaccine Injury Act of 1986, the United States Court of Federal Claims, Office of Special Masters, discussed PET scans in the context of evaluating brain damage suffered by infants and adolescents who had been administered vaccines.<sup>25</sup> Additionally, there are criminal cases from around the country where PET was admitted for the purposes of assessing brain function or it was error to refuse a criminal defendant the opportunity to have a PET scan to measure brain function.<sup>26</sup> There

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<sup>25</sup> McCullum v. Secretary of Health and Human Services, 1998 WL 338237 (Fed. Cl. 1998) ; Bushell by Bushell v. Secretary of Health and Human Services 1993 WL 212472 (Fed. Cl. 1993); Lewis v. Secretary of HRS, 1991 WL 262943 (Cl. Ct. 1991) (Government could not prevail in arguing pre-existing abnormality of dysgenesis, since Government failed to conduct PET in this case where all prior cases involving this abnormality were supported by identifiable abnormality on PET); See also Barnes v. Secretary, Dept. of Health and Human Services, 1997 WL 620115 (Fed. Cl. 1997) (testimony that one can identify tuberous sclerosis on PET, MRI, and EEG); McCarren v. Secretary, Dept. of Health and Human Services, 1997 WL 341694 (Fed. Cl. 1997) (SPECT scan); Vitale v. Secretary, Dept. of Health and Human Services, 1997 WL 39498 (Fed. Cl. 1997); and Pertnoy v. Secretary, Dept. of Health and Human Services, 1995 WL 579827 (Fed. Cl. 1995).

<sup>26</sup> People v. Weinstein, 591 N.Y.S. 2d 715 (N.Y. Crim. Ct. 1992) (PET admitted as corroborative evidence, concluding “PET is a highly advanced form of medical technology”); State v. Reid, 2001 WL 584283 (Tenn. Crim. App. 2001) (neuropsychologist testified for defendant and state agrees with finding of abnormality on PET); Coe v. State, 17 S.W. 3d 193 (Tenn. 2000) (expert opined defendant has congenital brain damage, maldevelopment, and some acquired brain damage, based upon, among other tests, PET scan); State v. Slocumb, 336 S.C. 619, 521 S.E. 2d 507 (S.C.App. 1999) (expert opined defendant had organic brain abnormalities based upon, among other tests, SPECT); Bolin v. State, 736 So. 2d 1160 (Fla. 1999); United States Court of Appeals for the Armed Forces v. Gray, 51 M. J. 1 (U.S., 1999) (trial court funded, among other tests, SPECT and neuropsychological battery prior to trial); Wilkins v. Delo, 886 F. Supp. 1503 (W.D. Mo 1995) (Defendant not competent to plea on neurological history, EEG, MRI, SPECT); People v. Beeler, 9 Cal.4th 953, 891 P.2d 153, 39 Cal.Rptr.2d 607 (Cal. 1995); Hoskins v. State, 702 So.2d 202 (Fla. 1997) (Abuse of discretion in refusing to permit death row defendant from having PET scan); Black v. State, 2005 WL 2662577 (Tenn.Crim.App. 2005) (a proof in a post-conviction hearing, expert testified at to petitioner’s PET scan results); Rogers v. State, 783 So. 2d 980 (Fla. 2001) (The Supreme Court in footnote #5, “the scientific reliability of PET scan evidence was never an issue in the trial.” Moreover, the United States Court of Appeal for the Eighth Circuit has determined that “[t]here is also no question that the PET scan is scientifically reliable for measuring brain function.” Hose v. Chicago Northwestern Transportation Co., 70 F. 3d 968 (8th Cir. 1995)).

are many cases addressing PET and SPECT<sup>27</sup> in personal injury cases involving claims of injuries to the brain.<sup>28</sup> Simply put, there is no basis in law or fact to exclude the PET study as being *per se* inadmissible as Defendants advocate.<sup>29</sup>

**VII. THE UNREBUTTED SCIENTIFIC LITERATURE SUPPORTS THE CONCLUSION THAT CHANGES IN AREAS OF THE BRAIN AS IDENTIFIED IN THE EMORY STUDY AS HAVING BEEN AFFECTED BY ISOTRETINOIN, ARE ASSOCIATED WITH MOOD, EMOTION, BEHAVIOR, AND PSYCHIATRIC ILLNESS.**

There is a robust body of scientific peer reviewed literature demonstrating objective evidence that the orbitofrontal cortex plays a role in depression and dysfunctional behavior, including near universal evidence that decreases in cerebral blood flow, metabolism and volume of brain matter are found in depressed (and behaviorally dysfunctional) patients as

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<sup>27</sup> SPECT, another method for measuring brain functioning, involves measuring blood flow to the brain. Again, this is a method for measuring functioning of the brain tissues. Increased or decreased metabolism in a brain cell is associated with a corresponding increase or decrease in blood flow. PET is a tool to measure the metabolic activity of the cells by measuring glucose utilization. Therefore, in analyzing the concepts surrounding the usefulness of measuring brain functioning through concepts of metabolic rates, it is useful to look to the body of literature and case law involving both PET and SPECT scans.

<sup>28</sup> Blodgett-McDeavitt v. University of Nebraska, 2004 WL 2792453 (Neb.App. 2004) (PET admissible for purpose of measuring brain functioning); Williamson v. Haynes Best Western of Alexandria, 688 So.2d 1201 (La.App.4Cir. 1997) (SPECT scan admissible); Miller v. Consolidated Rail Corp., 1999 WL 89668 (E.D.Pa. 1999) (SPECT Scan and interpretation admissible); Friedrich v. Intel Corp., 181 F.3d 1105 (9th Cir. 1999) (SPECT scan of brain, interpretation and opinion regarding etiology admissible); Aronson v. State Farm Ins. Co., 2000 WL 667285 (C.D.Cal. 2000) (PET scan admissible); Kent v. Apfel, 75 F. Supp. 2d 1170 (D.Kan. 1999) (PET scan admissible); Berry v. CSX Transportation, Inc., 709 So. 2d 552 (Fla.App. 1 Dist. 1998) (SPECT scan admissible); People v. Holt, 15 Cal.4<sup>th</sup> 619, 800, 937 P.2d 213, 231 63 Cal.Rptr.2<sup>nd</sup> 782 (1997) (PET scan images of brain admitted); Hando v. Shalala, 13 F.3d 405, 1993 WL 523213 (C.A. 10 (WYO.) 1993) (PET scan admissible ); McCormack v. Capital Electric Construction Company, Inc., 159 S.W.3d 387 (Mo.App. W.D. 2004) (PET scan results admitted without objection.).

<sup>29</sup> Defendants' reliance on M.C. v. Yeargin, 11 S.W.3d 604 (Mo.App. E.D. 1999), for their arguments in support as to why Dr. Bremner's testimony should be excluded is misplaced, and in fact, the case is no longer good law. In State Bd. of Registration for Healing for the Arts v. McDonagh, 123 S.W.3d 146 (Mo. Dec. 23, 2003), the court held that Missouri statute 490.065 supplies the relevant standard for admission of expert testimony over the rulings in Frye and Daubert. The court went on to say that any confusion as to which standard applies should have been resolved by the decision in Lasky v. Union Electric Company, 936 S.W.2d 797 (1997) (holding that section 490.065 provides that applicable standard in evaluating the admission of expert testimony in all civil cases). Yeargin was specifically cited as a case confused at to the proper standard. See, State Bd. at 153 (footnote 9). Therefore, Yeargin's holding is effectively overruled due to its reliance of the Frye standard. That being said, the admission of PET scan was not the issue in the case, but how the plaintiffs counsel attempted to then use the PET findings alone to diagnose in a particular patient.

compared to non-depressed and control group patients in the prefrontal cortex (of which the orbitofrontal cortex is a part).<sup>30</sup> Further, there is significant peer reviewed literature from authoritative and leading scientists in this area showing increases in brain function in the same brain regions after patients were treated for their depression, supporting the hypothesis and conclusion that metabolic decreases in the orbitofrontal cortex are associated with dysfunctional behavior and depression. See Exhibit 18 listing the thirty-one (31) articles and providing context for the support of the Dr. Bremner's opinion. These articles represent a fundamental basis of neuroscience work involving PET scanning. See Exhibit 3, 5/24/06 Tr. at p. 148-49, 151.

Even the Defendants had to stipulate that the Orbitofrontal Cortex modulates behavior. See Exhibit 3, 5/24/06 Tr. 159-163.<sup>31</sup> And, it is unrebutted that the circuitry of these regions supports the conclusions of Dr. Bremner even if the findings are not involving the identical regions. See Exhibit 12, 7/13/06 Tr. at p. 94-96. It is also undisputed :

- the Orbital Frontal Cortex has a role in mediating behavior (See Exhibit 38 11/17/05 p. 327);
- the hypothesis that medial orbital frontal cortex is involved in stimulus reinforcement and emotion modulation (See Exhibit 40, Mintun 12/6/05 p. 570);
- there are studies which demonstrate and support the conclusion that damage to the OFC impairs the learning and reversal of stimulus reinforcement (See Exhibit 40, Mintun 12/6/05 p. 570);

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<sup>30</sup> In the context of these scientific articles, references to decreased blood flow and metabolism are equivalent methods of measuring brain function in a particular region. The suffix "hypo" means decreased such that hypometabolism means decreased metabolism.

<sup>31</sup> Dr. Mintun has been quoted in articles he has written as having said "Case studies since Phineas Gage have linked lesions in the [OFC] with behavioral disinhibition and loss of social constraint." as well as "[r]ecent studies suggest that these lesions may disrupt visceral and emotional responses to the environment that helps humans predict consequences and make decisions." See Exhibit 20, Mintun, 5/3/07 pp. 139. In fact, Dr. Mintun has even authored an article establishing that the greatest changes in metabolic function of the brain involving dopamine were in the OFC. See Exhibit 20, Mintun 5/3/07, pp. 139-140; See also Exhibit 62.

- it is well accepted that if the OFC is damaged, you can see disinhibition, affective lability and other behavioral changes described as psychiatric behaviors (See Exhibit 38, Mintun 11/17/05 p. 328);
- frontal lobe hypometabolism is emerging as a common final pathway for most types of primary and secondary depression regardless of the original cause (See Exhibit 40, Mintun 12/6/05 p. 571-572);
- there is considerable face validity in that mood changes are a frequent concomitant of frontal lobe pathological states (See Exhibit 40, Mintun 12/6/05 p. 563).<sup>32</sup>

When this scientific body of work and foundation is applied to the issues surrounding the Emory PET study, is clear why the eight (8) study authors stated:

- Multiple positron emission tomography, PET, and single photon emission computed tomography, SPECT, studies have shown low metabolism and/or blood flow at baseline in depressed subjects in the left and bilateral, dorsolateral prefrontal cortex and medial prefrontal cortex/anterior cingulate or blunted activation with cognitive tasks in the anterior cingulate.
- Other PET and SPECT studies of patients with unipolar depression showed low metabolism and/or blood flow in the caudate, thalamus, temporal cortex, parietal cortex, and left putamen.
- Experimental induction of depression resulted in a specific decrease in metabolism in the orbitofrontal cortex, part of the prefrontal cortex.

See Exhibit 26, p. 984.

**IX. THE HYPOTHESIS, METHODOLOGY AND CONCLUSIONS OF THE PET STUDY WERE THE RESULT OF A SCIENTIFIC CONSENSUS AND AGREEMENT.**

The team of well-qualified academicians, researchers and clinicians agreed and approved the hypothesis, methods and conclusions of the study. See Exhibit 3, 5/24/06 Tr. 105-111; 175-177. The team included: physicist, chemist, medical doctor, computer scientist, radiologist, epidemiologist, and nuclear medicine physician – from 2 different well respected universities, Yale University and Emory University. Id. Dr. Votaw, who was responsible for

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<sup>32</sup> Dr. Mintun did not review any of studies cited above for his report in this case though these are seen as the leading articles in this area. See Exhibit 38, Mintun 12/6/05 pp. 570-571.

aligning the heads of the study participants in the scanner and for calibrating the scanners, has written many peer reviewed articles; in the opinion of Roche's expert, Dr. Votaw is a respected scientist. See Exhibit 38, Mintun 11/17/05 p. 400. Even Dr. Mintun agreed the co-authors of the article are respected scientists. See Exhibit 40, Mintun 12/6/05 p. 528-529.

This study was done in a blinded fashion. The PET scans were not analyzed or reviewed until after the completion of the process of all scans were completed for all subjects. See Exhibit 3, 5/24/06 Tr. at p. 187. Moreover, as it has been conceded the study is re-producible and could be replicated. See Exhibit 39, Tr. 10/2/06 at p. 195; See also Exhibit 20, Mintun, 5/3/07 pp. 194-195.

While the Defendants string together a series of criticisms, in reality, there is little that Dr. Mintun disagrees with except for the final conclusion.<sup>33</sup> That with which he disagrees with is best characterized as subjective criticisms unsupported by any peer-reviewed literature or expertise. Dr. Mintun had no criticisms:

- telling patients there is a controversy involving Accutane (See Exhibit 40, p. 532);
- including women in the study who were on oral contraceptives (See Exhibit 40, p. 532);
- height and weight differences of subjects (See Exhibit 40, p. 533);

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<sup>33</sup> Dr. Mintun had no opinions regarding the volume of adverse events reports (See Exhibit 38, p. 102); the class effect of retinoids (See Exhibit 38, p. 102); the temporal relationship of Accutane and psychiatric side effects established through the post marketing safety surveillance or dechallenge/rechallenge (See Exhibit 38, pp. 102-110); whether or not isotretinoin or its metabolites effect the brain. (See Exhibit 38, p. 110); the side effect profile of Accutane, admitting he did not know what the side effects were (See Exhibit 38, pp. 114-116); whether utilizing different antibiotics effected outcome (See Exhibit 38, p. 207); whether or not possible to construct a blinded study with Accutane since he is not an expert on isotretinoin or the side effects. (See Exhibit 38, pp. 113-114; 197-198); Dr. Mintun is not an isotretinoin expert (See Exhibit 38, Mintun 11/17/05 p. 203) and in fact, has no opinions regarding Dr. Bremner's report outside of the Emory Study.

<sup>34</sup> Defendants suggest without any record support that the differences between the groups, even if not statistically significant to the analysis, render the study invalid and unscientific. The case cited by Defendants is distinguishable and not compelling in any manner. In Penney v. Praxair, Inc., 116 F. 3d 330, 333-334 (8th Cir. 1997) the plaintiff was in an automobile accident and attempted to submit evidence of his PET scan to

- if off Zoloft or anti-depressant more than a year (See Exhibit 40, pp. 540-541);
- 4 month interval for serial PET scans (See Exhibit 38, p. 203);
- permitting treating physicians to choose which antibiotic to put patients on (See Exhibit 38, pp. 205-06);
- Utilizing Structured clinical interviews from DSM-IV edition for establishing psychiatric diagnosis (See Exhibit 38, p. 207);
- the exclusion criteria stated by the authors (See Exhibit 38, pp. 199, 201);
- exclusion of patients with past psychiatric diagnosis (See Exhibit 40, p. 544);
- inclusion of patients with prior drug use (See Exhibit 40, p. 544);
- pixel by pixel examination of the PET study images (See Exhibit 40, p. 531);
- Conclusion that isotretinoin subjected had fewer years of education and were younger, but there latter differences was not statistically significant (See Exhibit 38, p. 247);
- The subjects did not differ significantly from the antibiotic group in their reasons for receiving treatment (cystic acne, psychological distress, scarring, or a combination) (See Exhibit 38, p. 248);
- According to the self-ratings there were no difference in acne on the face or back or in feelings of depression related to the acne (See Exhibit 38, pp. 248-49);
- There were no difference between the two groups in behavioral, emotional, and functional effects of acne as measured by the skindex at baseline<sup>35</sup> (See Exhibit 38, p. 250); See Exhibit 20, Mintun 5/3/07 p. 75;
- No differences in baseline depressive symptom levels as measured by the Hamilton depression scale (See Exhibit 38, p. 250).

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show a closed head injury. However, in order to diagnose the closed head injury, his physician expert used a control group of 31 subjects ranging in age from 18 to 70. The plaintiff was 66. Moreover, the control subjects had been instructed not to take any medication before or during their scans while the plaintiff remained on his medication during his scan. The appellate court acknowledged that it had previously upheld the admission of PET scan evidence, but that in this case, it was not clear from the trial court record how accurate a comparison to the control group could be. Therefore, the court declined to overrule the trial court's decision to exclude the PET scan imaging. This is hardly persuasive in this context.

<sup>35</sup> Dr. Mintun was not prepared to testify that the Skindex is even a validated tool for measuring feelings related to acne. See Exhibit 20, Mintun p. 441. While it is apparent that the Skindex was not used for every subject, the purpose of the study was not to diagnose depression – it was to measure any affect of Isotretinoin on patients' brains. However, Roche's use of this criticism is to suggest that perhaps the differences observed objectively on PET scan were due to active rumination, or thinking, during the PET scan itself. Issues of active rumination were (1) controlled through the methodology deemed scientifically valid and (2) would have been logically been observed across both arms of the study if an issue. Skindex has nothing to do with this criticism and to associate the concerns regarding the actual results and the completion of the Skindex is to confuse the important scientific principles.

In examining the methodology for the PET and MRI scanning, neither Roche nor Dr. Mintun alleges the methodology of performing the PET scans was scientifically invalid.<sup>36</sup> (See Exhibit 38, Mintun 11/17/05 pp. 212-214)<sup>37</sup> As to the Image Processing and Analysis set forth in the peer reviewed Emory Study, Dr. Mintun again either agrees with the methodology or agrees that the methodology is scientifically valid or is unable to cite a single peer reviewed article supporting any criticism.<sup>38</sup>

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<sup>36</sup> Dr. Mintun did not claim the following methodology statements was scientifically invalid: Two PET scans of resting brain metabolism were performed 4 months apart, before and after treatment with isotretinoin of antibiotic; The PET scans took place at 11:00am; the subjects were scanned with an ECAT EXACT 921 and 951 PET camera (CTI Molecular Imaging, Knoxville Tenn.); each subject was placed in a preparation room adjacent to the PET scanner room and an intravenous line was inserted in the hand and warmed with a hearing pad for measurement of arterialized venous blood samples; this method has been shown to yield metabolic values equivalent to those obtained by arterial line placement; the subject then received an intravenous injection of 10 mCi (970MBq) of FDG in a single bolus; Twenty-three arterIALIZED venous blood samples were obtained at multiple time points after injection for measurements of radioactivity in the plasma, where were used for construction of a plasma time activity curve; three blood samples were also obtained for measurement of plasma glucose concentrations; the subject was then placed in the scanner with his or her head held holder to minimize patient motion; the head was positioned with the canthomeatal line parallel to the external laser light; following position within the camera gantry, post-injection transmission data were collected by using rod windowing with three orbiting Ga/Ge rod sources; these data were used to correct the emission data for attenuation due to overlying bone and soft tissue; the subject underwent emission scanning of the brain over the 40-50 minutes after injection with his or her eyes open in a dimly lit room; brain and tissue measurements were used to estimate the cerebral glucose metabolic rate (in milligrams per minute per 100 milliliters); in one patient blood samples could not be obtained and this patient's data were used only for analysis of the ratio of regional metabolism to whole brain metabolism; A 20-cm cylindrical fluid filled phantom with a known amount of radioactivity was scanned in order to obtain calibration factors for conversion of native pixel values into units of millicuries per milliliter; MRI scans were obtained in all subjects for coregistration with the PET scans and determination regions of interest from the MRI scans resliced to correspond to the PET slices (while Dr. Mintun would use a different methodology, Dr. Mintun concedes that using this method is not scientifically invalid. See Exhibit 20, Mintun, 5/3/07 p. 144-145. Moreover, he has no articles to cite to support his criticism – it is just his opinion. Id.); MRI scans in the same subjects were obtained on a 1.5 T Philips Gyroscan Intera Device (Phillips Medical Systems, Andover Mass.) ; axial images were acquired with a T1-weighted gradient echo three dimensional sequences with TR=35m sec, TE=msec, flip angle=\_\_ degree, number of excitations=2, matrix=256x256, field of view=22 cm, and slice thickness =3mm).

<sup>37</sup> While Dr. Mintun stated criticisms of the process of reslicing the MRI to correspond to the PET slices he could not cite to any peer-reviewed literature supporting this criticism. More importantly, despite the criticisms offered by Dr. Mintun he had to agree that the methodology is scientifically valid. See Exhibit 38, Mintun p. 212-215. A dispute between experts alone is not sufficient to exclude scientific testimony and take this matter from the jury.

<sup>38</sup> The PET and MRI scans were transferred to a workstation for analysis; A surface matching algorithm and the ANALYZE software package (Mayo Clinic, Rochester Minn.) were used for coregistration of images; Brain surfaces from PET and MRI were matched by using this program; The MRI scan was resliced to

In the totality of the circumstances, Dr. Mintun agrees with the methodology utilized by the authors of the Emory study. More importantly, as Dr. Mintun conceded, the methodology is sufficiently precise that the study could be replicated if so desired. See Exhibit 20, Mintun 5/3/07 pp. 197-195.<sup>39</sup>

**X. ROCHE'S CRITICISMS ARE AT BEST A DISPUTE AMONGST EXPERTS, WHICH IS A MATTER FOR CROSS-EXAMINATION.**

Roche's criticisms are not sufficient to exclude scientific testimony and take this matter from the jury. Each have been disputed by Dr. Bremner and the fact that Roche disagrees there is insufficient evidence to exclude Dr. Bremner's opinions.

**A. Roche's Expert agrees, notwithstanding the criticisms of the Defendants, that the Emory Study was a large study.**

While Roche repeatedly criticizes the size of the study, the fact is that Dr. Mintun testified this was a big scientific work. See Exhibit 20, Mintun 5/3/07 p. 531. Not a single study Dr. Mintun has ever performed involving PET scans and measuring the effect of agents on the brain matched the size of the Emory Study; his largest study involving such was with 20 subjects. See Exhibit 38, Mintun 11/17/05 p. 296.

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correspond to the PET slices; Using this technique we have shown a registration error of 2.86 mm; Regions of interest were drawn on the resliced MRI scans by a blinded rater using specific criteria based on anatomical landmarks with a method that we have shown to be highly reliable; Multiple brain regions were selected for analysis, including the temporal cortex, inferior, middle and superior frontal gyri, superior portion of the dorsolateral prefrontal cortex, thalamus, putamen, caudate, occipital cortex, subcallosal gyrus, orbitofrontal cortex, anterior cingulate, post-central gyrus, hippocampus, amygdale and mid brain; These regions correspond to the regions measured in our prior studies of neural findings associated with a return of depressive symptoms induced by tryptophan depletion and alphas-methylparatyrosine since a primary aim of the current study was to replicate the brain findings of those prior studies

<sup>39</sup> After years of litigation involving this study and having the opportunity to actually meet with Dr. Bremner to discuss what might be needed for calculations, for the first time on May 3, 2007, Dr. Mintun suggested he needed to see information regarding this particular issue, even though he had no criticisms of the methodology. See Exhibit 20, Mintun 5/3/07, pp. 120-121. It is not even relevant to the analysis as this is a standard control. See Exhibit 41 (Mintun co-author, where does not even mention use of phantoms but most have used such), Exhibit 42 (co-author on the Emory Study, Dr. John Votaw explaining use of phantoms as was used later in the Emory Study)

**B. The methodology of the scientific team to correct for head tilt is valid and there is no evidence to conclude otherwise.**

While Roche cross-examined Dr. Bremner on the process of reslicing the MRI to correspond to the PET slices they could not cite to any peer-reviewed literature supporting this criticism. Referred to as co-registration, this process is generally accepted and there is no evidence to the contrary. See, e.g., Exhibit 3, Tr. 5/24/06 p. 79.<sup>40</sup> And, importantly, the process of co-registration was done in a blinded fashion. See Exhibit 3, 5/24/06 Tr. pp. 201-203.

In deposition Dr. Mintun put forward an opinion that there are concerns regarding head movement – but, he can not point to a single scan where head movement was even seen. See Exhibit 20, Mintun, 5/3/07 pp. 166-167. Moreover, Dr. Bremner disagrees with Dr. Mintun that there is any issue regarding head tilt and the methodology stated in the Emory study clearly addresses the method for controlling for head tilt amongst different scans.

**C. Roche's criticism of utilizing two scanners is not well founded or supported by any literature or competent evidence.**

While much is made of the fact that two separate scanners were used, and it was clear that there was an oversight by one of the authors of the study responsible for that aspect of the PET study in simply not setting forth that fact in the published paper, these are two cameras manufactured by the same company. See Exhibit 14, 5/31/06 Tr. p. 195-196. This issue was addressed with the physicist. See Exhibit 12, 7/13/06 Tr. at p. 97-99. These are not cameras with different resolutions. See Exhibit 14, 5/31/06 Tr. at 198-199. In fact, Dr.

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<sup>40</sup> The co-registration method of reslicing the PET to match the MRI is predicated on the fundamental scientific principle that since PET measures function, and MRI gives a picture of the brain anatomy, matching the MRI landmarks in the brain to the PET scan permits you to match up serial scans to correct for head tilt and other variations. See, e.g., Exhibit 3, Tr. 5/24/06 at p. 79-80; See also Exhibit 39, Tr. 10/2/06 at p. 212-215

Mintun agreed that the Seimans 921 and 951 are very similar if not identical in terms of resolution and there is no objective evidence that resolution is any different. See Exhibit 40, Mintun 12/6/05 pp. 409-410. These cameras were cross-calibrated and there is no scientific evidence to the contrary that such a cross-calibration process is unscientific. See Exhibit 14, 5/31/06 Tr. at p. 196.

The methodology utilized by Dr. Votaw of utilizing Hoffmann brain phantoms is considered the scientifically acceptable method for cross-calibration. See Exhibit 38, Mintun 11/17/05 p. 221. In fact, Dr. Votaw has published peer reviewed literature regarding the methodology related to the calibration of the two machines at Emory University. See Woodward, J, *Compensatory Recruitment of Neural Resources During Overt Rehearsal of Word Lists in Alzheimer's Disease*, *Neuropsychology*, 1998, 12:491-504 (Multiple scanners utilized for PET imaging study of participants.) See Exhibit 63. See also Silverman, D, *Positron Emission Tomography in Evaluation of Dementia*, *JAMA*, 2001; 286:2120-2127 (long-term study with Dr. Phelps as co-author, where patients followed serially with different scanners). See Exhibit 45.

**D. The methodology for drawing the regions of interest is well accepted, the product of years of training and experience, and scientifically sound.**

It is undisputed that the scientific methodology utilized for drawing the Regions of Interest is generally accepted and utilized throughout the world. See Exhibit 3, 5/24/06 Tr. at 85. In the PET study, the drawing of the regions was performed by a medical doctor who had been trained and whose work and product had been verified for other studies unrelated to Accutane. See Exhibit 3, 5/24/06 Tr. at 81-89. This work of drawing the regions in the Emory Study was done blind, meaning whatever implied arguments by Roche that this study

was slanted, the scientific team was not aware of the drug used by any particular participant. See Exhibit 3, 5/24/06 Tr. at p. 86. Roche's claim that any of the regions could not be used to measure metabolic activity is entirely unsupported by any peer review literature and instead simply represents the contrary view of their hired expert. See Exhibit 20, Mintun, 5/3/07 pp. 175-180.

**E. The limitations of the study were evident on the face of the article and addressed by the scientific team, and did not impair or negatively effect the conclusions of the authors or Dr. Bremner.**

While Roche cross-examined Dr. Bremner on the limitations of the study, these were all noted in the paper and therefore accepted by the scientific team in the context of the conclusions. See Exhibit 14, 5/31/06 Tr. at 174. Any such limitations certainly do not mandate the study is unscientific, and rather are the subject of cross examination.

**F. The PET scans were sufficiently visible for the purpose of determining brain function in the region.**

Again, lodged as a complaint, Roche suggests that the head positioning was such that there was insufficient evidence for evaluation of certain patients. The evidence is that scientific team had sufficient OFC for measurement of metabolic activity. There is no valid scientific evidence adduced to conclude that "clipped" scans are invalid for measuring metabolic activity and certainly to record evidence upon which this Court could rely to dispute Dr. Bremner's testimony that either the scans shown by the Defendants were not "off the brain" or such that there was not sufficient OFC region to measure metabolic activity appropriately. See, e.g., Exhibit 20, Mintun 5/3/07 pp. 33-34 (not saying need the entirety of the OFC to measure metabolic activity and has no peer review literature to cite that supports

any argument that not visualizing all the OFC means the scan is invalid). This is just a disagreement amongst experts. See Exhibit 20, Mintun 5/3/07 p. 34; 86-88.<sup>41</sup>

**G. Dr. Bremner has addressed other potential explanations for the changes in metabolic activity and ruled those out appropriately.**

Roche's complaint regarding ruling out other causes of the changes observed on PET scan also lacks compelling force. Dr. Bremner considered and ruled the other causes out – not a single other potential cause was identified by Roche which was not considered and ruled out. While Roche may want to disagree with the conclusion, it is the process of considering and ruling out that the Court must concern itself with, not developing an independent opinion as to which side the Court believes is correct.

**H. Defendants' references to mistakes and errors in study do not render the present state of the Dr. Bremner's opinions unscientific or science upon which he relies invalid.**

Any identified mistakes at another point in time do not render the current opinions unscientific or invalid or inadmissible. The methodology was valid and while there was mistakes in calculations, that does not render the methodology invalid.<sup>42</sup>

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<sup>41</sup> Interestingly, despite having the original scans, Dr. Mintun did not even bother to try draw the Regions of Interest, or consult with anyone on how to accomplish that task, to further test the work of the Emory scientific team. See Exhibit 20, Mintun 5/3/07 pp. 127-129.

<sup>42</sup> The suggestion that the Defendants must be able to verify every calculation before admissibility misstates the standard for admissibility under Rule 702 and Daubert. See, e.g., Cook, supra, at \* 42 (citing Bitler v. A.O. Smith Corp., 400 F.3d 1227, 1233 (10<sup>th</sup> Cir. 2004) (not necessary for party to demonstrate expert is indisputably correct to establish reliability under Rule 702); In re Paoli R.R. Yard PCB Litig., 35 F.3d 717, 744 (3<sup>rd</sup> Cir 1994) (“evidentiary requirement of reliability is lower than the merits standard of correctness) (Exhibit 43). The criticisms and attacks go to the weight not the admissibility of the testimony.

**I. Defendants invite error and scientific folly by confusing the import of the Skindex and the difference in metabolic activity at baseline.**

Serially, the Emory Study demonstrated overall a 16% decrease in brain activity in the Isotretinoin arm and a 1% increase in the antibiotic arm. This result was highly statistically significant. In an effort to undermine these results, Defendants confuse and mix-and-match scientific principles as to the significance of the Skindex questionnaire in relation to the changes seen on the PET scans.

First, as to the Skindex, the purpose of the questionnaire was not to substitute for, but to supplement, the constellation of clinical evaluations and represents only an evaluation by the dermatological clinicians as to the effect of acne on patients' feelings. There is no evidence that Skindex is validated as a psychological evaluation tool.<sup>43</sup> While it is apparent that the Skindex was not used for every subject, the purpose of the study was not to diagnose depression – it was to measure any affect of Isotretinoin on patients' brains. There was no correlation however at baseline between differences in OFC metabolic activity and feelings related to acne. See Exhibit 14, Tr. 5/31/06 at pp. 34-35. There is no dispute about this basic fact. See Exhibit 20, Mintun 5/3/07 at p. 75. However, Roche's speculates that perhaps the differences observed objectively on PET scan were due to active rumination, or thinking, during the PET scan itself. Issues of active rumination were (1) controlled through the methodology deemed scientifically valid and (2) would have logically been observed across both arms of the study if an issue.

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<sup>43</sup> As noted above, the one dermatologist on the scientific team, Dr. Chen, had unbeknownst to the scientific team at Emory, been retained by Roche during the pendency of the study.

Dr. Bremner provided a re-analysis of the Skindex information. Admittedly, these calculations had not initially been performed utilizing the post-treatment data since there was no correlation at baseline. Data, however, for 17 of the subjects was available and then considered by Dr. Bremner (for 16 as E13 was an excluded subject). The result was that:

There was no relationship in all subjects combined, Accutane subjects alone, or antibiotic subjects alone, between baseline orbitofrontal function or change in orbitofrontal function with treatment, and baseline total skindex score, Skindex item related to worry about skin condition, Skindex item related to effect of acne on work function, or depression related to skin condition.

Exhibit 44. However, Dr. Mintun did not even bother to analyze that data and therefore the testimony is unrebutted. See Exhibit 20, Mintun 5/3/07, p. 146.

Fundamentally, there is no scientific literature at all to support any claim or finding that normal worrying affects metabolic activity in brains of “normal” patients. See Exhibit 14, Tr. 5/31/06 at pp. 36-37. Yet, for this criticism Dr. Mintun relies upon articles involving patients with diagnosed Obsessive-Compulsive disorder or patients with drug addiction who were told to think about specific issues that affect them during the PET scan. See Exhibit 20, Mintun 5/3/07 pp. 76-82. Dr. Mintun can not point to a single peer reviewed article that suggests normal worrying could affect the results of a PET scan – instead, he relies upon studies with psychiatrically diagnosed patients and confirmed drug addicts. Id. Importantly, the scientific team utilized the Hamilton Depression Scale and other clinical evaluations to exclude and screen such study participants. See Exhibit 14, Tr. 5/31/06 at pp. 36-37.

**J. The secondary analysis of ratio of orbitofrontal cortex to global metabolism does not alter the important findings of the PET study, which was a highly statistically significant decrease in absolute OFC metabolic activity in the Accutane arm as compared to the antibiotic arm.**

Defendants spend a great deal of time arguing that the ratio of orbitofrontal cortex to global metabolism is an important finding. However, there is no peer reviewed literature to dispute Dr. Bremner's testimony that this secondary analysis is not important to the study findings and to his opinions, notwithstanding the calculation. The important statistic, according to Dr. Bremner, is the absolute metabolic changes as compared between the two groups. The conclusion is that there is a 16 percent decrease in the absolute metabolic activity of the orbitofrontal cortex for those in the Accutane arm as compared to a 1 percent increase in absolute metabolic activity in the antibiotic arm. As testified to by Dr. Bremner:

Well, the most important outcome of the study was absolute change in brain function, and that's why we went through the trouble of putting in the intravenous lines in the hand, feeding the hand and drawing the blood samples, so we could get the measurement of absolute brain metabolism.

The ratio of orbital frontal to global metabolism is a secondary analysis, and was not even touched on anywhere in the -- in the introduction or discussion in the paper, because the main discussion of the findings is related to the absolute measurement of the orbital frontal metabolism, it is a replication of what we have done in prior studies and was the primary outcome of the study.

See Exhibit 14, Tr. 5/31/06 at pp. 43-44.

The Defendants attempt to characterize the ratio as a mechanism for somehow correcting or controlling for error. However, Dr. Bremner absolutely and unequivocally disputed this characterization by Roche. See Exhibit 14, Tr. 5/31/06 at pp. 44-45; see also Exhibit 15, Tr. 7/12/06 at p. 82 (I would not agree with the word correction); at p. 85 ("I would not agree with the word control."). See also, Exhibit 12, Tr. 7/13/06 at pp. 80-81

(corrections for multiple comparisons does not mean error which had to be corrected for). Importantly, Dr. Mintun, Roche's own expert has authored articles involving the orbitofrontal cortex, and the effect of dopamine, finding that the greatest effect was in the OFC – and reported the absolute metabolic changes as the results for the that region. See Exhibit 20, Mintun 5/3/07, pp. 139-140; Exhibit 62.

In short, regardless of the statistical outcome of that secondary analysis the important results for the purposes of this case are the absolute metabolic changes. All other efforts to distract from the important findings are without evidentiary support and are not sufficient argument to restrict or strike Dr. Bremner's opinions.

**X. Dr. Mintun's opinion that the Emory Study would not have been published is sheer and utter speculation and not appropriate admissible scientific testimony.**

Roche now puts forward Dr. Mintun to speculate what reviewers might have done with the information obtained through the discovery and what decisions would have been made two years ago by a journal. This is sheer speculation. See Exhibit 20, Mintun 5/3/07, pp. 165-166. This testimony is inadmissible and should not be considered by the Court in this motion.

**XI. Defendants arguments with respect to the remaining Mechanisms of Action do not compel exclusion of the testimony.**

Dr. Bremner's report specifically set forth grounds for mechanism of action which are biologically plausible. See Exhibit 46, 23-26. Each of the additional grounds, Biotinadese,<sup>44</sup>

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<sup>44</sup> As outlined in Dr. Bremner's report, Exhibit 46, Accutane inhibits the biotinidase enzyme. See Exhibit 47, Schulpis, K; *The Effect of Isotretinoin on Biotinidase Activity*, Skin Pharmacol Appl Skin Physiol, 1999; 12:28-33. This can lead to decrease in biotin. Subjects fed a special diet with egg white and no biotin developed depression. See Exhibit 48, Sydenstricker, VP, *Observations on the "Egg White Injury" in Man and its Cure with a Biotin Concentrate*, JAMA 1942, 118(14):1199-1200. Therefore, Defendants' claim that the

Homocysteine,<sup>45</sup> Genetic Damage,<sup>46</sup> Galanin<sup>47</sup> and Serotonin<sup>48</sup> are supported by scientific basis or peer reviewed literature. Id. Roche entirely ignores the various citations in support and instead uses gross generalizations to attack Dr. Bremner. As outlined above,

The assessment process, that is, the process of examining whether “good grounds” exist, focuses on the methodologies the witness used to reach the opinion he or she will express, not the scientific *correctness* of the opinion. It is not part of the trial judge's gatekeeping role to determine whether the proffered opinion is scientifically *correct* or *certain* in the way one might think of the law of gravity. The gatekeeping role is addressed to mere evidentiary admissibility; it is the role of the fact-finder (usually a jury) to determine whether the opinion is correct or worthy of credence. For the trial court to overreach in the gatekeeping function and determine whether the opinion evidence is correct or worthy of credence is to usurp the jury's right to decide the facts of the case. All the trial judge is asked to decide is whether the proffered evidence is based on “good grounds” tied to the scientific method.

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biotin opinion is based upon case reports is simply not true. The study above is an experimental study demonstrating the effects of biotin deficiency on depression.

<sup>45</sup> Studies have in fact shown the homocysteine concentrations “in the normal range” are in fact associated with depression. Further, Roche's suggestion that there is no evidence that homocysteine levels in the normal range are not associated with depression is simply wrong. See, e.g. Exhibit 54, Chen, CS; *Homocysteine Levels, MTHFR C677T Genotype, and MRI Hyperintensities in Late-Onset Major Depressive Disorder*, Am J Geriatr Psychiatry, 2005; 13(10):869-875 (statistically significant higher number of patients as compared to controls had depression even though homocysteine levels measured in “normal” range). See also Exhibit 55, Martins, PJF; *Increased plasma homocysteine concentrations in shift working bus drivers*, Occup Environ Med 2003; 60:662-666.

<sup>46</sup> In fact, there is peer reviewed scientific literature supporting Isotretinoin causes DNA changes and damage. See, e.g., Exhibit 56 Georgala, S; *Isotretinoin therapy induces DNA oxidative damage*, Clin Chem Lab Med, 2005; 43(11):1178-1182. See also Exhibit 57, Bjelokovic, G, *Mortality in Randomized Trials of Antioxidant Supplements for Primary and Secondary Prevention*, JAMA, 2007; 297(8):842-857 (overall vitamin a and beta carotene increase cancer risk in a trial in which most of the participants were not smokers.

<sup>47</sup> Of tremendous significance, and not disputed, is that Accutane effects Galanin function.

<sup>48</sup> As set forth in the articles cited by Dr. Bremner, agomelatine blocks the 5HT2B receptor, developed as a treatment for depression. See Exhibit 58, Pandi-Perumal, SR, *Could agomelatine be the ideal antidepressant?*, Expert Rev. Neurotherapeutics; 6(11):1595-1608. Accutane has an effect on this receptor. See Exhibit 64. As such, it is clear that Accutane has an effect on receptors implicated in depression. the fact that multiple neurotransmitter and neuropeptide systems seem to be affected by Accutane does not diminish the evidence that Accutane affects brain regions involved in depression. See Exhibit 59, Holtzheimer, PE; *Future prospects in depression research*, Dialogues Clin Neurosci, 2006; 8:175-189. In fact, since depression is seen as a multi transmitter disease this actually strengthens the evidence for an association.

Brasher v. Sandoz Pharmaceuticals Corp., 160 F. Supp.2d 1291, 1295 (N.D. Ala., 2001). Importantly, biological plausibility is not equated with biological certainty. The mechanism of this drug on acne is a perfect example. As outlined above, while the company does not understand why Accutane effects acne production to a level of a certainty, there is no doubt it does. Science and medicine does not require biological certainty -- nor should this Court impose a higher standard upon science.

I HEREBY CERTIFY that on May 31, 2007, I electronically filed the foregoing Opposition to Defendants' Motion to Exclude the Testimony of J. Douglas Bremner, M.D. with the Clerk of the Court by using the CM/ECF system which will send a notice of electronic filing to counsel of record.

Respectfully submitted,

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**Index of Exhibits to Opposition to Defendants' Motion to Exclude Testimony  
of J. Douglas Bremner, M.D.**

| Exhibit |  |
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| 1       | Bremner's CV   |
| 2       | November 22, 2005 letter from Department of Health & Human Services to Executive Associate Dean of Emory University School of Medicine   |
| 3       | Excerpts of transcript of 5/24/06 hearing in Palazzolo v. Hoffmann-La Roche, pending in Essex County, New Jersey   |
| 4       | Isotretinoin (13-cis-Retinoic Acid) Drug Substance Stability Studies   |
| 5       | Protocol 471B  |
| 6       | ROCHE in Dermatology   |
| 7       | Manuscript No. W-141992  |
| 8       | Interoffice Correspondence from Robert J. Floody, M.D.   |
| 9       | Report No. N-34168   |
| 10      | Manuscript No. N-120035  |
| 11      | Accutane Product Info 1993   |
| 12      | Excerpts of transcript of 7/13/06 hearing in Palazzolo v. Hoffmann-La Roche, pending in Essex County, New Jersey   |
| 13      | O'Connell, K; <i>Isotretinoin (Accutane) and serious psychiatric adverse events</i> , J Am Acad Dermatol, 2003; 48(2):306-307  |
| 14      | Excerpts of transcript of 5/31/06 hearing in Palazzolo v. Hoffmann-La Roche, pending in Essex County, New Jersey   |
| 15      | Excerpts of transcript of 7/12/06 hearing in Palazzolo v. Hoffmann-La Roche, pending in Essex County, New Jersey   |
| 16      | Excerpts of Pharmacoepidemiology (Strom)   |
| 17      | Friedman, T; <i>Increased use of mental health services related to Isotretinoin treatment: A 5-year analysis</i> , Eur Neuropsychopharmacol, 2005; 16(6):413-416                       |
| 18      | List of articles reviewed by Dr. Bremner   |
| 19      | O'Reilly, K; <i>Chronic Administration of 13-Cis-Retinoic Acid Increases Depression-Related Behavior in Mice</i> , Neuropsychopharmacol, 2006; 31:1919-1927                            |
| 20      | Excerpts of the transcript of the deposition of Mark Mintun, M.D. taken on 5/3/07  |
| 21      | Temple, R; <i>Adverse Effects of Newly Marketed Drugs</i> , NEJM, 1979; 300(18):1046-1047  |
| 22      | Excerpts of transcript of Food and Drug Administration Center for Drug Evaluation and Research Meeting of The Dermatologic and Ophthalmic Drugs Advisory Committee, September 19, 2000 |
| 23      | FDA Memorandum of Meeting Minutes, July 17, 2001   |
| 24      | Memo from Kathryn O'Connell, August 1, 2001  |

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| 25 | Memo from Kathryn O'Connell, February, 1998   |
| 26 | Bremner, JD; <i>Functional Brain Imaging Alterations in Acne Patients Treated with Isotretinoin</i> , Am J Psychiatry, 2005; 162:983-991  |
| 27 | Excerpts of the transcript of the deposition of J. Douglas Bremner, M.D., taken on November 10, 2005  |
| 28 | Accutane White Paper: Epidemiology, authored by Kenneth Rothman   |
| 29 | Scheinman, P; <i>Acute depression from isotretinoin</i> , J Am Acad Derm, 1990; 22(6):1112-1114   |
| 30 | January 25, 2002 Email from Eileen Leach  |
| 31 | February 17, 2002 Email from Susan Ackermann  |
| 32 | Excerpts of the transcript of the deposition of John McLane taken on March 23, 2004   |
| 33 | Accutane Label Changes, February 1998   |
| 34 | NDA 21-177  |
| 35 | Accutane Meeting Minutes, October 10, 2000  |
| 36 | November 6, 1997 email from John McLane   |
| 37 | Document Bates No. PAL002611  |
| 38 | Excerpts of the transcript of the deposition of John McLane taken on November 17, 2005  |
| 39 | Excerpts of transcript of 10/2/06 hearing in Palazzolo v. Hoffmann-La Roche, pending in Essex County, New Jersey  |
| 40 | Excerpts of the transcript of the deposition of John McLane taken on December 6, 2005   |
| 41 | Black, K; <i>A possible substrate for dopamine-related changes in mood and behavior: Prefrontal and limbic effects of a D3-preferring dopamine agonist</i> , PNAS, 2004; 99(26):17113-17118 |
| 42 | Li, H; <i>Optimization of PET Activation Studies Based on the SNR Measured in the 3-D Hoffman Brain Phantom</i> , IEEE, 1998; 17(4):596-605   |
| 43 | Cook v. Rockwell International Corp., 2006 WL 3533049 (D. Colo.)  |
| 44 | August 1, 2006 Supplemental Report of Dr. Bremner   |
| 45 | Silverman, D; <i>Positron Emission Tomography in Evaluation of Dementia</i> , JAMA, 2001; 286(17):2120-2127   |
| 46 | Report of Dr. Bremner   |
| 47 | Schulpis, K; <i>The Effect of Isotretinoin on Biotinidase Activity</i> , Skin Pharmacol Appl Skin Physiol, 1999; 12:28-33   |
| 48 | Sydenstricker, VP; <i>Observations on the "Egg White Injury" in Man</i> , JAMA, 1942; 118(14):1199-1200   |

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| 49 | Chia, C; <i>Isotretinoin Therapy and Mood Changes in Adolescents With Moderate to Severe Acne</i> , Arch Dermatol, 2005; 141:557-560   |
| 50 | Ng, CH; <i>Prospective study of depressive symptoms and quality of life in acne vulgaris patients treated with isotretinoin compared to antibiotic and topical therapy</i> , Australasian Journal of Dermatology, 2002; 45:262-268 |
| 51 | March 25, 1999 email from Peter Schifferdecker; March 24, 1999 email from Hilal Kremers  |
| 52 | May 22, 2001 email from Saveria Scavone and attached Preclinical Presentation  |
| 53 | Defendants' Joint Response to Plaintiffs' Interrogatories dated December 2, 2005   |
| 54 | Chen, CS; <i>Homocysteine Levels, MTHFR C677T Genotype, and MRI Hyperintensities in Late-Onset Major Depressive Disorder</i> , Am J Geriatr Psychiatry, 2005; 13(10):869-875   |
| 55 | Martins, PJF; <i>Increased plasma homocysteine levels in shift working bus drivers</i> , Occup Environ Med, 2003; 60:662-666   |
| 56 | Georgala, S; <i>Isotretinoin therapy induces DNA oxidative damage</i> , Clin Chem Lab Med, 2005; 43(11):1178-1182  |
| 57 | Bjelakovic, G; <i>Mortality in Randomized Trials of Antioxidant Supplements for Primary and Secondary Prevention</i> , JAMA, 2007; 297(8):842-857  |
| 58 | Pandi-Perumal, SR; <i>Could agomelatine be the ideal antidepressant?</i> , Expert Rev. Neurotherapeutics, 2006; 6(11):1595-1608  |
| 59 | Holtzheimer, P; <i>Future prospects in depression research</i> , Dialogues Clin Neurosci, 2006; 8:175-189  |
| 60 | NDA 18-662 to FDA  |
| 61 | Abstract of Ferguson, S; <i>Chronic Oral Accutane (ACC), but not all-trans-retinoic acid (ATRA), treatment causes behavioral alterations in the forced swim test</i>   |
| 62 | Black, K; <i>A possible substrate for dopamine-related changes in mood and behavior: Prefrontal and limbic effects of a D3-preferring dopamine agonist</i> , PNAS, 2004; 99(26):17113-17118  |
| 63 | Woodard, J; <i>Compensatory Recruitment of Neural Resources During Overt Rehearsal of Word Lists in Alzheimer's Disease</i> , Neuropsychology, 1998; 12(4):491-504   |
| 64 | April 18, 2002 email from Linda Brady  |
| 65 | Ferguson, S; <i>Chronic Oral Treatment with 13-cis-Retinoic Acid (Isotretinoin) or all-trans-Retinoic Acid Does Not Alter Depression-Like Behaviors in Rats</i> , Toxicol Sciences, 2005; 87(2):451-459                            |

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| 66 | Wysowski, D; <i>Relationship Between Headache and Depression in Users of Isotretinoin</i> , Arch Dermatol, 2005; 141:640-641 |
| 67 | Meyskens, FL; <i>Short Clinical Reports</i> , Am Acad Dermatol, 1982   |