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ATLANTIC COUNTY
LAW DIVISION

COURT INITIATED

IN RE: ACCUTANE LITIGATION	SUPERIOR COURT OF NEW JERSEY LAW DIVISION: ATLANTIC COUNTY CIVIL ACTION NO.: 271 (MCL) ACCUTANE® MULTICOUNTY LITIGATION **ORDER**

THIS MATTER having come before the Court on Defendants' Motion to bar expert testimony; and the court having conducted a plenary hearing on February 6, 7, 8, 10, 13, 14 and March 8, 9, 10 and 13, 2017, at which time the court heard from Paul W. Schmidt, Esquire, Colleen M. Hennessey, Esquire, and Russell L. Hewit, Esquire, on behalf of Defendants in support of their application; and Plaintiffs opposing this Motion, David R. Buchanan, Esquire, Stephen F. Bolton, Esquire, Maryjane Bass, Esquire, Troy Rafferty, Esquire, Peter Samberg, Esquire, and Bill Cash, Esquire, appearing; and the Court having received expert testimony and oral argument of counsel conducted pursuant the standards articulated by our Supreme Court in *Kemp vs. The State of New Jersey* 174 *N.J.* 412 (2002), and for the reasons stated in the Memorandum of Decision of even date herewith; and for good cause shown;

IT IS ON THIS 13th DAY OF APRIL 2017, **ORDERED**:

1. Defendant's Motion to bar the testimony of Dr. David B. Sachar and Dr. April Zambelli-Weiner is hereby GRANTED.

2. Defense counsel shall prepare a form of Order reciting those lawsuits effected by this ruling – including Captions and Docket Numbers - and submit the same to the Court on or before May 19, 2017. Said Order will not be entered until Plaintiffs' counsel have an opportunity to be heard on the form of the same, particularly the precise Captions and Docket Numbers.

NELSON C. JOHNSON, JSC

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IN RE: ACCUTANE LITIGATION	**SUPERIOR COURT OF NEW JERSEY** **LAW DIVISION: ATLANTIC COUNTY** **CIVIL ACTION NO.: 271 (MCL)** **ACCUTANE® MULTICOUNTY LITIGATION** ***OPINION***

RE: *KEMP* HEARING ON BROAD ISSUE OF ULCERATIVE COLITIS

DECIDED: APRIL 13, 2017

APPEARANCES: DAVID R. BUCHANAN, ESQUIRE, PLAINTIFF
STEPHEN F. BOLTON, ESQUIRE, PLAINTIFF
MARYJANE BASS, ESQUIRE, PLAINTIFF
TROY RAFFERTY, ESQUIRE, PLAINTIFF
PETER SAMBERG, ESQUIRE, PLAINTIFF
BILL CASH, ESQUIRE, PLAINTIFF

PAUL W. SCHMIDT, ESQUIRE, DEFENDANT
COLLEEN M. HENNESSEY, ESQUIRE, DEFENDANT
RUSSELL L. HEWIT, ESQUIRE, DEFENDANT

NELSON C. JOHNSON, J.S.C.

HAVING CAREFULLY REVIEWED THE MOVING PAPERS AND RESPONSES FILED, I HAVE RULED ON THE ABOVE CAPTIONED MATTER AS FOLLOWS:

FORWARD

The issues raised herein arise out of the proceedings known as the "Accutane Litigation." The instant matter is before the Court on the Motion of the Defendants, Hoffman La Roche, et al., seeking an Order to bar the expert testimony of Plaintiffs' two witnesses on general causation. The claims of the Plaintiffs herein assert that the prescription medication Accutane (hereinafter "isotretinoin"), has caused them to develop Ulcerative Colitis, a chronic condition

which is one of the gastrointestinal illnesses generally referred to as Inflammatory Bowel Disease. A similar challenge involving the experts on the claims involving Crohn's Disease was addressed by this Court in its ruling of February 20, 2015.

Defendants' challenge to the admissibility of the testimony of Plaintiffs' experts was heard at a plenary hearing conducted pursuant to the standards articulated by our Supreme Court in *Kemp v. State of New Jersey*, 174 *N.J.* 412 (2002), (hereinafter the "*Kemp* Hearing"), and in accordance with the standards of *Evid. R.* 104. The Court conducted said hearing on February 6, 7, 8, 10, 13, 14 and March 8, 9, 10 and 13, 2017. The undersigned has made every effort to respect, consider, and fairly weigh the testimony of the witnesses and the arguments of counsel.

I. INTRODUCTION: OVERVIEW OF ACCUTANE LITIGATION

"Insane." That was the word chosen by Plaintiffs' expert to denigrate an aspect of the methodology of a peer-reviewed scientific treatise presented to him by counsel. Dr. David Sachar is a well-educated, well-traveled, and well-paid witness who tends to be a bit too enthusiastic. When considering the many hearings the undersigned has conducted on the validity of an expert's opinions, Dr. Sachar's exclamations from the witness chair are a memorable first. His testimony is at odds with his Curriculum Vitae; from a review of the same, one anticipates a person more precise, concise and restrained. Restrained, this gentleman is not. On multiple occasions, Dr. Sachar's own words revealed: a lack of respect for colleagues in his field; an inability to concede that some of his present opinions contradict past opinions; and all too frequently, indifference to the scientific method, particularly the medical-science hierarchy. Dr. Sachar's enthusiasm for his opinions on behalf of Plaintiffs betray his stature.

Pursuant to *R.* 4:38A, on May 2, 2005, the New Jersey Supreme Court designated this litigation as a Multi-County Litigation (MCL), to receive centralized management by this Court. To date, a total of 8,431 Complaints have been filed with this Court. Of those a total of 13 matters have gone to trial in 8 separate jury trials. The record/status of each proceeding and the ailment(s) complained of by the individual Plaintiffs has, with assistance of counsel, been compiled in a "scorecard" (so termed by the Court and counsel) attached hereto as "Addendum A" (Plaintiff) and "Addendum A-1" (Defendant). As confirmed by the Addenda, the initial trials in the Accutane Litigation – and the proofs presented therein – went forward without

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regard to any distinction being made as to the precise nature of those Plaintiffs' conditions; a distinction presently urged upon the Court by Plaintiffs' counsel.

Throughout the past 14 years, Dr. Sachar has been a mainstay of this MCL. The record of the 8 separate trials on 13 individual Plaintiffs' claims is replete with his testimony. In various trials, Plaintiffs' claims have been referenced as Inflammatory Bowel Disease ("IBD") generally, or Ulcerative Colitis ("UC"), or Crohn's Disease ("CD"). In each instance, utilizing various lines of evidence, Dr. Sachar testified that Accutane was the cause of Plaintiffs' ailments. His testimony has been previously found admissible by the undersigned's predecessor. The Appellate Division confirmed that the trial court had not abused its discretion by permitting such testimony.

Notwithstanding the above, the distinction(s) between UC and CD cited by Plaintiffs' counsel appear to be of little consequence. During a colloquy between the Court and Dr. Sachar, he acknowledged that regardless of the differences in the risk factors and ailments, the biological mechanism for both UC and CD would essentially be one and the same. With regard to the beginning point of either disease, *viz.*, "the epithelial layer somehow gets damaged," Dr. Sachar testified that, "There's no dichotomy in terms of biological plausibility." (See Transcript of February 8, 2017, P12, L24 thru P15, L12.)

II. POSTURE OF ISSUES BEFORE THE COURT

The first lawsuit in the Accutane Litigation in the Superior Court of Atlantic County was filed on July 23, 2003. Throughout the past 13(+) years, significant efforts by many professionals have been exerted to clarify the issues raised by Plaintiffs' claims. Presently before the Court is a challenge brought by the Defendants to the Plaintiffs' contention that, among genetically pre-disposed persons, the ingestion of isotretinoin can be a proximate cause of Plaintiffs' UC.

Counsel for the Plaintiffs have argued repeatedly that this *Kemp* hearing is unnecessary and that the Court ought to abide by the several rulings of the Appellate Division sustaining the prior rulings of this Court's predecessor. As this Court reads the several opinions relied upon by Plaintiffs, to wit, (1) *McCarrell v. Hoffman-La Roche, Inc., et al.*, No. A-3280-07T1, 2009 *N.J. Super. Unpub.* LEXIS 558 *(App. Div. Mar. 12, 2009);* (2) *Kendall v. Hoffman[n]-La Roche, Inc.*, No. A-2633-08T3, 2010 *N.J. Super. Unpub.* LEXIS 1904 (App. Div. Aug. 5, 2010); (3)

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Sager, Speisman, Mace v. Hoffman[n] – La Roche, Inc., No. A-3427-09, A-3428-09, A-3702-09, 2012 *N.J. Super. Unpub.* LEXIS 1885 (App. Div. Aug. 7, 2012); (4) *Gaghan, Andrews, Marshall v. Hoffman[n] – La Roche, Inc.*, No. A-2717-11, A-3211-11, A-3217-11, 2014 *N.J. Super. Unpub.* LEXIS 1985 (App. Div. Aug. 4, 2014); and (5) *McCarrell v. Hoffman-La Roche, Inc., et al.*, No. A-4481-12T1, 2015 *N.J. Super. Unpub.* LEXIS 1925 (App. Div. Aug. 11, 2015), those rulings were unpublished, and thus subject to the limitations of *R.* 1:36-3. Moreover, though the opinions of Dr. Sachar were admitted at several trials, additional scientific evidence has come to the fore since then. [Note: This issue is addressed more fully in Section III below.]

In evaluating the totality of the evidence presented by Plaintiffs, the Court's task may be stated as follows: *Query*, have the Plaintiffs shown that their experts' theories of causation are sufficiently reliable as being based on a sound, adequately-founded scientific methodology, to wit, relying upon methods upon which experts in their field would reasonably rely in forming their own (possibly different) opinions about what caused the Plaintiffs' disease? Courts are experts in the law, not science. This Court's review "is as broad as the breadth of the proffer and the challenges thereto that the parties present." See *Hisenaj v. Kuehner*, 194 *N.J.* 6, 16 (2008). Accordingly, this Court's role is that of a "gatekeeper" who – based upon the proofs presented by the parties – must assess whether or not the methodology and hypothesis of causation advanced by Plaintiffs' experts is sufficiently reliable to be presented to a jury.

III. APPLICABILITY OF PRIOR RULINGS

Receiving guidance from the case law cited herein and acknowledging this Court's role as "gatekeeper," the Court considers the applicability of its predecessor's rulings. The law of the case doctrine is a non-binding, discretionary principle designed to prevent re-litigation of a previously resolved issue. *Lombardi v. Masso*, 207 *N.J.* 517 (2011). This doctrine applies to the question of whether a decision made by a trial court during one stage of the litigation is binding throughout the course of the action. *State v. Hale*, 127 *N.J. Super.* 407 (App. Div. 1974). The Court is cognizant that the law of the case doctrine is not definitive and "should not be used to justify an incorrect substantive result," *Hart v. City of Jersey City*, 308 *N.J. Super.* 487, 498 (App. Div. 1998). *State v. K.P.S.*, 221 *N.J.* 266, 276-82 (2015).

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Courts may give deference to prior rulings; however, analogous to the concept of collateral estoppel, the law of the case doctrine does not prevent a court from revisiting an issue "when it would be inequitable or contrary to the interests of fairness and justice." *Id.* at 278. "The distinction between the doctrine of 'law of the case' and *res judicata* is readily apparent: 'one directs discretion; the other supersedes it and compels judgment. In one it is a question of power, in the other of submission.' Law of the case therefore operates as a discretional rule of practice and not one of law." *Hale, supra*, 127 *N.J. Super.* at 411; *see also Ayers v. Jackson*, 106 *N.J.* 557, 612 (1987) (affirming that the law of the case doctrine "does not prohibit one judge from reviewing the prior ruling of another judge"). Accordingly, the Court recognizes that the law of the case doctrine does not preclude Defendants from renewing their challenges of Dr. Sachar's opinions in light of the most current scientific studies.

Furthermore, the dicta contained in the rulings made by the Court's predecessor, admitting the testimony of Dr. Sachar, are not binding upon this Court. In pertinent part, *R.* 1:36-3 states: "No unpublished opinion shall constitute precedent or be binding upon any court." Therefore, unpublished opinions may be considered by courts as informative, and possibly persuasive, but they are not precedential authority. Thus, the rulings made by the Court's predecessor are non-binding; this is particularly true in light of the more recent scientific studies, and the modified testimony of the witnesses presented.

Upon reviewing the relevant portions of the *New Jersey Multi County (Non-Asbestos) Resource Book*, 4th Edition 2014, the Court acknowledges that rulings in MCL litigation should be treated with deference. Parties should not be permitted to file the same motions repeatedly in an attempt to the change the Court's prior rulings. However, if there have been developments to the relevant science, which may change the appropriateness of the Court's earlier rulings, then such information is pertinent to future decisions in this litigation. The fields of science are dynamic; established scientific theories are frequently altered by newly discovered facts. Accordingly, if the scientific community has produced new studies that raise the need to revisit prior conclusions of the Court regarding a causal relation between isotretinoin and UC and IBD generally, then this Court is obligated to conduct a review of all reliable scientific evidence currently available.

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IV. REVIEW OF APPLICABLE SCIENTIFIC LITERATURE

As part of the Court's preparation for the *Kemp* Hearing, the undersigned reviewed an extensive assemblage of peer-reviewed articles and various scientific treatises, particularly those cited by the witnesses in their written reports.

A. BRADFORD HILL CRITERIA

The Bradford Hill criteria should be acknowledged, either initially or by way of summary, in any discussion of the method(s) by which scientists seek new knowledge on a given scientific question. This is particularly true when epidemiological studies are part of the proofs.

In 1965, respected scientist and pioneer in medical statistics, Sir Austin Bradford Hill (1897-1991), made a speech before a group of colleagues wherein he attempted to articulate those essential benchmarks which the scientific community must consider in distinguishing between causal and non-causal explanations of observed associations. That speech is likely the most widely-published and quoted after-dinner speech delivered by a physician. As posed by Hill, the question for scientists is, "In what circumstances can we pass from this observed association to a verdict of causation?"

In using the term "association," Hill meant a connection between an agent and an ailment arising from something more than mere chance, or as defined by the *Reference Manual,* "The term is used to describe the relationship between two events that occur more frequently together than one would expect by chance." And as noted by the *Reference Manual, "... an association is not equivalent to causation.*" (Emphasis in text, page 552.) Hill notes that his criteria were only meant to apply where chance could be ruled out. Namely, before assessing the potential of a causal association, Hill chides his fellow scientists: "Our observations [must] reveal *an association between two variables perfectly clear-cut and beyond what we would care to attribute to the play of chance*. What aspects of that association should we especially consider before deciding that the most likely interpretation of it is causation." (Emphasis added.)

Accordingly, in determining whether an observed association between a chemical and a disease is causal (*i.e.*, general causation), Hill advised scientists that they should focus upon various "aspects of that association." Those "aspects" or factors which must be scrutinized, are often referred to as the "Hill criteria."

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These factors include: (1) **strength** of association (*i.e.*, is the association "clear-cut," *viz.*, strong and statistically significant?); (2) **consistency** of the relationship (*i.e.*, whether it has been repeatedly observed in other persons?) (3) **specificity** of association (*i.e.,* is there a particular association between the substance and the condition it purportedly causes?*)*; (4) **temporality** (are the cause and effect bound in time, or as Hill states, "which is the cart and which is the horse?); (5) **biological gradient** (does the association reveal a dose-response curve?); (6) **plausibility** (*i.e.*, whether there exists a biologically plausible *mechanism* by which the agent could cause the disease?); (7) **coherence** (does cause-and-effect interpretation of the data conflict with the history and biology of the disease?); (8) **experiment** (is the frequency of the associated events affected by reducing the amount of the suspected substance?); (9) **analogy** (should science anticipate similar results from a consideration of alternative explanations?). Here, regarding isotretinoin and IBD (and UC), though most of the factors come in for consideration to varying degrees; this is particularly true for factors 1, 2, 3, 4, and 6.

When, as here, the relative risk is significantly less than "2.0", factor #6 becomes increasingly important. As advised by the *Reference Manual* (at page 554), "Three basic issues arise when epidemiology is used in legal disputes ..." (1) does the study reveal an association?; (2) could the association have resulted in bias, confounders, etc.?; and (3) "how plausible is a causal interpretation of the association?" Plausibility matters. If there is no coherent theory tying the scientific evidence together to postulate *how* the agent causes the ailment, the fact-finder is being asked to speculate.

Finally, Hill's criteria and overall philosophy admonish scientists to be faithful to the scientific method. Scientists (and our courts) must pursue the truth without regard to fear or favor. "The evidence is there to be judged on its merits and the judgment (in that sense) should be utterly independent of what hangs upon it – or who hangs because of it."

B. EPIDEMIOLOGICAL STUDIES

There are two types of epidemiological studies: (1) experimental studies; and (2) observational studies. Experimental studies, in the form of randomized clinical trials or true experiments, are the highest form of scientific evidence, usually comprised of two groups: one exposed to the agent in question, and the other not exposed. In observational studies,

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individuals who have been exposed to the agent at issue are observed and compared to a group of individuals who've never been exposed to the agent.

The two primary types of observational studies relevant to these proceedings (*viz.*, epidemiological studies) are (1) cohort studies, and (2) case-control studies. Cohort studies compare the incidence of disease among individuals exposed to a substance with an unexposed group. Case-control studies examine the frequency of exposure in individuals who presently have the disease and compare them to a group of individuals who do not have the disease.

Epidemiological studies provide "the primary generally accepted methodology for demonstrating a causal relation between a chemical compound and a set of symptoms or disease." See *Conde v. Velsicol Chem. Corp.*, 804 *F. Supp.* 972, 1025–26 (S.D. Ohio, 1992), *aff'd.*, 295 *F. 3d* 1194 (11th Cir. 2002). When a scientific rationale does not exist to logically explain the biological mechanism by which an agent causes a disease, courts may consider epidemiological studies as an alternate means of proving general causation. According to the *Reference Manual*, at page 723-24, large epidemiological studies present some of the strongest medical/scientific evidence. The typical use of large population-based studies is in connection with "general causation." As noted in the *Reference Manual* at page 623, general causation is concerned with "whether an agent increases the incidence of disease in a group and not whether the agent caused any given individual's disease." Nonetheless, the *Reference Manual* at page 552-3 cautions trial judges that "[a]n association is not equivalent to causation. An association identified in an epidemiological study may or may not be causal. Assessing whether an association is *causal* requires an understanding of the strengths and weaknesses of the study's design and implementation, as well as a judgment about how the study findings fit with other scientific knowledge." (Emphasis in the original text.)

Additionally, as noted by the Court in *Soldo vs. Sandoz Pharms Corp.*, 244 *F. Supp. 2d* 434 at 466 (W.D. PA. 2003), epidemiological studies are critical in proving cause and effect in a claim such as this.

> The very purpose of epidemiology is to serve the type of testing function required by *Daubert*, i.e., to discern accurately the effect of a particular agent on a disease against the background of the natural occurrence of the disease in the relevant population. Stated otherwise, epidemiology is the scientific methodology that allows testing of the hypothesis that substance A causes effect B.

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Epidemiological studies attempt to identify agents that are associated with an increased risk of disease. An association is "clear-cut" when the association between exposure to an agent and a disease occurs more frequently than by mere chance. In that situation, the association is referred to as *significant.* "Statistically significant" means that the scientific community recognizes that the association between two or more variables is caused by something other than "random chance." Once a significant association is observed, the scientist undertaking the study must assess the *strength* of the association, plus whether the reason for the observed association is due to *bias, chance or a genuine effect.*

A measure of the strength of an association in an epidemiological study can be expressed in terms of its "relative risk" (hereinafter "R/R"). R/R indicates the difference in the risk of contracting a disease in people exposed to a substance, as compared to those who are unexposed but are otherwise similar, here the young adult population suffering from acne. Determining the R/R is important in understanding the results of a study because virtually every disease associated with a risk factor also occurs, at some rate, in the general population among study participants who are unexposed to the risk factor.

Also relevant is the Odds Ratio ("O/R") which is similar to R/R in that it expresses in quantitative terms the association between exposure to an agent and a disease. "It is a convenient way to estimate the relative risk in case-control study when the disease under investigation is rare. The odds ratio approximates the relative risk when the disease is rare." *Reference Manual* at page 568.

R/R is commonly calculated by dividing the risk of developing a disease observed in an exposed group by the risk observed in an unexposed, but similar, group. If the risks of the unexposed and exposed are the same, then the relative risk estimate (which mathematically is simply the former divided by the latter) is "1.0", also termed "null." The null value indicates that exposure is not associated with the disease in that study. Thus, an R/R of "1.0" means that the agent has no effect on the incidence of disease. Similarly, if the R/R estimate is "1.3," then risk appears to be 30% higher among the exposed compared to the non-exposed. An R/R of "2.0" indicates that the risk is twice as high among the exposed group as compared to the unexposed group. As discussed in the *Reference Manual* at page 612, note 192, there exists "... considerable disagreement on whether a relative risk of 2.0 is required or merely a taking-off point for

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determining sufficiency ...". As cautioned by the *Reference Manual*, the closer the R/R is to the null (or the further it is from 2.0), the greater the concern for bias or confounding.

Generally, there are three reasons that a positive association may be observed: (a) bias (including confounding factors), (b) chance, and (c) real effect. Each must be evaluated to extract a valid message from the study. Evaluation of these factors measures the "internal validity" of an epidemiological study, *viz.*, the extent to which a particular study's findings are viable and sound. "Bias" in epidemiology is systematic error, which includes "confounding bias." The underlying impact of these biases is to make the two groups being compared different in more ways than just the variable being studied. Sources of bias must be considered in interpreting an epidemiological study because bias can produce an erroneous association. *Reference Manual* at pages 591-3.

The record of the *Kemp* Hearing conducted by the Court is replete with testimony, argument, and legal briefs regarding the significance to be attached to various studies conducted by epidemiologists on the possible association of isotretinoin and IBD. That said, this Court's review of the various studies is also informed by the admonishment of the *Reference Manual* at page 576:

> Common sense leads one to believe that a large enough sample of individuals must be studied if the study is to identify a relationship between exposure to an agent and disease that truly exists. Common sense also suggests that by enlarging the sample size (the size of the study group), researchers can form a more accurate conclusion and reduce the chance of random error in their results...With large numbers, the outcome of test is less likely to be influenced by random error, and the researcher would have greater confidence in the inferences drawn from the data.

Finally, as to epidemiological studies, the more familiar the undersigned has become with such studies, the greater the respect for the significance of "size." A significant portion of peer-reviewed articles are the product of what essentially amounts to *mining the numbers*. That phrase is intended to convey the reality (and methodology) in the scientific community that many studies utilize the same data; different scientists revisit the data gathered in earlier studies to extract (or *mine)* new conclusions as a result of further analysis. Thus, the "size" of an epidemiological study is fundamental to its value to the scientific community.

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C. PEER-REVIEWED SCIENTIFIC TREATISES

When assessing scientific evidence, judges must make use of the institutional mechanisms developed by the scientific community to assure that the opinions expressed by scientists are consistent with the appropriate scientific criteria. One of the primary mechanisms is the peer-review process. Research subjected to the peer-review process undergoes a level of scrutiny that non-reviewed research does not. Trial judges must independently assess the scientific evidence offered; evaluating the validity of scientific information entails considering a variety of authorities. Research, which has survived the peer-review process affirmatively stating that there is a causal association between isotretinoin and IBD, would inform the Court that there is some consensus in the scientific community supporting Plaintiffs' contentions.

In one of the early subchapters of the *Reference Manual* entitled, "Some Myths and Facts About Science," the authors address the ethics of scientists:

> *Myth:* Scientists are people of uncompromising honesty and integrity.
>
> *Fact:* They would have to be if [Sir Francis] Bacon were right about how science works, but he was not. Most scientists are rigorously honest where honesty matters most to them: in the reporting of scientific procedures and data in peer-reviewed publications. In all else, they are ordinary mortals. (Page 50.)

In this instance, the scientific method does not demand a definitive etiology of IBD, nor precisely how isotretinoin causes that ailment but, rather, the articulation of a plausible hypothesis arrived at by reliable methodology and scientific evidence. The most direct means for demonstrating the plausibility of such a hypothesis and the reliability of the methodology utilized in support of the same is through the peer-review process. The U.S. Supreme Court encouraged trial courts to inquire as to whether or not Plaintiffs' experts have submitted their methodology and findings to the peer-review process. In *Daubert v. Merrell Dow Pharms.* 509 *U.S.* 579, 593 (1993), the Court stated, "Another pertinent consideration is whether the theory or technique has been subjected to peer review and publication."

Daubert's stress on the presence of peer-review and publication corresponds well with scientists' perceptions. "If something is not published in a peer-reviewed journal, it scarcely counts. Scientists only begin to have confidence in findings after peers, both those involved in the editorial process and, more important, those who read the publication, have had a chance to

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dissect them and to search intensively for errors either in theory or in practice. It is crucial, however, to recognize that publication and peer-review are not in themselves enough. The publications need to be compared carefully to the evidence that is proffered." (See the *Reference Manual* at page 786.)

D. META-ANALYSES

Meta-Analysis is a scientific tool for pooling the results of multiple epidemiological studies and thereby blend their results so as to arrive at a single figure which best illustrates the fullness of all the studies being considered. The goal is to better understand the results of all of the studies within the context of one another. Because of differences in size, populations, potential biases, methods utilized, and results, sometimes a meta-analysis is the only means to achieve a definitive conclusion regarding an "association." As noted by the *Reference Manual*, meta-analysis is "...a way of systematizing the time-honored approach of reviewing the literature, which is characteristic of science, and placing it in a standardized framework with quantitative methods for estimating risk. In a meta-analysis, studies are given different weights in proportion to the sizes of their study populations and other characteristics." (Page 607.)

Yet the analysis of multiple epidemiological studies, involving large and diverse populations, poses a greater challenge than a review of the scientific "literature" and the results of controlled clinical trials. Again, as noted by the *Reference Manual*, "...when meta-analysis is applied to observational studies – either case-control or cohort – it becomes more controversial. The reason for this is that often methodological differences among the studies are much more pronounced than they are in randomized trials. Hence, the justification for pooling the results and deriving a single estimate of risk, for example, is problematic." (Page 607.) By way of illustration, a sampling of the issues which can create instant challenges to the results of a meta-analysis include everything from the size of the studies and the potential confounders, to the heterogeneity (or lack thereof) of a study and whether or not a study has been peer-reviewed. An example of this final challenge/issue is the non-peer-reviewed Sivaraman abstract.

The challenges inherent in the results of virtually any meta-analysis should give rise to concerns by the "gatekeeper." Absorbing, and fully understanding the terminology and methods of epidemiological studies and meta-analyses can be a daunting task for the lay person serving as

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a juror. This Court had several weeks to review the witnesses' reports and the information and studies they relied upon in developing their opinions. Permitting an epidemiologist to take the witness stand before a panel of lay jurors heightens the trial court's obligation to carefully scrutinize the evidentiary foundations and methodology of every scientific witness. [NOTE: the meta-analyses performed by Plaintiffs are attached hereto as Addendum D; those for Defendant are attached as Addendum E.]

E. ANIMAL STUDIES

There was much discussion of animal studies, primarily those involving dogs, throughout the *Kemp* hearing. This Court does not understand why Plaintiffs' counsel and experts placed reliance on the mere fact that a dose of isotretinoin given to a beagle could cause inflammation in the dog's intestines. Such inflammation may be hypothesis-generating, but it is not evidence of causation. The *Reference Manual* advises trial judges on the value to be assigned to animal studies and states, at page 563:

> Animal studies have two significant disadvantages, however. *First*, animal study results must be extrapolated to another species – human beings – and differences in absorption, metabolism, and other factors may result in interspecies variation in responses. ... In general, it is often difficult to confirm that an agent known to be toxic in animals is safe for human beings. The *second* difficulty with inferring human causation from animal studies is that the high doses customarily used in animal studies require consideration of the dose-response relationship and whether a threshold no-effect does exists. Those matters are almost always fraught with considerable, and currently unresolvable, uncertainty.

Because dogs are also mammals and their intestines are similar to those of humans, the results of such testing may be helpful in determining whether or not a particular chemical substance can cause harm to the intestines. That said, the results of the tests proffered by Plaintiffs' experts, namely, those performed by Defendant prior to marketing Accutane, provide no meaningful support for Dr. Sachar's opinions. Whether or not any of the harm caused by isotretinoin to the dogs' intestines is permanent cannot be known for two reasons: *first,* the dogs in the experiment are dead, euthanized upon completion of the testing; and *second*, dogs cannot develop IBD. Both Dr. Sachar and Dr. Zambelli-Weiner agree that IBD is not a condition from which dogs ever suffer.

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F. CASE REPORTS OF ADVERSE EVENTS

On multiple occasions during the *Kemp* hearing Plaintiffs' counsel and expert witnesses cited to individual case reports as basis for asserting a causal relationship between isotretinoin and UC. It is generally accepted in the scientific community, and a maxim of accepted scientific methodology that case reports are hypothesis-generating *only*, and may be relied upon to postulate a scientific theory but are not scientific proof of anything. Stated simply, case reports are little more than anecdotes. Anecdotal information can be helpful in possibly serving as a catalyst for further scientific inquiry and analysis, but it proves little.

The *Reference Manual* (page 724) ranks case reports at the bottom of the medical-evidence hierarchy. Such reports are typically based upon a single, or relatively small number of individual patients and the particular anecdotes concerning those patients as reported by a treating physician. Such information can be extremely valuable in creating "signals" which may form the basis of a hypothesis, but such information is no more than hypothesis-generating and not capable of testing a hypothesis.

The FDA has issued guidelines for the use of case reports. At page 7 of *Guidance for Industry-Good Pharmacovigilance*, the FDA says:

> For any individual case report, it is rarely possible to know with a high level of certainty whether the event was caused by the product. To date, there are no internationally agreed upon standards or criteria for assessing causality in individual cases, especially for events that often occur spontaneously (e.g. stroke, pulmonary embolism). Rigorous pharmacoepidemiologic studies, such as case-control studies and cohort studies with appropriate follow-up, are usually employed to further examine the potential association between a product and an adverse event.

G. RISK FACTORS FOR IBD

Providing the Court with further "context" as to risk factors for IBD were two extensive review articles. Those treatises are: Dr. Siew C. Ng, "Geographical variability and environmental risk factors in inflammatory bowel disease." *GUT,* January 18, 2013, [NOTE: presented at the CD *Kemp* hearing] and, Alexis Ponder and Millie D. Long, "A clinical review of recent findings in the epidemiology of inflammatory bowel disease." *Clinical Epidemiology,* 2013:5 237-247. These are comprehensive reviews. The S.C. Ng, et al. study reviews nearly 200 treatises; Ponder and Long nearly 100. The authors of these two review articles agree on many

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findings, but one in particular which concurs with the *Federal Manual*, namely, the need for large epidemiological studies to learn more about IBD.

S.C. Ng., et als. conclude in part, and recommend:

> Multicentre prospective cohort studies that follow large numbers of healthy individuals and at-risk first-degree relatives with high-risk genotypes to a new diagnosis of IBD are required to determine environmental risk factors.

Ponder and Long conclude in part, and recommend:

> As IBD is a relatively rare disorder, with complicated interactions between potential inciting agents, very large cohorts with detailed, prospectively collected, environmental exposure data will be needed.

Finally , after 30(+) years following FDA approval of Accutane, neither of these extensive studies even mentions isotretinoin as a "risk factor" for IBD.

H. ROCHE INTERNAL DOCUMENTS

Plaintiffs' counsel made extensive use of memoranda prepared by Roche staff members during the early years of marketing Accutane. Some of those memos reported on concerns that users of Accutane might be developing intestinal disorders as result of their exposure to the drug. Some of those memos expressed thoughts about various marketing and labeling issues by Roche staff regarding the introduction of Accutane to the market. Plaintiffs placed particular emphasis on the "LeFrancq Memo." With the exception of animal studies, the contents of the various memos were largely based upon anecdotal information collected from various sources, in a generally unsystematic manner.

Plaintiffs' counsel likewise made extensive use of highly selective portions of various deposition testimony of Roche staff members regarding certain concerns about various marketing and labeling decisions by Roche staff. Taken out of context, some of that testimony raised issues regarding what Roche knew as it was making its presentations to the FDA; considered within a broader context, they raised few issues of substance.

Though the Roche internal documents and deposition designations would likely be admissible at a trial, what Roche employees were thinking in the early years of marketing Accutane is not the issue presently before the Court. The issue before the Court is the validity of the methodology used by Plaintiffs' expert witness in arriving at their opinions. Defendants have

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made a motion to bar the testimony of Plaintiffs' two experts. It is their testimony and methodology utilized in arriving at their opinions which is under scrutiny.

I. INDIVIDUAL TREATISES SCRUTINIZED BY THE COURT

A listing of those scientific articles on which a very significant portion of the testimony before the Court was presented and examined in assessing the methodology of the Plaintiffs' experts is attached as Addendum B. The "Joint Master Exhibit List – Court Exhibit C-UC17-23" prepared by legal counsel (with exceptions) is a complete list of those scientific articles, studies and reports of epidemiological studies submitted by counsel in preparation for the *Kemp* hearing. That Exhibit List is part of the Court's record on this *Kemp* hearing.

What follows is a brief discussion of those scientific articles discussed more frequently by the several witnesses during the *Kemp* hearing.

A. Crockett, 2009. "A Causal Association Between Isotretinoin and Inflammatory Bowel Disease has yet to be Established." This report begins by stating "In a recent court case in New Jersey, a jury awarded $12.9 million to three patients who were diagnosed with inflammatory bowel disease..." and appears to have been written shortly after the decision in *Sager, Speisman, Mace vs. Hoffman[n]-LaRoche, Inc.*, No. A-3427-09, A-3428-09, A-3702-09, 2012 *N.J. Super. Unpub.* LEXIS 1883 (App. Div. Aug. 7, 2012). The article references the Reddy, et al. review of "the FDA Med Watch reports of IBD cases occurring in association with isotretinoin use." Dr. Crockett notes that "published case reports and case series, as well as related court decisions, must be interpreted with caution" and that case reports are "hypothesis generating" only. He then lists the flaws associated with case reports.

   At p. 2389 of his report Dr. Crockett compares the background incidence of IBD in the U.S. with that of people taking isotretinoin. His analysis of the then number of Med Watch reports reveals fewer case reports than expected and "demonstrates that a certain number of cases of IBD are likely to develop in isotretinoin users simply on the basis of chance." As to biological plausibility, Dr. Crockett notes, "Given that the etiology of IBD is largely unknown, it is difficult to assess the plausibility of isotretinoin as a trigger of IBD. In fact, the mechanistic studies that are available in the published literature could support a beneficial effect of vitamin A derivatives in regard to the development and perpetuation of IBD."

B. Bernstein, 2009. "Isotretinoin Is Not Associated With Inflammatory Bowel Disease: A Population-Based Case-Control Study." The case-control study comprised approximately 21,500 subjects and found that 1.2% of IBD cases used isotretinoin before IBD diagnosis, which was significantly similar to the controls (1.1% users).

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The authors concluded: "Although there may be anecdotes of isotretinoin causing acute colitis, our data suggest that isotretinoin is not likely to cause IBD."

C. Crockett, 2010. "Isotretinoin Use and the Risk of Inflammatory Bowel Disease: A Case-Control Study." This study was pointed to repeatedly by Plaintiffs' experts and legal counsel in support of their contention that there is a causal association between isotretinoin and UC. The case-control study comprised approximately 29,000 subjects and found that there was a "possible association" between UC but not CD. Once again, Dr. Crockett notes that "Evidence supporting a causal connection between isotretinoin and IBD largely consists of isolated case reports." The authors compared 8,819 cases with 21,832 controls. Exposure to isotretinoin was assessed in a 12-month period before case ascertainment. Dr. Crockett reported that UC was associated with previous isotretinoin exposure (OR 4.36, 95% CI 1.97-9.66) but not with CD (OR 0.68, 95% CI 0.28-1.68). The authors concluded that notwithstanding the possible association between isotretinoin and UC, the absolute risk for UC was likely small. Finally, the OR for UC stated in this report has not been replicated in any other epidemiological study during the past six years.

D. Alhusayen, 2012. "Isotretinoin Use and the Risk of Inflammatory Bowel Disease: A Population-Based Cohort Study." This was a very large population-based cohort study comprised of approximately 1,700,000 subjects. The participants were newly treated with isotretinoin or topical acne medications. They identified 46,922 participants treated with isotretinoin, 184,824 treated with topical acne medication and 1,526,964 untreated individuals. The authors found no significant association between isotretinoin use and IBD (RR 1.14; 96% CI 0.92-1.41). As noted at p. 5 of the study, the authors "We restricted the analysis to patients aged 12-29 years because they represent the majority isotretinoin recipients." The authors concluded that the risk of IBD during isotretinoin therapy was quite similar to that seen with patients who had used topical acne medications. Dr. Alhusayen and his colleagues opined that the results of their study "...suggest[ing] a possible association between IBD and acne itself. Additional research is needed to explore this possibility."

E. Etminan, 2013. "Isotretinoin and Risk for Inflammatory Bowel Disease: A Nested Case-Control Study and Meta-Analysis of Published and Unpublished Data." The study comprised approximately 45,5000 subjects. The authors performed both a case-control study and a meta-analysis of prior epidemiological studies. They formed a cohort of women age 18 to 46 who had received oral contraceptives over an eight-year period; they also adjusted for two confounders, viz., diagnosis of acne and use of oral tetracycline antibiotics. The authors identified 2,159 cases and matched them with 43,180 controls. The authors of the Etminan study directed one of their conclusions to dermatologists, advising, "Because inflammatory acne in children and adolescents carries a high psychological burden, clinicians should not be discouraged from prescribing this drug owing to a putative association with IBD."

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F. Fenerty, 2013. "Impact of Acne Treatment on Inflammatory Bowel Disease." This study (may not have been peer-reviewed) was comprised of approximately 176,000(+) subjects. The authors utilized a Medicaid dataset to identify patients who had received a diagnosis of acne in 2003 and had no prior IBD diagnosis. The authors concluded there is an inverse association between oral antibiotics and the development of IBD in acne patients with a dose-response relationship. Clinicians and prospective patients should be cognizant of the lack of a causal relationship between isotretinoin for acne and the development of IBD.

G. Racine, 2014. "Isotretinoin and the Risk of Inflammatory Bowel Disease: A French Nationwide Study." This population-based case-control study comprised approximately 40,000(+) subjects gleaned from a national health insurance data base containing more than 50 million individuals. The study included 7,593 cases of IBD and 30,372 controls. Based on the data, the authors concluded that isotretinoin exposure was not associated with an increased risk for UC, but was associated with a decreased risk for CD.

H. Rashtak, 2014. "Isotretinoin Exposure and the Risk of Inflammatory Bowel Disease." The retrospective single center cohort study at the Mayo Clinic comprised approximately 1,100 subjects whose medical records showed a reference to isotretinoin over a 16-year period. According to the author, none of the published epidemiological studies have found a significant positive association between isotretinoin and IBD risk as a whole. Only one (Crockett) has found a UC risk but this finding has not been replicated by any other study or by 2 more recent meta-analyses. Finally, the author believes that the meta-analyses performed by Dr. Goodman indicates that when all new data is included there is no increased risk of development of UC regardless of the calculation used to perform the evaluation.

I. Lee, 2016. "Does Exposure to Isotretinoin Increase the Risk for the Development of Inflammatory Bowel Disease? A Meta-Analysis." This meta-analysis was based upon an extensive literature search of multiple databases, seeking articles discussing the relationship between isotretinoin and IBD. Initially, 70(+) studies were identified. Following what appears to be demanding scrutiny, all but six of the studies were eliminated. As noted by the authors at p. 211 of their article: " On pooling six studies (N= 9 724 069 patients), the rates of development of IBD were exactly the same among patients exposed to isotretinoin and those not exposed to isotretinoin (0.32 vs. 0.32%). Overall, there was no increased risk of development of IBD among patients exposed to isotretinoin relative to those not exposed to isotretinoin [OR 1.08 95% confidence interval (CI) 0.82, 1.42, P = 0.59].

J. Ponder and Long, 2013. "A Clinical Review of Recent Findings in the Epidemiology of Inflammatory Bowel Disease." This treatise was based upon an extensive literature search. The authors did not focus upon relationship between isotretinoin and IBD, rather they were seeking to gain a better understanding of the epidemiology of

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IBD. They appear to have labored mightily in an effort to identify risk factors for IBD as expressed in the extensive literature on the epidemiology of IBD.

At p. 244 of the authors' report, Figure 1 is an informative graphic which illustrates the risk factors for UC and CD. Isotretinoin is not recited as a risk factor. The authors conclude by advising the scientific community that much more work and large cohort studies are needed to gain a better understanding of the risk factors for IBD. "As IBD is a relatively rare disorder, with complicated interactions between potential inciting agents, very large cohorts with detailed, prospectively collected, environmental exposure data will be needed. Of equal importance, particularly to patients with established disease, is a better understanding of the effects of environmental exposures on disease course. Again, large, well-phenotyped cohorts of IBD patients are needed, with detailed prospective collection of environmental exposure data."

K. Reddy, 2006. "Possible Association Between Isotretinoin and Inflammatory Bowel Disease." This study examines MedWatch reports filed with the FDA regarding patients prescribed isotretinoin. The authors readily acknowledged the "limitations" of case reports such as those filed with the FDA. Using the Naranjo Adverse Drug Reaction Probability Scale, the authors evaluated a total of 85 cases of IBD and concluded that "It is conceivable that isotretinoin is acting as a trigger for IBD in patients with preexisting but subclinical conditions." The record of the *Kemp* Hearing is replete with testimony regarding this study.

L. Passier, 2006. "Isotretinoin-Induced Inflammatory Bowel Disease." This is a well-written and informative case report which reports on three individual teenagers who developed severe gastrointestinal symptoms requiring hospitalization shortly after beginning treatment with isotretinoin. Plaintiffs' counsel and witnesses gave much attention during the *Kemp* Hearing.

M. Shale, 2009. "Isotretinoin and Intestinal Inflammation: What Gastroenterologists Need to Know." This is an informative scientific essay, not a report on an epidemiological study. Dr. Shale did not perform any new research of his own, rather he was reporting on what he had learned from reading the peer-reviewed studies of other scientists. As noted by Dr. Sachar on direct-examination, the authors quoted "...what other articles themselves didn't show, but what other articles alluded to. So indirectly they are saying there are well-documented effects of retinoic acid upon epithelial cell[s]..." This essay recites one possibility after another, without postulating a hypothesis, and suggests that additional research is necessary. Dr. Shale concludes by stating, "Significant unanswered questions remain regarding the natural history, disease behavior and optimal therapy of isotretinoin induced intestinal disease." (see Dr. Sachar's testimony, Tr. 2-7-17, P159, L7 thru P161, L2)

N. Oehlers, 2012. "Retinoic Acid Suppresses Intestinal Mucus Production and Exacerbates Experimental Enterocolitis." The subject of this study is novel; it examines the intestinal epithelium of zebra fish larvae, and compares it with the

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mammalian intestinal inflammatory processes. The authors of this study believe that "The zebrafish larva is an emerging model system for investigating the pathogenesis of IBD." According to Dr. Sachar, "This study illustrates a direct effect of retinoid administration on intestinal mucus physiology and subsequently on the progression of intestinal inflammation." As he did routinely, Mr. Bolton asks regarding this study, "that supports a theory of biological plausibility, correct?" And Dr. Sachar answers that "It provides a mechanism of biological plausibility, a mechanism by which it reasonably could." The Court doesn't challenge Dr. Sahar's opinion, but must note that it is limited to the inflammation of the intestines of zebrafish larva. Though this may be cutting-edge science, it is a long way from examining the intestines of dogs. The Reference Manual discusses the limitations of experiments on animals and equating the results of the same with humans. The Court will not digress. (see Dr. Sachar's testimony, Tr. 2-7-17, P167, L2 thru P168, L10).

O. Sivaraman, 2014. "Risk of Inflammatory Bowel Disease from Isotretinoin: A Case Control Study." This is a non-peer-reviewed abstract that was not reduced to a formal written report. It comprises 1/4 page in the October, 2014, Edition of the American Journal of Gastroenterology. It was posted on a bulletin board at a conference in a hotel in Las Vegas. The study comprises a total of 509 subjects. Dr. Sachar confirmed the Court's view on this document, namely, it is not of the nature, character nor quality which scientists would normally rely upon. Nevertheless, Plaintiffs' experts make use of it in their opinions.

V. EXPERT WITNESSES

The four witnesses who testified at the *Kemp* Hearing are exceptionally learned and accomplished professionals. Their credentials are impressive and each is a leader in his/her profession. The Court benefited greatly from their opinions. A brief profile for each witness follows:

A. Witnesses for Plaintiffs

(1) April Zambelli-Weiner, Ph.D., M.P.H.:

Credentials: Dr. Zambelli-Weiner is an Epidemiologist with a Ph.D. in Epidemiology and Human Genetics from the Johns Hopkins Bloomberg School of Public Health. She was educated at Washington & Jefferson College and received a Master of Public Health in Epidemiology/Community Health from Saint Louis University. She has published several peer-reviewed articles and serves as a peer-reviewer for the Journal of Women's Health and for the National Eye Institute.

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Though Dr. Zambelli-Weiner's credentials are laudable, her lack of knowledge on the subject of IBD and other issues related to this hearing was apparent. By way of illustration, the questioning at P99, L8 thru P109, L10 reveals that her experience in these types of matters is thin. (See Transcript of February 10, 2017, P99, L8 thru P112, L8.) Moreover, see this witness's testimony of the same date at P196, L17 thru P197, L15. The witness's unfamiliarity with the names of Marcia Angell of the New England Medical Journal, and Robert Temple of the FDA says much. It reveals an unexpected lack of knowledge by a witness who has been presented as an expert in pharmaco-epidemiological matters. Though the Court respects Dr. Zambelli-Weiner's knowledge, such testimony is telling of her limitations in the field of pharmaco-epidemiology. Finally, when the Court considers the fact that Dr. Zambelli-Weiner has yet to submit a single meta-analysis of her own for peer-review, her palpable discomfiture in the witness chair is understandable. The Court is confident that her time in Court was a valuable learning experience, one from which she will benefit greatly.

Summary of Opinions: Throughout her testimony and in her report, Dr. Zambelli-Weiner places limited value on nearly every epidemiological study except Crockett, 2010. She didn't seem concerned that it has not been replicated. On direct examination, she was critical of the other studies to such an extent that the Court wondered why/how she did a meta-analysis of reports for which she had so little respect. [NOTE: her meta-analyses are attached as Addendum D.]

Dr. Zambelli-Weiner structured her causal assessment of isotretinoin and UC by referencing each of the Hill criteria. Her discussion of Biological Plausibility was a subject for which she appears unqualified, and to which this Court assigns little weight.

(2) David B. Sachar, M.D.:

Credentials: Dr. Sachar is a distinguished physician and scientist. He is graduate of Harvard University and Medical School, and serves as Clinical Professor of Medicine and Director Emeritus of the Dr. Henry D. Janowitz Division of Gastroenterology at the Institute for Medical Education. He is Board-Certified in Internal Medicine and in the subspecialty of Gastroenterology. He has received the Distinguished Service Award of the Research Development Committee of the Crohn's and Colitis Foundation of America and has published

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extensively, including 220(+) published papers on IBD and 60 (+/-) books or book chapters on gastroenterology. He has served on editorial boards for several GI journals.

Summary of Opinions: Dr. Sachar opines that isotretinoin can cause ulcerative colitis, can act as a substantial contributing factor in the development of ulcerative colitis, and is also capable of aggravating a pre-existing ulcerative colitis. In forming his opinion, he performed a causation analysis to analyze the lines of evidence available to him. According to Dr. Sachar, "Each of these lines of evidence is of the type relied upon by doctors and scientists in determining whether a substance causes an effect." (Page 2 of Report of October 31, 2016.)

Dr. Sachar considered the pre-approval clinical studies that were performed with Accutane. These studies showed adverse effects on the mucous membranes, diarrhea, and other GI effects, suggestive of Accutane's ability to cause severe GI effects. He also reviewed reports of UC in connection with Accutane exposure made by physicians and others to Roche. Many of these reports contain case histories of patients' response to Accutane and describe the development of UC during or after taking the drug. Further, Dr. Sachar reviewed the available epidemiological studies and considered their reported findings, as well as their methods, limitations, and potential biases, in assessing the information they provide to inform the risk of UC with Accutane use. He places particular emphasis on Crockett, 2010, and views it as "the most robust and valid study, particularly for the assessment of risk in the U.S. population." (Page 5 of Report of October 31, 2016.)

B. Witnesses for Defendant

(1) Steven N. Goodman, M.D., M.H.S. Ph. D.:

Credentials: Dr. Goodman is a distinguished scientist and physician who specializes in epidemiology. Educated at Harvard University, New York University, and Johns Hopkins University, he has A.B., M.D. and Ph. D. degrees. He has worked in several institutional settings and is currently at Stanford University where he is a Professor and Associate Dean for Clinical Research. He has devised standards and procedures for numerous epidemiological reports. He has worked as an editor on various publications and received numerous awards and academic certifications in his area of expertise.

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Summary of Opinions: According to Dr. Goodman, a causal association between isotretinoin and IBD, or UC in particular is "highly improbable." He rejects Plaintiffs' contention that UC is all that different from CD. Further he opines that the data in the several epidemiological studies is better understood via an IBD analysis, and that the same "takes precedence" over the CD and UC numbers..." According to him, "Since CD in the colon has a clinical profile similar to UC, there can be diagnostic errors in the in the initial diagnosis of IBD, with both UC and CD mistaken for the other, a well-recognized phenomenon."

Dr. Goodman is of the opinion that two new studies, viz., Fenerty and Rashtak along with that by Racine and a fourth by Etminan "...now pushes the central estimate from 1.0 towards a protective effect of Accutane on IBD, with a relative risk of .87, a 13% reduction in the IBD incidence. He concludes that the current data and analysis of the same in the more recent studies, "...strongly supports a protective effect than a hazardous one." [NOTE: Dr. Goodman's meta-analyses is at Addendum E. His inclusion of Sivaraman in the second analysis was to demonstrate his overall assessment.]

(2) Maria Oliva-Hempker, M.D.:

Credentials: Dr. Oliva-Hempker is a Professor of Pediatric IBD and Chief of Division of Pediatric Gastroenterology & Nutrition at Johns Hopkins University School of Medicine. She has published 70(+) peer-reviewed treatises, book chapters in seven medical texts, and is Editor-in-Chief of *Your Child and Inflammatory Bowel Disease.* She regularly serves as a peer-reviewer of treatises on IBD and is a member of the National Committee which prepares examinations for board certification by practicing gastroenterologists. Dr. Oliva-Hempker has served on and chaired various gastroenterology committees, and maintains a visible profile educating the public on IBD.

Summary of Opinions: Dr. Oliva-Hempker begins by noting that there is no established biological mechanism for Accutane causing UC. Hypothetical biological pathways have been proposed but none have been proven. UC is a disease that may result from a possible multitude of triggers, both known and unknown. For most individuals developing UC, a trigger or triggers are never identified. Although the exact cause of UC has not been identified, environmental factors are believed to play important roles in its pathogenesis.

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Dr. Oliva-Hempker reviewed multiple epidemiological studies that have been conducted to evaluate whether there may be an association between Accutane and the development of IBD. According to her, none of the published epidemiological studies have found a significant positive association between isotretinoin and IBD risk as a whole. Only one, Crockett, 2010, has found a UC risk but this finding has not been replicated by any other study or by two more recent meta-analyses. Finally, she opines that the meta-analysis performed by Dr. Goodman indicates that when all new data is included there is no increased risk of development of UC regardless of the calculation used to perform the evaluation.

VI. LEGAL STANDARD APPLICABLE TO THE COURT'S ANALYSIS

Until the final decade of the 20th Century, the time-honored test for the admissibility of expert testimony based upon a body of knowledge peculiar to a field of scientific study was that it had to be "generally accepted" or had been accepted by at least a substantial minority of the scientific community. *See Frye v. United States,* 54 *App. D.C.* 46 (D.C. Cir. 1923). Over time, that standard became unjust. New Jersey's courts were among the first to recognize that litigants claiming that they were harmed by the use of a product may never recover if they must await general acceptance by the scientific community of a reasonable, but not as yet certain, theory of causation linking the harm claimed to the product ingested.

In *Rubanick v. Witco Chem. Corp.,* 125 *N.J.* 421, 432 (1991), our Supreme Court modified that test with regard to evidence proffered for use in toxic tort cases. The Court held that a less stringent test than the general acceptance test should apply with regard to "new or developing theories of causation in toxic-tort litigation." *Id.* at 432. In writing for the Court, Justice Handler spoke of a methodology based test, that is, if the methodology by which the expert reached a conclusion is "sound," the conclusion may be introduced into evidence. *Id.* at 438-40. Pursuant to *Rubanick,* the key to reliability is the determination that the expert's opinion is based on a "sound, adequately-founded scientific methodology involving data and information of the type reasonably relied on by experts in the scientific field." *Id.* at 449. In order to be *valid methodology* (*viz.*, accepted by others in the scientific community), the expert's opinions must be supported by "prolonged, controlled, consistent, and validated experience." *Id.* at 436.

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In determining whether a scientific methodology is valid, trial courts must consider whether other scientists in the field use similar methodologies in forming their opinions and also should consider other factors that are normally relied upon by medical professionals. The appropriate inquiry is not whether the Court thinks that the expert's reliance on the underlying data was reasonable, but rather whether comparable experts in the field would actually rely on that information. With regard to evaluating the testimony of knowledgeable experts in order to determine the acceptability of a theory, the *Rubanick* Court cautioned trial courts to attend to "the hired gun phenomenon," *i.e.*, that an expert can be found to testify to the truth of almost any factual theory or to disagree with almost any theory and to discount the research of others. *Rubanick, supra* at 453 (citations omitted).

Following *Rubanick,* in *Landrigan v. Celotex Corp.,* 127 *N.J.* 404 (1992), *Caterinicchio v. Pittsburgh Corning Corp.*, 127 *N.J.* 428 (1992), and *Dafler v. Raymark Industries, Inc.*, 259 *N.J. Super.* 17, 36 (App. Div. 1992), *aff'd. o.b.,* 132 *N.J.* 96 (1993), the Court held that experts relying on epidemiological studies could provide sufficient reliable evidence for the causes of diseases in specific individuals to present the issue of causation to juries. *Landrigan* and *Caterinicchio* involved the relationship of asbestos to colon cancer; *Dafler* addressed the relationship of cigarette smoking and asbestos to lung cancer.

In *Landrigan,* an occupational asbestos exposure case, the trial court dismissed the case on the ground that there was a lack of medical evidence to establish asbestos exposure as the cause of the disease. The Appellate Division affirmed. The Supreme Court reversed and held that epidemiologists could help juries determine causation in toxic tort cases and rejected the proposition that epidemiological studies must show a relative risk factor of "2.0" before gaining acceptance by a court. *Landrigan, supra* at 419. The Supreme Court in *Landrigan* ruled that a trial judge must consider all the scientific data, sources thereof, and the methodology by which an expert reaches a conclusion, "includ[ing] an evaluation of the validity both of the studies on which he relied and of his assumption that the decedent's asbestos exposure was like that of the members of the study populations." *Id.* at 420. Additionally, the Supreme Court advised that "to determine the admissibility of the witness's opinion, [a] court, without substituting its judgment for that of the expert, should examine each step in [the expert's] reasoning." *Id.* at 421.

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One case, in particular, provided valuable guidance, namely *Magistrini v. One Hour Martinizing Dry Cleaning*, 180 *F. Supp.* 2d 584 (D.N.J. 2002), *aff'd*, 68 F. Appx. 356 (3d Cir. N.J. 2003). The Court in *Magistrini* noted "[a]s a general matter, the Rules of Evidence 'embody a strong and undeniable preference for admitting any evidence' that could potentially assist the trier of fact and Rule 702 is liberally interpreted by the district courts." *Id.* 595 (citations omitted). *New Jersey Evidence Rule* 702 is identical to the Federal Rule. That said, the Court in *Magistrini* also cautioned, "[t]he Court's inquiry 'must be solely on principles and methodology, not on the conclusions that they generate.'" *Id.* (citing *Daubert v. Merrell Dow Pharms.*, 509 *U.S.* 579, 595 (1993)). In articulating the mental process of the "gatekeeper," the Court in *Magistrini* cited the Supreme Court decision in *GE v. Joiner*, 522 *U.S.* 136 (1997), wherein Chief Justice Rehnquist advised trial judges:

> But conclusions and methodology are not entirely distinct from one another. Trained experts commonly extrapolate from existing data. But nothing in either *Daubert* or the Federal Rules of Evidence requires a district court to admit opinion evidence that is connected to existing data only by the *ipse dixit* of the expert. A court may conclude that there is simply too great an analytical gap between the data and the opinion proffered. *Id.* at 146.

In preparing for these proceedings the Court reviewed what other courts have done on a relative risk factor of less than "2.0". In reviewing the case law found by the Court and that submitted by counsel, it is apparent that most courts across the nation – federal and state alike – discourage a dogmatic insistence upon a showing of a relative risk factor of "2.0" to support general causation. This Court concurs with that thinking. Nonetheless, the closer to the "null" the relative risk is, the Plaintiff has an increased responsibility to explain why and how the agent can cause the ailment.

A reading of the case law as to the weight attached to a relative risk factor of less than "2.0" shows that it is only one of the factors to be considered by the Court. What must also be examined are the foundational sources of the expert's opinions. As discussed herein in connection with the Court's examination of the "Bradford Hill" criteria, although no single criterion is dispositive, research performed prior to litigation and peer-reviewed essays on the scientific issue at hand are the basic means by which to demonstrate reliability of an expert witness's methodology. Where neither exists, an expert witness is obligated to explain to the Court how she/he proceeded in arriving at his/her conclusions by referencing some objective

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source(s), *e.g.*, a peer-reviewed article in a reputable medical/science journal, the public pronouncements of an agency with respected authority on the issue, or a learned treatise on the issue, in order to demonstrate that she/he has followed the scientific method at the standards maintained by some recognized minority of scientists in his/her area of science.

Accordingly, as this Court understands New Jersey law and our Supreme Court's holding in *Landrigan,* the admissibility of expert testimony in a case such as this "depends on the expert's ability to explain pertinent scientific principles and to apply those principles to the formulation of his or her opinion. Thus, the key to admission of the opinion is the validity of the expert's reasoning and methodology." *Landrigan, supra* at 414. The ruling in *Landrigan* likewise addresses the principal type of study before the Court, namely, that "when an expert relies on such data as epidemiological studies, the trial court should review the studies, as well as other information proffered by the parties, to determine if they are of a kind on which such experts ordinarily rely." *Id.* at 417.

Ten years after *Landrigan,* in *Kemp v. State of New Jersey,* 174 *N.J.* 412, 430-32 (2002), the Supreme Court applied the *Rubanick* standard to a case involving an injury allegedly caused by vaccination, and implied its applicability to all tort cases in which a medical cause-effect relationship has not yet been confirmed by the scientific community but for which "compelling" evidence suggests that such a relationship does exist. In *Kemp,* the Supreme Court suggested that an *Evid. R.* 104 hearing is the preferred procedural practice in every case involving an expert's theory that has not yet achieved "general acceptance," finding that the trial court has an obligation, *sua sponte*, to conduct such a hearing and that the failure to do so is plain error.

Thus, from this Court's perspective, the inquiry at a *Kemp* Hearing must be "flexible." Its focus must be on principles and methodology and not necessarily on the conclusions/opinions that such scientific methodology may generate. The trial court's role is to determine whether the expert's opinion is derived from a sound and well-founded methodology. "There must merely be *some expert consensus* that the methodology and the underlying data are generally followed by experts in the field." *Rubanick, supra* at 450 (emphasis added). Accordingly, at this *Kemp* Hearing, Plaintiffs' burden is to demonstrate that the methodologies used by their experts are consistent with valid scientific principles accepted in the scientific and medical communities and for which there is *some expert consensus.*

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Finally, the Court is guided by the words of Justice Handler in *Rubanick, supra,* 125 *N.J.* 451, wherein he cautioned trial court judges that they must exercise restraint.

> We do not believe that in determining the soundness of the methodology the trial court should directly and independently determine as a matter of law that a controversial and complex scientific methodology is sound. The critical determination is whether comparable experts accept the soundness of the methodology, including the reasonableness of relying on this type of underlying data and information. *Great difficulties can arise when judges, assuming the role of scientist, attempt to assess the validity of a complex scientific methodology.* (Emphasis added.)

VII. DEVIATIONS FROM SCIENTIFIC METHODOLOGY OF PLAINTIFFS

As noted by our Supreme Court in *Townsend v. Pierre*, 221 *N.J.* 36, 55 (2015), "Given the weight that a jury may accord to expert testimony, *a trial court must ensure that an expert is not permitted to express speculative opinions* or personal views that are unfounded in the record." (Emphasis added.) In examining the worthiness of the experts' opinions, the Court is guided by our Supreme Court's rulings, and by the *Reference Manual*, a text that is virtually "the Bible" on questions arising from the intersection of the science and the law. The animating principle of the *Reference Manual* encourages trial courts to scrutinize scientific evidence thoroughly, and to avoid the presentation to jurors of putative scientific evidence which does not reflect the application of scientific principles. Its ethos is one of healthy skepticism.

In these proceedings, the witnesses are learned scientists and the lawyers possess exceptional knowledge of the subject matter. Nonetheless, there were instances, both on direct and cross-examination, when the colloquy between the lawyers and witnesses "got into the weeds," and the testimony bordered inscrutability, and where it was necessary for the Court to read and re-read the hearing transcript to gain a better understanding of the testimony. What are lay jurors to make of such testimony? Thus, the need for a rigorous review by the trial court.

April Zambelli-Weiner, Ph.D., M.P.H.:

As noted hereinabove in Section V, Dr. Zambelli-Weiner is well-educated and highly credentialed professional; experienced in the field of epidemiology generally. Yet when it comes to issues related to pharmaco-epidemiology, she appears to have had very limited exposure to

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such matters. Additionally, she frequently ignores the fundamentals of the scientific method, particularly, the medical-evidence hierarchy. Her methodology is not "sound".

What follows *ad seriatim* are references to portions of her testimony and findings thereon, revealing significant deviations from accepted scientific methodology. This list could be enhanced but would serve no purpose. Dr. Zambelli-Weiner's testimony must be barred.

1. The witness's inclusion of the *non*-peer-reviewed Sivaraman abstract in her meta-analysis, and her exclusion of the Rashtak study from the Mayo clinic bespeak of litigation-driven science. Plaintiffs' other expert, Dr. Sachar, commented on Sivaraman: "...they got back what they got back." (February 6, 2017, P108, L9-10.) He continued, "I don't know what it means." (February 6, 2017, P109, L7.) Finally, see Dr. Sachar's testimony of February 7, 2017, P81 L24 thru P82, L22, when in response to a question from the Court, Dr. Sachar conceded that the Sivaraman abstract was "Generally not[.]" something the scientific community gives serious weight to. Nevertheless, Dr. Zambelli-Weiner includes Sivaraman in her meta-analysis. The exclusion of Rashtak and the inclusion of Sivaraman is a vivid example of "cherry picking." Rashtak is a peer-reviewed study published in *JAMA Dermatology*. The authors are affiliated with the Mayo Clinic. Sivaraman's big moment was being posted on a bulletin board at some hotel in Las Vegas. Yet Dr. Zambelli-Weiner disregards Rashtak in favor of Sivaraman.
2. The witness's reliance upon Case Reports of anecdotal information on individual occurrences, and her characterization of the same as "quite compelling" demonstrate a disregard for the hierarchy of scientific evidence. The *Reference Manual* informs trial courts that the "Passier" Case Report (see Addendum B) and all the others of similar type which Dr. Zambelli-Weiner may have examined are hypothesis-generating, only. The Court must be mindful that as advised by the *Reference Manual* Case Reports are at the very bottom of the medical-evidence hierarchy. This witness's reliance upon the same is a deviation from standards maintained by other scientists.
3. Dr. Zambelli-Weiner's testimony regarding R/R is inconsistent with the standards articulated at pages 602 and 612-13 (and the notes therewith) of the *Reference Manual.* The general thrust of those portions of the *Reference Manual* is that despite the best methods and efforts, frequently "epidemiology is sufficiently imprecise to accurately

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measure small increases in risk… [there is] the likelihood that an association less than 2.0 is noise rather than reflecting a true causal relationship." (See note 193 at page 612.) During her cross-examination, defense counsel presented her with the aforesaid standards and the questioning proceeded as follows:

Testimony of February 10, 2017, P191, L21 thru P192, L12

Q And the first thing they discuss in discussing how strong is the association is the relative risk. In fact, they say relative risk measures the strength of the association. The higher the relative risk, the greater the likelihood that the relationship is causal. Do you agree with that?

A I -- no, not necessarily. I think it's a general guidance, but there are plenty of high associations that are noncausal and, you know, lower relative risks that are causal.

Q Okay. Let's look at what they say in the next paragraph. They say, "The higher the relative risk, the stronger the association and the lower the chance that the effect is spurious." Do you agree with that?

A No, I don't.

The complete testimony of the witness on R/R is too lengthy to be repeated herein verbatim; the entirety of the colloquy between the witness and defense counsel on this issue is set forth at P190, L25 thru P198, L25. The reader is encouraged to review the aforesaid testimony in full. It does not reflect well on the witness's understanding of interplay between R/Rs and when the same may be supportive of a causal association.

4. The witness's reliance upon articles such as "Reddy" (Addendum B), which is a genuinely thorough examination of multiple case reports which found a "possible association" between isotretinoin and IBD, ignores the fact – and scientific standard – that such evidence is little more than anecdotal information that there may have been a temporal relationship between Accutane exposure and an acute effect on the colon disregards the evidence-based medical hierarchy. The Court must be mindful that as advised by the *Reference Manual* Case Reports are at the very bottom of the medical-evidence hierarchy. This witness's reliance upon the same is a deviation from standards maintained by other scientists.

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5. Dr. Zambelli-Weiner's assertion that the results from a "challenge-dechallenge-rechallenge" regimen are evidence in support of a causal association between isotretinoin and IBD ignores the evidence-based medical hierarchy. What's more such assertions disregard the admonition of the peer-reviewed article upon which she and Dr. Sachar rely most heavily, viz., Crockett, 2010. As noted by Dr. Crockett at page 2390, Figure 2: "If isotretinoin is discontinued when IBD is initially diagnosed, and reintroduced when disease activity is quiescent, subsequent flares of disease typical of the natural history of IBD could be mistaken for the effects of re-exposure to the drug."
6. Preliminary to conducting her meta-analysis, as encouraged by "Cochrane" §9.7, this witness made no effort to contact the authors of Rashtak study. In lieu of trying to learn more about the Rashtak study, she simply excluded it, which as per "Cochrane" §9.5.3(7), is a deviation from the standards required of an epidemiologist. That same section of "Cochrane" encourages a sensitivity analysis via excluding Crockett, 2010, and see how that impacts the results of the meta-analysis. She failed to do that.
7. Dr. Zambelli-Weiner's unswerving reliance upon Crockett, 2010, ignores an important admonishment of the *Reference Manual*.

> Rarely, if ever, does a single study persuasively demonstrate a cause-effect relationship. It is important that a study be replicated in different populations and by different investigators before a causal relationship is accepted by epidemiologists and other scientists. (Page 604.)

David . Sachar, M.D.:

Dr. Sachar frequently disregards the fundamentals of the scientific method. The medical-evidence hierarchy is a basic principal that cannot be ignored by scientists, yet he has little compunction disregarding it. His methodology is not "sound".

As noted by the *Reference Manual*, the "explosion of available medical evidence" in our modern society has heightened the need for "assembling, evaluating, and interpreting medical research evidence. A fundamental principle of evidence-based medicine is that the strength of medical evidence supporting a therapy or strategy is *hierarchical*. When ordered *from strongest to weakest*, systematic review of randomized trials (meta-analysis) is at the top, followed by single randomized trials, systematic reviews of observational studies, single observational

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studies, physiological studies, and unsystematic clinical observations." (Emphasis added, see page 723-4.)

Whether in the laboratory, classroom, the conducting of a scientific study, *or in the courtroom*, the medical-evidence hierarchy must be respected. When the following testimony is considered in light of the standards of the *Reference Manual,* it is found wanting and deemed contrary to sound science and conventional scientific methodology.

What follows *ad seriatim* are references to portions of this witness's testimony and this Court's findings thereon, revealing significant deviations from accepted scientific methodology. This list could be enhanced but would serve no purpose. Dr. Sachar's testimony must be barred.

1. **Testimony of February 7, 2017, P17, L2 thru L19 [see P16, L2 thru P18, L25 for further context]**

Q So, as such and since they are hypothesis generating as opposed to a type of evidence that can test a hypothesis like an epidemiological study, you would agree that case reports would go lower on the list of this that I have made here on the board of lines of evidence in terms of weight that you would provide to these types of evidence, correct?

A Well, not correct. The case report with a good challenge/rechallenge evidence is better than a lousy epidemiologic study.

Q So, in terms of your methodology, you would put some case reports on a higher level of evidence, above an epidemiological study or a randomized control trial; is that what you're saying, Doctor?

A I would put it the other way around. I would say that some epidemiologic studies I would drop so far to the bottom that I might even throw them in the wastebasket.

This gentleman's cavalier use of disparaging language toward the peer-reviewed treatises of other scientists is indicative of the "hired gun" mentality. It's difficult to imagine that when speaking before his colleagues at a professional symposium, Dr. Sachar would cast aspersions on the methods and conclusions of peer-reviewed literature as freely as he did before the Court. The Court must be mindful that as advised by the *Reference Manual* Case Reports are at the very bottom of the medical-evidence hierarchy.

2. **Testimony of February 7, 2017, P22, L1 thru L15 [see P21, L21 thru P24, L7 for further context]**

Q And you would agree then that animal studies are hypothesis generating only?

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A No, I certainly wouldn't agree on that. I think they are hypothesis testing, and if your putting them below the other three is meant to imply that they are a lower level of evidence, I would respectfully disagree with you.

Q Okay. Would you agree, Doctor, that in order to -- in terms of research, you cannot take the results of an animal study alone in order to have a medication approved, for example, to be used in humans?

A Well, that's a totally different question. I would agree with that. I certainly wouldn't agree that animal studies as a class are less -- of less evidentiary value than the things on the list above it.

Dr. Sachar's vaunted ranking of animal studies as "hypothesis testing" defies the medical-evidence hierarchy and puts him out of step with the scientific community.

3. **Testimony of February 7, 2017, P25, L8 thru L23**

Q Okay. Well, my question is: In your methodology, do you put cell culture studies above any of these other lines of evidence that we have on the list?

A In my methodology, I don't make lists like that. I look at each study and each category of evidence on its own merits.

Q Doctor, do you recognize this list I have made as a recognized scientific hierarchy of medical and scientific evidence that starts with randomized controlled trials on the top, with epidemiological studies below it, with case reports and animal studies below epidemiological studies?

A Well, of course, you can find plenty of publications that have a list in that hierarchical order, but that's in a different context.

Dr. Sachar's lumping of the *Reference Manual* along with "plenty of publications that have a list" demonstrates his disregard for the standards which this trial court is obligated to observe. As he made this flippant statement (candidly, one of many) the undersigned imagined Dr. Sachar coming face-to-face with the authors of the "Reference Guide on Medical Testimony" (page 687) of the *Reference Manual*. Would he tell them that the medical-evidence heirarchy was just another "list" which he is free to ignore?

4. **Testimony Re: The Alhusayen study, February 6, 2017, P117, L24 thru P118, L7 [see P111, L22 thru P118, L15 for further context]**

During the initial day of his testimony, during direct-examination, the witness and the Court engaged in a colloquy regarding Dr. Sachar's characterization of the methodology utilized by the authors of the Alhusayen study.

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THE WITNESS: I think what it does is undermine your confidence in my objectivity... And I think that's because I got a little emotional.

This cite to testimony is too lengthy to be repeated herein verbatim; one portion is from the direct-examination, another is a colloquy between the Court and the witness. The reader is encouraged to review the aforesaid testimony in full. It was during this testimony that Dr. Sachar denigrated another scientist's methodology as "insane." (See February 6, 2017, P111, L22 thru P113, L10.) It's difficult to imagine that were Dr. Sachar meeting with the author of this study that he would tell him that a portion of his methodology was "insane." He saves those types of comments for the courtroom.

5. **Testimony Re: The Sivaraman abstract, February 7, 2017, P82 [see P81, L24 thru P82, L24 for further context]**

THE COURT: So, the question I ask of you: Is this one page abstract that seemed to have its big moment in life posted on a bulletin board at some hotel in Las Vegas now has found its way on a piece of paper into my courtroom, is this -- because I'm going to ask all the other witnesses the same question. Is this something scientists take seriously?

THE WITNESS: Generally not.

Notwithstanding Dr. Sachar's candid assessment of this *non*-peer-reviewed abstract, he references it, and relies upon its findings in his written opinion.

6. **Testimony Re: The Etminan study, February 7, 2017, P135, L18 thru P136, L3**

Q Are you offering an opinion here about whether or not the Etminan study is underpowered?

A An opinion. I think it's underpowered. With how much confidence am I saying that it's underpowered, I -- I can't say. I think it's underpowered. I don't know it for a fact.

Q So that's your guess from looking at it without having done any calculations? Is that what you're saying, Doctor?

A Yeah, that's a guess without having done a calculation.

The above testimony is but one illustration of this witness's lack of "restraint" in his role as an advocate. Dr. Sachar's "guess" that the Etminan study is underpowered is, quite literally, a first in the undersigned's courtroom. Prior to this gentleman, not a single expert witness has ever

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had the temerity to offer a "guess" in support of his opinion. Offering a negative opinion on peer-reviewed study, that of necessity would ordinarily require further inquiry and calculations, demonstrates the lengths the witness will go in his role as a "hired gun."

7. Dr. Sachar has yet to propose a hypothesis on the purported causal association between isotretinoin and IBD, nor do any of the peer-reviewed articles cited by him propose such a hypothesis. Time and again, Mr. Bolton asked Dr. Sachar questions regarding one of several different articles, and the witness testified as to instances in which these articles discussed various issues; e.g., toxic metabolites and inflammation, or mucosal drying and T-cells, etc. Plaintiffs' counsel would ask a question such as, "Doctor, does this – is this article support biological plausibility for Accutane causing these things?" The witness generally answered in the affirmative, routinely explaining his thoughts on each article. (See Transcript of February 7, 2017, P161, L7 thru P164, L3.)

The Court can envision how the various lines of evidence cited by Dr. Sachar might prove valuable in support of a hypothesis on a causal association between isotretinoin and IBD. Yet absent a hypothesis pulling together the lines of evidence like links in a chain, Dr. Sachar's opinions lack in theoretical coherency.

8. **Testimony Re: Witness's Peer-Review Articles, February 7, 2017, P231, L4 thru P232, L1**

THE COURT: Has a peer-reviewed -- have you published a peer-reviewed article?

THE WITNESS: Ever?

THE COURT: I know you published over 200. Okay. But have you ever published a peer reviewed article setting forth an articulation of the biological plausibility of the cause and effect between isotrentinoin and IBD?

THE WITNESS: Oh, dozens of other people have done that.

THE COURT: I didn't -- I'm not interested in what other people did. I've been reading those. I want to know what you wrote.

THE WITNESS: I haven't written an article outlining biological plausibility yet.

THE COURT: Yet. Okay. Fine.

THE WITNESS: I'm planning to.

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THE COURT: Looking forward to it. Sixteen years you've been working on this, you testified to yesterday.

THE WITNESS: Yes. And it's still under active litigation. I'm a little reluctant to write a paper on it while it's under active litigation.

VIII. ANALYSIS OF TOTALITY OF THE EVIDENCE AND RULING

A. As learned at the *Kemp* Hearing, Dr. Sachar has submitted neither his "theory" that isotretinoin causes IBD, nor his "technique" *viz.*, his methodology by which he supports his hypothesis to the peer-review process. After 15(+) years of offering himself as an expert in litigation on a highly-contested scientific issue, why is Dr. Sachar still *planning to* write a peer-reviewed article on isotretinoin? The Court's record of the Accutane Litigation proceedings reveals that he encouraged his colleague Dr. Arthur Kornbluth to opine on such a causal association in the "UC practice guidelines" which Dr. Kornbluth was working on in 2008 and Dr. Kornbluth refused. (See testimony of A.A. Kornbluth, M.D., February 11, 2015, Page 111, L3 thru P120, L21.) Might Dr. Sachar be concerned that his peer-reviewed article on isotretinoin and IBD would be rejected for publication, and that fact would become known in this litigation?

It seems likely that one of the reasons Dr. Sachar has declined to subject his opinion on isotretinoin to the greater scientific community is that he knows that in the peer-review process he would have to be "rigorously honest." (*Reference Manual*, page 50.) In the courtroom he can point to, and highlight, various threads of marginal proofs such as animal studies (including zebrafish larva) and case reports, and cite them as "compelling evidence." Yet Dr. Sachar knows that in the peer-review process his editors will scrutinize the plausibility of the opinions on which he stands quite alone in the scientific community, and force him to defend his contentions or risk rejection of his article.

The failure to write a peer-reviewed article supporting the claimed causal association, of isotretinoin with IBD is not in and of itself, disqualifying to an expert in a *Kemp* Hearing. Nonetheless, such failure bespeaks an expert who expresses a different set of opinions in the courtroom than he is willing to express to his colleagues. Moreover, as noted by the *Reference Manual,* "If something is not published in a peer-reviewed journal, it scarcely counts." (Page 786.) The scientific community has little regard for opinions confined to the courtroom.

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B. On multiple occasions throughout the *Kemp* Hearing, Plaintiffs' counsel would point to the R/R of an epidemiological study or the O/R of a subgroup within a particular study and highlight the fact that according to that study, that people treated with isotretinoin were 31% more likely, or 25% more likely or (choose a #)% more likely to develop IBD because they had ingested isotretinoin. Yet neither of Plaintiffs' experts were able to point to any consistent showing across studies in various populations that the R/R increased to anything reasonably close to 2.0. It's been six years (+) since Crockett, 2010; nothing has replicated its findings on UC since then.

C. Dr. Sachar made effective use of metaphors and analogies throughout his testimony. One metaphor comes to mind which illustrates the fatal flaw in his discussion of biologic plausibility. His testimony is akin to an unconstructed house. He details the style and size of doors for each entrance; he explains the number and location of the windows; he tells us about the bathroom and kitchen fixtures; and describes the wood framing and sheathing which will envelope and give shape to the house. All of those materials are presented vividly, yet one thing is missing. There are no architectural drawings. Dr. Sachar has what he says are the components for constructing a home, but he has no plans by which to erect a dwelling. Absent a reasonably articulated hypothesis, his opinions lack theoretical coherency. He would have a jury of lay people put the components together by themselves. In short, there is no clear framework for Dr. Sachar's thoughts on the purported causal association between isotretinoin and IBD.

Dr. Sachar has had more than ample time to organize his thoughts and present them for scrutiny by the scientific community. He refuses to provide both his colleagues and this Court with a clear articulation of *why* and *how* isotretinoin *can* cause UC. Absent the *whys and wherefores* of his opinion on the purported causal relationship between isotretinoin and IBD, Dr. Sachar's opinion is little more than conjecture, and a net opinion.

D. The Court's comments on Dr. Zambelli-Weiner at pages 28 thru 31 are sufficient bases to bar her testimony.

RULING

As the proponent of the evidence on general causation, "The plaintiff bears the burden of establishing admissibility." *Kemp, supra*, 174 *N.J.* at 429. As discussed herein, the testimony of the Plaintiffs' experts suffers from multiple deficiencies, the most salient of which is their

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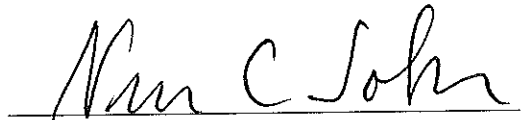
selectivity of the evidence relied upon in disregard of the medical-evidence hierarchy. Ultimately the admissibility of these experts' opinions depends "on the trial court's assessment of both [their] qualifications and [their] methodology." *Landrigan, supra*, 127 *N.J.* at 422. "The key to the admission of the opinion is the validity of the expert's reasoning and methodology." Id. at 414. As instructed by our Supreme Court in *Landrigan, supra*, 127 *N.J.* at 420, the trial court must make an "evaluation of the validity of ... the studies on which [the experts] relied," and, in determining admissibility, must "examine each step in [the expert's] reasoning." *Id.* at 421.

Although one of Plaintiffs' experts is considerably more qualified than the other, both utilize a methodology which is slanted away from objective science and in the direction of advocacy. It is this Court's conclusion that the opinions expressed by Plaintiffs' experts are motivated by preconceived conclusions, and that they have failed to demonstrate "that the data or information used were soundly and reliably generated and are of a type reasonably relied upon by comparable experts." *Rubanick, supra*, at 477.

For the reasons stated herein, the Defendant's Motion to bar the testimony of Dr. David B. Sachar and Dr. April Zambelli-Weiner is hereby GRANTED. An Order accompanies this Memorandum of Decision. Defense counsel is instructed to prepare a form of Order reciting those lawsuits effected by this ruling – including Captions and Docket Numbers - and submit the same to the Court on or before May 19, 2017. Said Order will not be entered until Plaintiffs' counsel have an opportunity to be heard on the form of the same, particularly, the precise Captions and Docket Numbers.



NELSON C. JOHNSON, J.S.C.

Date of Decision: April 13, 2017

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ADDENDUM A

In Re: Accutane® Multicounty Litigation, Case No.: 271 MCL – Trial Plaintiffs' Diagnoses and Results (Corrected)

TRIALS	PLAINTIFFS' DIAGNOSIS - FORM OF IBD	VERDICTS	APPELLATE STATUS
May, 2007 McCarrell I	UC on Nov 26, 1996 Chronic Pouchitis in June, 1997 (Ex. 1: Jan. 8, 2004 Response to Interrogatory 20; Medical Records) Crohn's of the pouch developed eight years later, in Spring 2004, secondary to surgeries related to UC (Ex. 1: Medical Records)	Failure to Warn – for Plaintiff Medical Cause – for Plaintiff Proximate Cause – for Plaintiff	Remanded and retried
April, 2008 Kendall I	UC (Ex. 2: PFS)	Failure to Warn - for Plaintiff Medical Cause – for Plaintiff Proximate Cause – for Plaintiff	Remanded and retried
Oct.-Nov., 2008 Mace Sager Speisman	Mace - UC (Ex. 3: PFS) Sager – Crohn's (Ex. 4: PFS) Speisman – UC (EX. 5: PFS)	Failure to Warn - for all Plaintiffs Medical Cause – for all Plaintiffs Proximate Cause – for all Plaintiffs	Reversed on proximate cause under FL law
Jan.-Feb., 2010 McCarrell II	UC on Nov 26, 1996 Chronic Pouchitis in June, 1997 (Ex. 1: Jan. 8, 2004 Response to Interrogatory 20; Medical Records) Crohn's of the pouch developed eight years later, in Spring 2004, secondary to surgeries related to UC (Ex. 1: Medical Records)	Failure to Warn - for Plaintiff Medical Cause – for Plaintiff Proximate Cause – for Plaintiff	Reversed by App. Div. on SOL under AL law; Reinstated by S.Ct. on SOL under NJ law; Remanded to App. Div.

In Re: Accutane® Multicounty Litigation, Case No.: 271 MCL – Trial Plaintiffs' Diagnoses and Results (Corrected)

TRIALS	PLAINTIFFS' DIAGNOSIS - FORM OF IBD	VERDICTS	APPELLATE STATUS
Feb.-Apr., 2011 Andrews Gaghan Marshall	Andrews - Crohn's (Ex. 6: PFS) Gaghan – UC (Ex. 7: PFS, Medical Records) Mr. Marshall – UC (Ex. 8: PFS)	Failure to Warn - for all Plaintiffs Medical Cause – for Plaintiffs in Andrews & Gaghan; for Defense in Marshall Proximate Cause – for Defense in Andrews; for Plaintiff in Gaghan	Andrews/Marshall appeal denied Gaghan reversed on proximate cause under CA law and SOL under NJ law
Nov.-Dec., 2011 Tanna	UC (Ex. 9: PFS)	Hung Jury Voluntarily dismissed	No appeal
May-June, 2012 Reynolds Rossitto Wilkinson Young	Reynolds - UC (Ex. 10: Jan. 8, 2004 Response to Interrogatory 20) Rossitto - UC (Ex. 11: PFS) Wilkinson - UC (EX. 12: PFS) Young - UC (Ex. 13: PFS)	Failure to Warn - for all Plaintiffs Medical Cause – for all Plaintiffs Proximate Cause – for Plaintiffs Rossitto and Wilkinson; for Defense in Reynolds and Young	Remanded for a new trial in Rossitto and Wilkinson No appeal in Reynolds and Young
Jan.-Mar., 2014 Kendall II	UC (Ex. 2: PFS)	Failure to Warn - for Plaintiff Medical Cause – for Plaintiff Proximate Cause – for Plaintiff	Settled while appeal pending

ADDENDUM A-1

Defense Trial Chart -- NJ Cases
By Plaintiff -- Disease(s) in Complaint and PFS, Contentions at Trial and Trial/Appeal Results

In Re: Accutane® Multicounty Litigation
Case No.: 271 MCL
Accutane Trials -- 13 Plaintiffs; 8 trials; 2 of the 8 trials include re-trials for McCarrell and Kendall

Dates	Plaintiff	Disease Alleged in Complaint	Disease Alleged in Interrogatories or PFS	Diagnosis	Parties' Contention of Disease at Trial		Result
					Plaintiff	Defense	
May 3 – 29, 2007	McCarrell I	IBD	UC, pancolitis, Chronic Pouchitis	UC -- Nov 1995 Crohn's -- Apr 2004 Chronic Pouchitits	IBD - UC IBD - Crohn's of the Pouch after surgery	IBD - Crohn's	Trial -- Plaintiff verdict on failure to warn, proximate cause and medical causation. Appeal -- Reversed, remanded for new trial.
Apr 3 – 22, 2008	Kendall I	IBD	UC	UC	IBD - UC	IBD - UC	Trial -- Plaintiff verdict on failure to warn, proximate cause and medical causation. Appeal -- Reversed, remanded for new trial.
Oct 20 – Nov 19, 2008	Mace	IBD, UC	UC	UC	IBD - UC	IBD - UC	Trial -- Plaintiff verdict on failure to warn, proximate cause and medical causation in all 3 cases. Appeal -- Reversed. Judgment for defense on proximate no cause under FL law in all 3 cases.
	Sager	IBD, UC	Crohn's and colitis	Crohn's	IBD - Crohn's	IBD - Crohn's	
	Speisman	IBD, UC	UC	UC	IBD - UC	IBD - UC	
Jan 13 to Feb 16, 2010	McCarrell II	IBD	UC, pancolitis, Chronic Pouchitis	UC -- Nov 1995 Crohn's -- Apr 2004 Chronic Pouchitits	UC Crohn's of the Pouch	Crohn's	Trial -- Plaintiff verdict on failure to warn, proximate cause and medical causation. Appeal -- Reversed by App. Div. on AL SOL. Reinstated by S. Ct. on NJ SOL. Remanded to App. Div. for remaining issues. Appeal pending.
Feb 22 to Apr 8, 2011	Andrews	IBD, Crohn's	Crohn's	Crohn's	Crohn's colitis	Crohn's	Trial -- Defense verdict on no proximate cause. Appeal -- Defense verdict affirmed.
	Marshall	Not answered.	UC	UC	UC	UC	Trial -- Defense verdict on no case specific causation. Appeal -- Defense verdict affirmed.
	Gaghan	IBD, Crohn's	Crohn's	Records mention UC and Crohn's	UC	Crohn's	Trial -- Plaintiff verdict on failure to warn, proximate cause and medical causation. Appeal --Reversed. Judgment for defense on no prox cause under CA law and SOL under NJ law.
Nov 10 to Dec 22, 2011	Tanna	IBD, UC	UC	UC	UC	UC	Trial -- Hung jury, no verdict. Voluntarily dismissed.
May 7 to Jun 29, 2012	Reynolds	Bondily injury etc. No specific GI injury	UC, regional ileitis [Crohn's], proctitis, chronic colitis	UC	UC	UC	Trial -- Defense verdict on no proximate cause. Appeal -- No appeal.
	Rossitto	UC	UC	UC	UC	UC	Trial -- Plaintiff verdict on failure to warn, proximate cause and medical causation. Appeal -- Reversed. Remanded for new trial.
	Wilkinson	IBD	UC	UC	UC	UC	Trial -- Plaintiff verdict on failure to warn, proximate cause and medical causation. Appeal -- Reversed. Remanded for new trial.
	Young	IBD	UC	UC	UC	UC	Trial -- Defense verdict on no proximate cause. Appeal -- No appeal.
Jan 30 to Mar 11, 2014	Kendall II	IBD	UC	UC	UC	UC	Trial --Plaintiff verdict on failure to warn, proximate cause and medical causation. Appeal -- Settled while appeal pending.

ADDENDUM B

Individual Items Scrutinized by the Court

1	**Crockett, S., Kappelman, M., et al., "A Causal Association Between Isotretinoin and Inflammatory Bowel Disease Has Yet to Be Established." Am J Gastroenterol, 2009, p 2387-2393** This report begins by stating "In a recent court case in New Jersey, a jury awarded $12.9 million to three patients who were diagnosed with inflammatory bowel disease..." and appears to have been written shortly after the decision in *Sager, Speisman, Mace vs. Hoffman[n]-LaRoche, Inc.*, No. A-3427-09, A-3428-09, A-3702-09, 2012 N.J. Super. Unpub. LEXIS 1883 (App. Div. Aug. 7, 2012). The article references the Reddy, et al. review of "the FDA Med Watch reports of IBD cases occurring in association with isotretinoin use." Dr. Crockett notes that "published case reports and case series, as well as related court decisions, must be interpreted with caution" and that case reports are "hypothesis generating" only. He then lists the flaws associated with case reports. At page 2389, a comparison is made of the background incidence of IBD in the U.S. with people taking isotretinoin. His analysis of the then number of Med Watch reports reveals fewer case reports than expected and "demonstrates that a certain number of cases of IBD are likely to develop in isotretinoin users simply on the basis of chance." As to biological plausibility, Dr. Crockett notes, "Given that the etiology of IBD is largely unknown, it is difficult to assess the plausibility of isotretinoin as a trigger of IBD. In fact, the mechanistic studies that are available in the published literature could support a beneficial effect of vitamin A derivatives in regard to the development and perpetuation of IBD."
2	**Bernstein, C.N., et al., "Isotretinoin Is Not Associated With Inflammatory Bowel Disease: A Population-Based Case-Control Study." Am. J. Gastroenterol, p 1-5, DOI:10.1038/ajg.2009.417, published online July 21, 2009** This case-control study comprised approximately 21,500 subjects and found that 1.2% of IBD cases used isotretinoin before IBD diagnosis, which was significantly similar to the controls (1.1% users). The authors concluded: "Although there may be anecdotes of isotretinoin causing acute colitis, our data suggest that isotretinoin is not likely to cause IBD."
3	**Crockett, S.D, et al., "Isotretinoin Use and the Risk of Inflammatory Bowel Disease: A Case-Control Study." Am J. Gastroenterol advance online publication, 30 March 2010: doi: 10,1038/ajb2010.124** This study was pointed to repeatedly by Plaintiffs' experts and legal counsel in support of their contention that there is a causal association between isotretinoin and UC. The case-control study comprised approximately 29,000 subjects and found that there was a "possible association" between UC but not CD. Once again, Dr. Crockett notes that

	"Evidence supporting a causal connection between isotretinoin and IBD largely consists of isolated case reports." The authors compared 8,819 cases with 21,832 controls. Exposure to isotretinoin was assessed in a 12-month period before case ascertainment. Dr. Crockett reported that UC was associated with previous isotretinoin exposure (OR 4.36, 95% CI 1.97-9.66) but not with CD (OR 0.68, 95% CI 0.28-1.68). The authors concluded that notwithstanding the possible association between isotretinoin and UC, the absolute risk for UC was likely small. Finally, the OR for UC stated in this report has not been replicated in any other epidemiological study during the past six years.
4	**Kappelman MD. "Is Isotretinoin a Causative Factor in IBD?" Gastroenterology & Hepatology 2010; 6(3):167 169** This article recites portions of an interview with Dr. Michael Kappelman who worked with Dr. Crockett on the preceding study. The reader is encouraged to examine the entire interview which is part of the record [See Ex. DML1028]. Particular attention is directed to page168 and 169 and the questions and answers therein which read. **G&H** As these individual reports began to appear, were there any hypotheses about how isotretinoin could lead to IBD? **MK** From an epidemiologic standpoint, this question is crucial. Biologic plausibility is one of the criteria developed by Sir Austin Bradford Hill in 1965 to evaluate whether the relationship between two factors might be causal. However, the etiology of IBD, thought to involve an interplay between host genetics, immune response, and environmental triggers, has not been clearly elucidated. Therefore, it is impossible to answer the question of how this drug could lead to IBD.
5	**Alhusayen, R., et al., "Isotretinoin Use and the Risk of Inflammatory Bowel Disease: A Population-Based Cohort Study." Oct 25, 2012, Journal of Investigative Dermatology, advanced online publication, p. 1-6, DOI:10.1038/jid.2012.387** This was a very large population-based cohort study comprised of approximately 1,700,000 subjects. The participants were newly treated with isotretinoin or topical acne medications. They identified 46,922 participants treated with isotretinoin, 184,824 treated with topical acne medication and 1,526,964 untreated individuals. The authors found no significant association between isotretinoin use and IBD (RR 1.14; 96% CI 0.92-1.41). As noted by the authors at page 5 of the study, "We restricted the analysis to patients aged 12-29 years because they represent the majority isotretinoin recipients." The authors reported that isotretinoin use was not associated with hospital admissions or physician visits for IBD. The authors concluded that the risk of IBD during isotretinoin therapy was quite similar to that seen with patients who had used topical acne medications. Interestingly, Dr. Alhusayen and his colleagues opined that the results of their study "...suggest [ing] a possible association between IBD and acne itself. Additional research is needed to explore this possibility."

6	**Etminan, M., et al., "Isotretinoin and Risk for Inflammatory Bowel Disease. A Nested Case-Control Study and Metaanalysis of Published and Unpublished Data." Feb 2013, JAMA Dermatol, Vol. 149, No. 2, p. 216-220** The study comprised approximately 45,5000 subjects. The authors performed both a case-control study and a meta-analysis of prior epidemiological studies. They formed a cohort of women age 18 to 46 who had received oral contraceptives over an eight-year period; they also adjusted for two confounders, viz., diagnosis of acne and use of oral tetracycline antibiotics. The authors identified 2,159 cases and matched them with 43,180 controls. The authors of the Etminan study directed one of their conclusions to dermatologists, advising, "Because inflammatory acne in children and adolescents carries a high psychological burden, clinicians should not be discouraged from prescribing this drug owing to a putative association with IBD."
7	**Fenerty, S., et al., Abstract, "Impact of Acne Treatment on Inflammatory Bowel Disease." April 2013, J Am Acad Dermatol, P6751, p. AB5** This study (may not have been peer-reviewed) was comprised of approximately 176,000(+) subjects. The authors utilized a Medicaid dataset to identify patients who had received a diagnosis of acne in 2003 and had no prior IBD diagnosis. The authors concluded there is an inverse association between oral antibiotics and the development of IBD in acne patients with a dose-response relationship. Clinicians and prospective patients should be cognizant of the lack of a causal relationship between isotretinoin for acne and the development of IBD.
8	**Racine, A., "Isotretinoin and Risk of Inflammatory Bowel Disease: A French Nationwide Study." 2014, American Journal of Gastroenterology, p. 1-7, doi: 10.1038/ajg.2014.8** This population-based case-control study comprised approximately 40,000(+) subjects gleaned from a national health insurance data base containing more than 50 million individuals. The study included 7,593 cases of IBD and 30,372 controls. Based on the data, the authors concluded that isotretinoin exposure was not associated with an increased risk for UC, but was associated with a decreased risk for CD.
9	**Rashtak S, et al., "Isotretinoin Exposure and Risk of Inflammatory Bowel Disease." JAMA Dermatol. 2014 Dec 1;150(12):1322-1326** The retrospective single center cohort study at the Mayo Clinic comprised approximately 1,100 subjects whose medical records showed a reference to isotretinoin over a 16-year period. According to the author, none of the published epidemiological studies have found a significant positive association between isotretinoin and IBD risk as a whole. Only one (Crockett) has found a UC risk but this finding has not been replicated by any other study or by 2 more recent meta-analyses. Finally, the author believes that the meta-analyses performed by Dr. Goodman indicates that when all new data is included there is no

	increased risk of development of UC regardless of the calculation used to perform the evaluation.
10	**Lee SY, et al., "Does Exposure to Isotretinoin Increase the Risk for the Development of Inflammatory Bowel Disease? A Meta-Analysis." Eur J Gastroenterol Hepatol. 2016 Feb;28(2):210-6. doi: 10.1097/MEG.0000000000000496** This meta-analysis was based upon an extensive literature search of multiple databases, seeking articles discussing the relationship between isotretinoin and IBD. Initially, 70(+) studies were identified. Following what appears to be demanding scrutiny, all but six of the studies were eliminated. As noted by the authors at page 211 of their article: " On pooling six studies (N= 9 724 069 patients), the rates of development of IBD were exactly the same among patients exposed to isotretinoin and those not exposed to isotretinoin (0.32 vs. 0.32%). Overall, there was no increased risk of development of IBD among patients exposed to isotretinoin relative to those not exposed to isotretinoin [OR 1.08 95% confidence interval (CI) 0.82, 1.42, P = 0.59].
11	**Ponder, A. and Long, M.D., "A Clinical Review of Recent Findings in the Epidemiology of Inflammatory Bowel Disease." Clinical Epidemiology 2013:5 237-247, 24 July 2013.** This treatise was based upon an extensive literature search. The authors did not focus upon relationship between isotretinoin and IBD, rather they were seeking to gain a better understanding of the epidemiology of IBD. They appear to have labored mightily in an effort to identify risk factors for IBD as expressed in the extensive literature on the epidemiology of IBD. At page 244 of the authors' report, Figure 1 is an informative graphic which illustrates the risk factors for UC and CD. Isotretinoin is not recited as a risk factor. The authors conclude by advising the scientific community that much more work and large cohort studies are needed to gain a better understanding of the risk factors for IBD. "As IBD is a relatively rare disorder, with complicated interactions between potential inciting agents, very large cohorts with detailed, prospectively collected, environmental exposure data will be needed. Of equal importance, particularly to patients with established disease, is a better understanding of the effects of environmental exposures on disease course. Again, large, well-phenotyped cohorts of IBD patients are needed, with detailed prospective collection of environmental exposure data."
12	**Brodin, M.D., "Inflammatory Bowel Disease and Isotretinoin" J Am Acad Dermatol, 14(5 Pt 1): 843** This is a "letter to the editor" from a practicing physician to the Journal of Dermatology informally submitting a case report to the Journal of Dermatology reporting a 26-year old young woman who developed severe gastrointestinal symptoms nine days after beginning treatment with isotretinoin. This item was referenced by Plaintiffs' counsel and witnesses during the *Kemp* hearing.

13	**Reddy, et al., "Possible Association Between Isotretinoin and Inflammatory Bowel Disease" Am. J. Gastroenterology, 2006: 01:1569-1573** This study examines MedWatch reports filed with the FDA regarding patients prescribed isotretinoin. The authors readily acknowledged the "limitations" of case reports such as those filed with the FDA. Using the Naranjo Adverse Drug Reaction Probability Scale, the authors evaluated a total of 85 cases of IBD and concluded that "It is conceivable that isotretinoin is acting as a trigger for IBD in patients with preexisting but subclinical conditions." The record of the *Kemp* Hearing is replete with testimony regarding this study.
14	**Passier, J. et al., "Isotretinoin-Induced Inflammatory Bowel Disease" – The Netherlands Journal of Medicine Vol. 64 No. 2, February, 2006.** This is a well-written and informative case report which reports on three individual teenagers who developed severe gastrointestinal symptoms requiring hospitalization shortly after beginning treatment with isotretinoin. Plaintiffs' counsel and witnesses gave much attention during the *Kemp* Hearing.
15	**Shale, et al., "Isotretinoin and Intestinal Inflammation: What Gastroenterologists Need to Know." Gut: June 2009 Vol 58 No.6** This is an informative scientific essay, not a report on an epidemiological study. Dr. Shale did not perform any new research of his own, rather he reported on what he had learned from reading the peer-reviewed studies of other scientists. As noted by Dr. Sachar on direct-examination, the authors quoted "...what other articles themselves didn't show, but what other articles alluded to. So indirectly they are saying there are well-documented effects of retinoic acid upon epithelial cell[s]..." This essay recites one possibility after another, without postulating a hypothesis, and suggests that additional research is necessary. Dr. Shale concludes by stating, "Significant unanswered questions remain regarding the natural history, disease behavior and optimal therapy of isotretinoin induced intestinal disease." (see Dr. Sachar's testimony, Tr. 2-7-17, P159, L7 thru P161, L2)
16	**Takci, et al., "Effect of Systemic Isotretinoin Therapy on Mucociliary Clearance and Nasal Surface Mucosa in Acne Patients," J D Dermatol Vol. 12, Issue 8, 124-128** The handling of this article and the questioning by Mr. Bolton is illustrative of the routine between counsel and Dr. Sachar on nearly all of the articles presented. "Doctor, does this – is this article support biological plausibility for Accutane causing these things?" Generally, in each instance Dr. Sachar replies in the affirmative, but only after providing his own take on the article. Here, Dr. Sachar says that this article's conclusions are acceptable "only if you believe" that "Inflammatory bowel disease is asthma of the GI tract." (see Dr. Sachar's testimony, Tr. 2-7-17, P161, L7 thru P164, L3)

17	**Basak, et al. "The Effects of Systemic Isotretinoin and Antibiotic Therapy on the Microbial Flora in Patients with Acne Vulgaris." JEADV 2012** The purpose of this study was to examine the effect, separately, of isotretinoin and antibiotics on the microbial flora of the upper part of the respiratory tract. In response to Mr. Bolton, Dr. Sachar opines that this article supports biological plausibility. Yet, Dr. Basak and his co-authors don't opine or conclude very much, they are merely reporting on what they learned. At page 127 of their article they concede the limitation of their investigation and conclude, "Therefore, we do not know whether or not there was any qualitative or quantitative alteration of the cilia due to isotretinoin therapy." (see Dr. Sachar's testimony, Tr. 2-7-17, P164, L8 thru P166, L3)
18	**Oehlers, et al., "Retinoic Acid Suppresses Intestinal Mucus Production and Exacerbates Experimental Enterocolitis," Disease Models & Mechanisms 5, 457-467 (2012) doi:10.1242/dmm.009365** The subject of this study is novel; it examines the intestinal epithelium of zebra fish larvae, and compares it with the mammalian intestinal inflammatory processes. The authors of this study believe that "The zebrafish larva is an emerging model system for investigating the pathogenesis of IBD." According to Dr. Sachar, "This study illustrates a direct effect of retinoid administration on intestinal mucus physiology and subsequently on the progression of intestinal inflammation." As he did routinely, Mr. Bolton asks regarding this study, "that supports a theory of biological plausibility, correct?" And Dr. Sachar answers that "It provides a mechanism of biological plausibility, a mechanism by which it reasonably could." The Court doesn't challenge Dr. Sahar's opinion, but must note that it is limited to the inflammation of the intestines of zebrafish larva. Though this may be cutting-edge science, it is a long way from examining the intestines of dogs. The *Reference Manual* discusses the limitations of experiments on animals and equating the results of the same with humans. The Court will not digress. (see Dr. Sachar's testimony, Tr. 2-7-17, P167, L2 thru P168, L10).
19	**Hall, et al., "The Role of Retinoic Acid in Tolerance and Immunity," Immunity Review 35:13-22. DOI 10.1016/j.immuni.2011.07.002** This article is very informative; it is an extensive review of the scientific literature on "The vitamin A metabolite, retinoic acid (RA)..." The authors review the article of other scientists and their findings regarding RA's impact on the epithelial layer of the gastrointestinal tract, and the role of RA in regulation of "T cells." According to Dr. Sachar, this article supports biological plausibility and the take away from it is "that if you pharmacologically administer more than the body's normal amount of retinoic acid it can potentially promote inflammatory disorders. Well, how? And this study discusses some of the ways it can happen." Notwithstanding D. Sachar's opinion, this study does not postulate a hypothesis of any sort, rather it suggests that additional research is necessary. The study concludes by noting that, "Greater understanding of how these factors play into RA synthesis during

	homeostasis and inflammation will be essential for assessing their efficacy as therapeutic modalities in the treatment of syndromes in which the retinoid imbalances may be involved." (see Dr. Sachar's testimony, Tr. 2-7-17, P168, L18 thru P170, L4)
20	**Kim et al., "Retinoic Acid Differentially Regulates the Migration of Innate Lymphoid Cell Subsets to the Gut," 43 Immunity 107 (2015)** This is a very detailed article based upon animal studies using mice to examine how various innate lymphoid cells (ILCs) which populate the intestines interact with RA. Though the Court read and re-read this article, much of what is said by the authors requires far more knowledge in science than the undersigned possesses. That said, the authors do not postulate a hypothesis of any sort regarding isotretinoin nor RA. Their entire discussion is limited to reporting on what they learned regarding how ILC subsets migrate to the gut and the different homing receptors required for that process. The Court can envision how the findings of this article (and several that follow hereinafter) may yield scientific evidence which might be valuable in the articulation of a hypothesis as to a causal association between isotretinoin and IBD. Regrettably, Dr. Sachar has declined to formally articulate such a hypothesis. (see Dr. Sachar's testimony, Tr. 2-7-17, P170, L18 thru P171, L23)
21	**Ruiter et al., "Vitamins A and D Have Antagonistic Effects on Expression of Effector Cytokines and Gut-Homing Integrin in Human Innate Lymphoid Cells," 45 Clin. Exp. Allergy 1214 (2015)** This article is akin to the "Kim" article hereinabove in that though the Court read and re-read this article, much of what is said by the authors requires far more knowledge in science than the undersigned possesses. That said, the authors do not postulate a hypothesis of any sort regarding isotretinoin nor RA. Their entire discussion is limited to reporting on how RA can have an antagonistic effect on effector cytokines and gut-homing integrin in human ILCs. Toward the end of their article, the authors note: "Allergic and other chronic immune-mediated diseases have become rapidly more prevalent in association with modernization around the world. There are myriad environmental changes suggested to explain this association. The 'vitamin hypothesis' that nutritional shifts accompanying these lifestyle changes, including increasing vitamin A sufficiency and vitamin D deficiency may contribute to this trend…" (see Dr. Sachar's testimony, Tr. 2-7-17, P171, L24 thru P172, L25)
22	**Do et al., "Colitogenic Effector T cells: Roles of Gut-Homing Integrin, Gut Antigen Specificity and γδ T cells," 92 Immunol. Cell Biol. 90 (2014)** This article is akin to the "Kim" and "Ruiter" articles hereinabove in that much of what is said by the authors requires far more knowledge in science than the undersigned possesses. That said, the authors do not postulate a hypothesis of any sort regarding isotretinoin nor

	RA. Their entire discussion is limited to reporting on how the disturbance of "T cell" homeostasis can lead to intestinal inflammation. (see Dr. Sachar's testimony, Tr. 2-7-17, P173, L2 thru L16)
23	**McCarthy et al., "Proinflammatory Vδ2+ T cells populate the human intestinal mucosa and enhance IFN-γ production by colonic αβ T cells," 191 J. Immunol. 2752 (2013)** This article is akin to the "Kim," "Ruiter," and "Do" articles hereinabove in that the focus is highly specialized. This study examined biopsies of human terminal ileum and colonic mucosa obtained from patients undergoing colonoscopy for colorectal screening. The authors focus is "T cells" and that particular types of such cells play a role in causing inflammation. According to D. Sachar, "It [R/A] enhances the binding to the adhesion molecule that's in the vessels and the gut. And it thereby generates a committed gut-tropic phenotype, which means it activates a particular set of inflammatory cells, lymphocytes, to come to the gut and do their dirty work." The Court can envision how the findings of this article may yield scientific evidence which might be valuable in the articulation of a requisite hypothesis. Regrettably, Dr. Sachar has declined to formally articulate such a hypothesis. (see Dr. Sachar's testimony, Tr. 2-7-17, P173, L17 thru P174, L7)
24	**Ohoka, et al., "Retinoic Acid-Induced CCR9 Expression Requires Transient TCR Stimulation and Cooperativity between NFATc2 and the Retinoic Acid Receptor/Retinoid X Receptor Complex," J Immunol 2011; 186:733-744. doi: 10.4049/jimmunol.1000913** Much like the several articles which precede this, Dr. Ohaka's study has a very specialized focus, namely, vitamin A metabolites. As noted by Dr. Sachar, the study "Takes it for granted that everybody knows that there's a retinoic acid-induced CCR9 expression on T-cells, which are the effector inflammatory cells." He later states that the findings of this study provide "...a biologically plausible mechanism by which Accutane can induce inflammatory bowel disease, specifically ulcerative colitis." Yet the authors do not state any such hypothesis. (see Dr. Sachar's testimony, Tr. 2-7-17, P174, L18 thru P175, L16)
25	**Mwanza-Lisulo and Kelly, "Potential for Use of Retinoic Acid as an Oral Vaccine Adjuvant," 19 Philos. Trans. R. Soc. London B Biol. Sci. 370 (2015)** This study discusses the lack of vaccines against diarrheal disease. The authors touch upon vitamin A and note that "There have been many studies which show an association between increased infectious disease and evidence of compromised vitamin A status." This study has limited relevance to these proceedings. Dr. Sachar apparently believes it creates another line of evidence in support of biological plausibility. As he states, "And I don't want to overemphasize the fact that this is proof

	that Accutane causes ulcerative colitis, but it is a biologically plausible mechanism by which it can." (see Dr. Sachar's testimony, Tr. 2-7-17, P175, L19 thru P176, L21)
26	**Wang, et al., "Retinoic Acid Determines the Precise Tissue Tropism of Inflammatory Th17 Cells in the Intestine." The Journal of Immunology, 2010, 184: 5519-5526** Much like several of the articles hereinabove, Dr. Wang's study has a very specialized focus, namely, "T Cells." Much of what is said by the authors requires far more knowledge in science than the undersigned possesses. Nonetheless, Dr. Sachar attempts to tie these findings to this litigation. He states, "Now, they're not saying that it's proven that Accutane causes spontaneous development of inflammatory bowel disease. But they are saying some people think so. And if it does, this is one way it could do it. In other words, they are proposing a biological plausibility." (see Dr. Sachar's testimony, Tr. 2-7-17, P177, L4 thru P179, L8)
27	**Sivaraman S, et al., "Risk of Inflammatory Bowel Disease from Isotretinoin: A Case-Control Study." Am J Gastroenterol. 2014; 109(S2):S506** This is a non-peer-reviewed abstract that was not reduced to a formal written report. It comprises 1/4 page in the October, 2014, Edition of the American Journal of Gastroenterology. It was posted on a bulletin board at a conference in a hotel in Las Vegas. The study comprises a total of 509 subjects. Dr. Sachar confirmed the Court's view on this document, namely, it is not of the nature, character nor quality which scientists would normally rely upon. Nevertheless, Plaintiffs' experts make use of it in their opinions.
28	**Farmer, M., et al., "The Importance of Diagnostic Accuracy in Colonic Inflammatory Bowel Disease," November 2000, Amer. J. Gastroenterol., Vol. 95, No. 11, p. 3184-3188** This study addresses the diagnostic issues, and problems of accuracy in distinguishing between UC and CD. The authors examined the histology of 119 patients who were initially believed to have colonic IBD. The authors note that "The definitive diagnosis of IBD – a complex process involving the patient, clinician, radiologist, and pathologist – often requires sequential investigations over time." The report provides statistics on the % of instances in which there was an initial misdiagnosis. It concludes that the study was not meant as a critique of pathologists, but rather "to highlight the extreme diagnostic difficulties of colonic IBD."
29	**Mozsik G, Bodis B, Figler M, Kiraly A, Karadi O, Par A, Rumi G, Suto G, Toth G, Vincze Gyula. (2001). "Mechanisms of Action of Retinoids in Gastrointestinal Mucosal Protection in Animals, Human Healthy Subjects and Patients. Life Sci 69(25 26): 3103 12**

	This article is one which opines that RA may have a positive effect upon the gastrointestinal tract. This study is a review paper that examines many other studies – and a variety of studies both animal and human - that have been performed over the years. In short, they conclude that retinoids are likely to have a helpful and protective effect on the mucosa and the gastrointestinal tract generally.
30	**Bai A, Lu N, Zen H, Li Z, Zhou X, Chen J, Liu P, Peng Z, Guo Y. "All Trans Retinoic Acid Ameliorates Trinitrobenzene Sulfonic Acid Induced Colitis by Shifting Th1 to Th2 Profile." Journal of Interferon & Cytokine Research 2010. 30(6): 37 44. Doi:10.1089/jlr.2009.00280** The authors of this study utilized a well-recognized mouse model of inflammatory bowel disease, and administered retinoic acid to the mice. In the process, they were able to show that the administration of retinoic acid improved the colitis, by calming it down and minimizing the effects. In short, the authors conclude that this is evidence showing that retinoids can be considered as therapies for IBD.
31	**Mielke LA, Jones SA, Raverdeau M, Higgs R, Stefanska A, Groom JR, Misiak A, Dungan LS, Sutton CE, Streubel G, Bracken AP, Mills KH. "Retinoic Acid Expression Associates with Enhanced IL 22 Production by γδ T Cells and Innate Lymphoid Cells and Attenuation of Intestinal Inflammation." J Exp Med. 2013 May 20. [Epub ahead of print] PubMed PMID: 23690441** This was a study in which the authors looked at colonic inflammation, again, as in "Bai," utilizing a mouse model of inflammatory bowel disease, their focus was whether or not retinoic acid, can improve or decrease the inflammation. They showed in this case that again RA decreased the inflammation in these animals.
32	**Hong K, Zhang Y, Guo Y, Xie J, Wang J, He X, Lu N, Bai A. "All Trans Retinoic Acid Attenuates Experimental Colitis Through Inhibition of NF κB signaling." Immunol Lett. 2014 Nov;162(1 Pt A):34 40. doi: 10.1016/j.imlet.2014.06.011. Epub 2014 Jul 6** Similar to the two preceding studies, the authors made use of a mouse model of IBD. Their focus was to determine whether or not RA might have an ameliorative effect on the inflammation of the GI tract. The authors of this study concluded that retinoic acid can be considered as therapy for IBD. This study together with the several preceding it are illustrative of a school of thought within the scientific community that retinoic acid has the potential to be used as a therapy for IBD.

ADDENDUM C

Epidemiologic Studies Examined by Dr. Steven N. Goodman

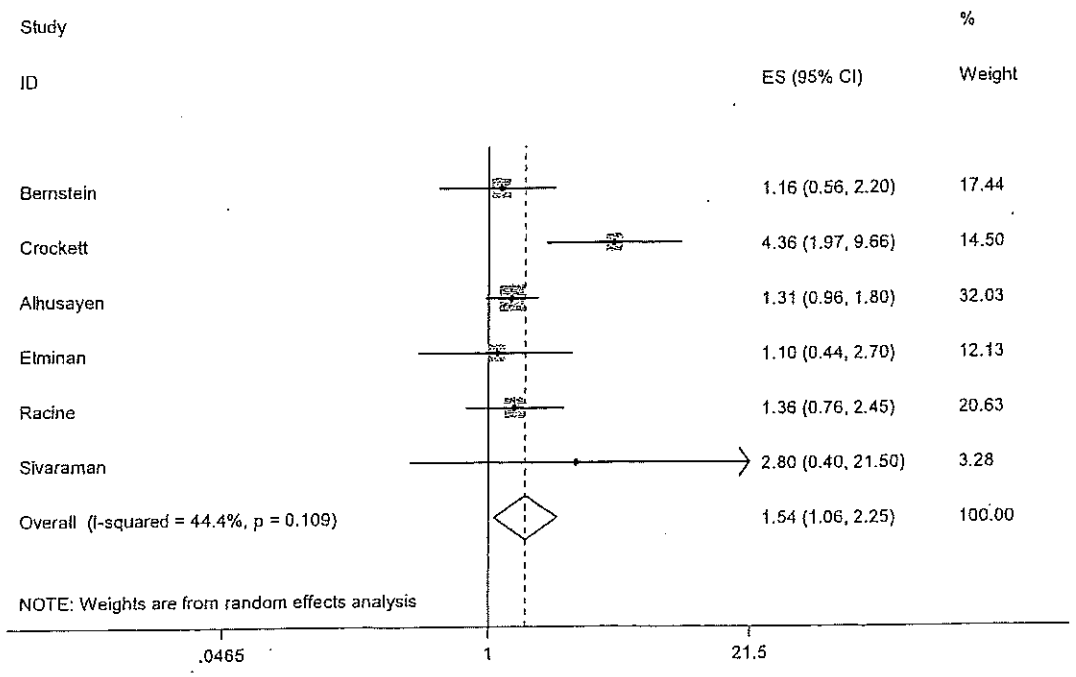
Table: Epidemiologic studies examining the relationship of isotretinoin, IBD and UC

Author, year	**M/A**[1]	**Primary outcome**	**N (approx.)**	**All IBD RR (95% CI)**	**UC RR (95% CI)**
Bernstein, 2009	M	IBD	21,500	1.16 (0.73-1.77)	1.16 (0.56-2.20)
Crockett, 2010	M	IBD	29,000	1.68 (0.98-2.86)	4.36 (1.97-9.66)
Etminan2, 2012	M[2]	IBD	80,000	0.62 (0.43-0.89)	***Not reported***
Alhusayen, 2013	M	IBD	1,700,000	1.14 (0.92-1.41)	1.31 (0.96-1.80)
Fenerty, 2013	A, PPT	IBD	175,000	0.57 (0.28-1.16)	***Not reported***
Etminan, 2013	M	IBD	45,500	0.99 (0.52-1.90)	1.10 (0.44-2.70)
Rashtak, 2014	M	IBD	1000	0.28 (0.10-0.80)	0.34[3] (0.11 – 1.04)
Racine, 2014	M	IBD	44,000	0.74 (0.49-1.13)	1.36 (0.76-2.45)
Sivaraman, 2014	A	UC, CD	500	***Not reported***	2.8 (0.4-21.5)
Meta-analytic summary		**Profile Likelihood**	**2,100,000**	**0.88 (0.62-1.18)** *p=0.36*	**1.36 (0.79-2.32)** *p = 0.26*
		DerSimonian-Laird		**0.87 (0.65-1.17)** *p=0.24*	**1.36 (0.88 – 2.1)** *p = 0.17*

ADDENDUM D

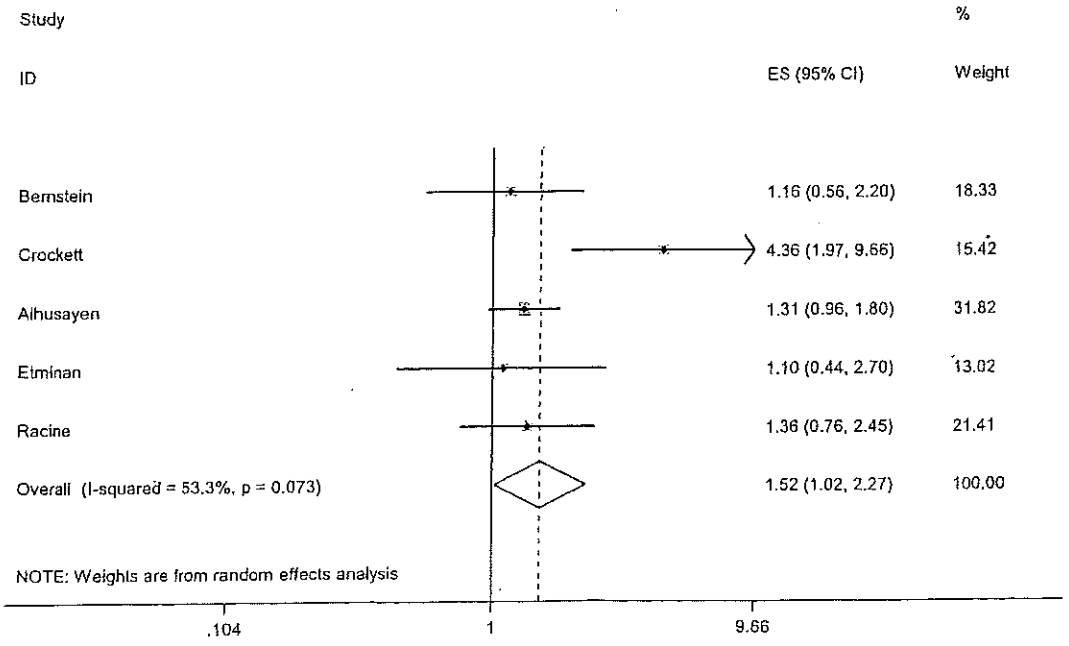
Meta-Analysis Performed by Dr. April Zambelli-Weiner

Figure 1: Forest plot of meta-analysis results, all adjusted analyses



The exclusion of Sivaraman had little impact on the results, producing a pooled odds ratio of 1.52, with a 95% confidence interval of 1.02 to 2.27 (**Table 5**), indicating a similar statistically increased risk of UC with isotretinoin exposure. Analysis also rendered an I^2 value of 53.3 percent (p=0.073).

Figure 2: Forest plot of meta-analysis results, all adjusted analyses and excluding Sivaraman



ADDENDUM E

Meta-Analysis Performed by Dr. Steven N. Goodman

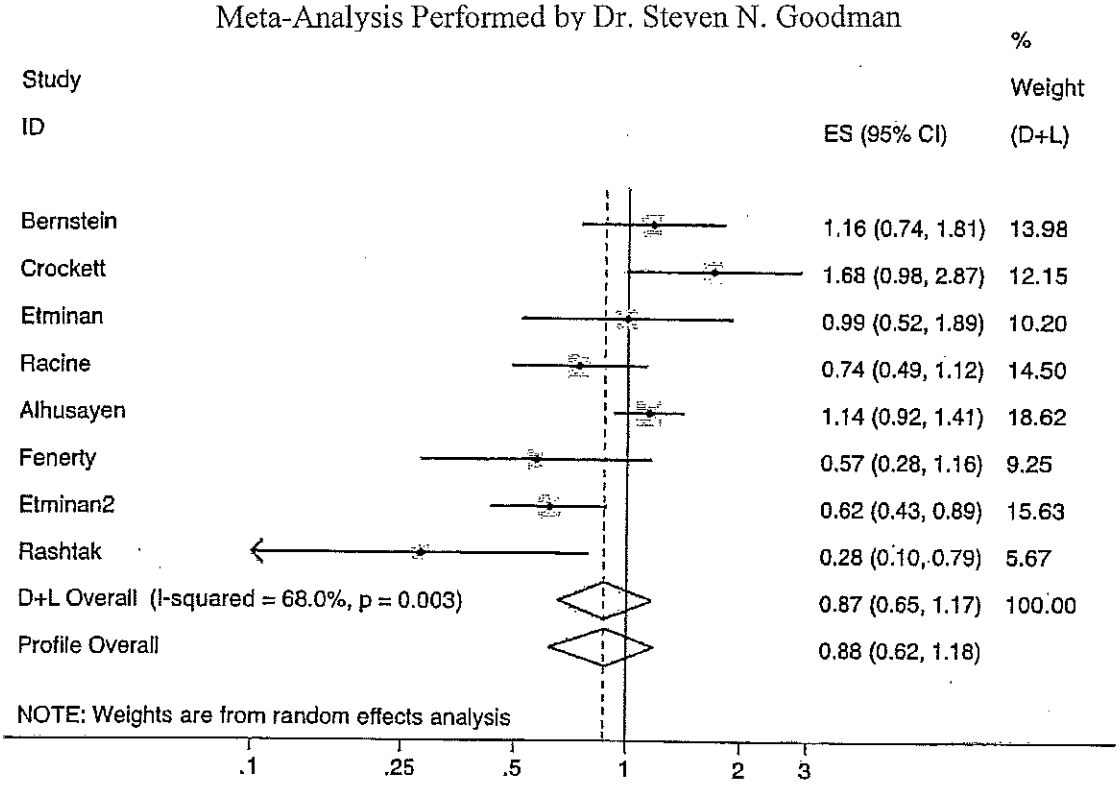


Figure 1: Display of effect sizes and 95% confidence intervals for existing studies of IBD and Accutane, with meta-analytic summaries. The summary based on the DerSimonian-Laird ("D-L") method is represented by the top diamond, and that by the profile likelihood method ("Profile") is the lower diamond, with the respective summary RR's and CIs on the right. The X-axis numbers represent the relative risk (or odds ratios, which are equivalent in this case).

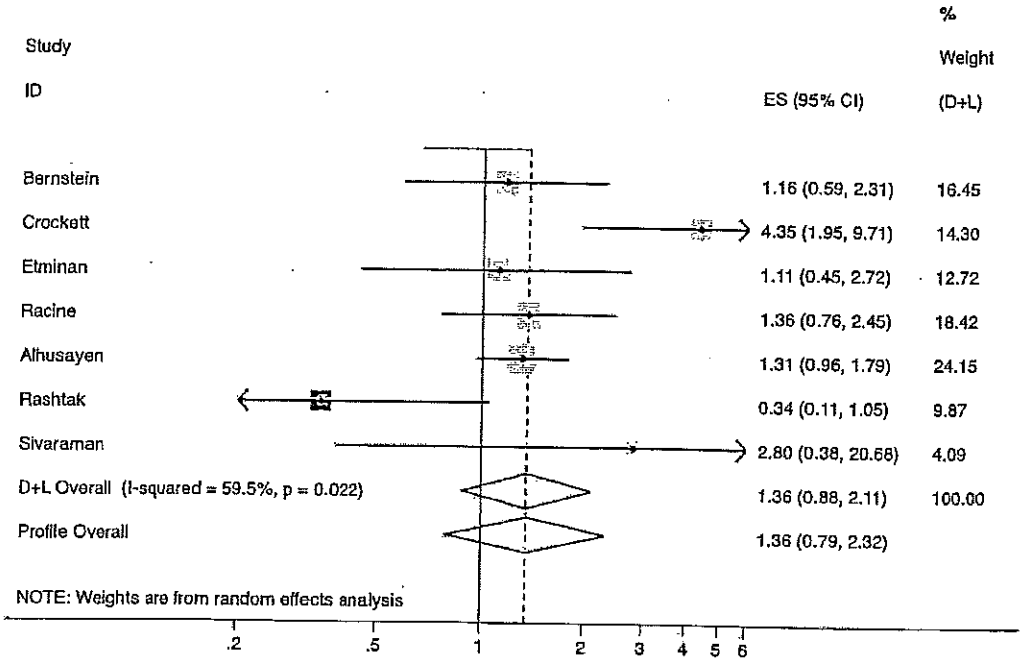


Figure 2: Display of effect sizes and 95% confidence intervals for existing studies of IBD and Accutane, with meta-analytic summaries. The summary based on the DerSimonian-Laird ("D-L") method is represented by the top diamond, and that by the profile likelihood method ("Profile") is the lower diamond, with the respective summary RR's and CIs on the right. (A Knapp-Hartung analysis was also conducted, with results similar to the profile likelihood result.) The X-axis numbers represent the relative risk (or odds ratios, which are equivalent in this case).