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PEER REVIEW

Scientific Evidence

As scientific evidence is central to most mass tort and product liability actions, it is important for counsel to consider the strengths and weaknesses of peer-review, and how peer-reviewed scientific literature may be challenged, say attorneys Bert L. Slonim and Lori B. Leskin in this BNA Insight. This article identifies potential areas of inquiry for counsel when facing a peer-reviewed, published article, as well as the possible remedies to invoke when scientific flaws are discovered.

A Primer on Challenging Peer-Reviewed Scientific Literature in Mass Tort and Product Liability Actions

BY BERT L. SLONIM AND LORI B. LESKIN

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Peer-review refers to the critical assessment of manuscripts submitted to scientific journals by unbiased independent experts who are not part of the journal's editorial staff.[1] Peer-review is widely used by journals to help determine which manuscripts are worthy of publication, and to help authors and editors improve the quality of published articles. In litigation, the Supreme Court's *Daubert* opinion recognized peer-

[1] *See* International Committee of Medical Journal Editors, Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Ethical Considerations in the Conduct and Reporting of Research: Peer Review, *available at* http://www.icmje.org/ethical_3peer.html.

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review as a critical factor – ''relevant, though not dispositive'' – in assessing the reliability of an expert's opinion.[2]

Because scientific evidence is central to most mass tort and product liability litigations, it is important for counsel to consider the strengths and weaknesses of peer-review, and how peer-reviewed scientific literature may be challenged. This article identifies potential areas of inquiry for counsel when facing a peer-reviewed, published article, as well as the possible remedies to invoke when scientific flaws are discovered.

Peer Review Failure

Peer-review is not fool-proof; the fact that an article has been peer-reviewed does not guarantee high quality or even scientific accuracy. Long before *Daubert*, the *New England Journal of Medicine* candidly admitted that ''peer review is not and cannot be an objective scientific process, nor can it be relied on to guarantee the validity or honesty of scientific research.''[3] Drummond Rennie, deputy editor of the *Journal of the American Medical Association* and director of the quadrennial International Congresses on Peer Review and Biomedical Publication, similarly observed that there is ''no study too fragmented, no hypothesis too trivial, no literature too biased or too egotistical, no design too warped, no methodology too bungled, no presentation of results too inaccurate, too obscure, and too contradictory, no analysis too self-serving, no argument too circular, no conclusions too trifling or too unjustified, and no grammar and syntax too offensive for a paper to end up in print.''[4]

Recent examples have highlighted significant failures of the peer-review process:[5]

- *Lumpectomy/breast cancer* – Breast cancer treatment was revolutionized when a study published in the *New England Journal of Medicine* reported that breast-conserving lumpectomy was just as effective as mastectomy for early stage breast cancer.[6] Unknown at the time was that one of the investigators had falsified surgical and laboratory study data. Even after the fraud was uncovered in the early 1990s, it was not disclosed to physicians, patients or the public. Although subsequent reanalysis of the data (excluding the falsified data) confirmed the study's key finding, for many patients, a life-and-death decision was made on the basis of the fraudulent data.[7]

- *MMR vaccine/autism* – In 1998, *Lancet* published a peer-reviewed study linking the measles-mumps-rubella vaccine to autism.[8] The study was the opening shot in a decades-long controversy over the safety of this required childhood vaccine. Undisclosed was the fact that the lead author of the study had received payments from a plaintiff's attorney, that the methods purported to have been used were not followed, and that required ethics approvals for pediatric subjects had not been obtained.[9] In 2010, the lead author was sanctioned and *Lancet* ''fully retract[ed] this paper from the published record.''[10]

- *Viagra/vision loss* – In 2006, a study published in the *British Journal of Ophthalmology* purportedly linked Viagra to NAION, a condition that can cause vision loss. That article fueled multidistrict product liability litigation and the lead author became plaintiffs' key expert witness. Subsequent discovery revealed substantial inaccuracies in the study data, errors in the statistical methods, and mistakes in the computer programming as well as other flaws. Ultimately, the court concluded that the study was unreliable, and the expert's opinion relying on it, inadmissible: ''Peer review and publication mean little if a study is not based on accurate underlying data.''[11]

- *Accutane/depression & suicide* – In 2005, the *American Journal of Psychiatry* published a study linking Accutane to depression.[12] The article disclosed funding by lawyers involved with Accutane litigation and acknowledged some methodological limitations. However, at a later court hearing, the researcher ''admitted that he did not in fact follow the steps described in the article.''[13] The researcher ''could not document much of the data on which his published results were based,'' ''admitted that some of the statistical analysis was inaccurate,'' and ''that some of the [data] he used in his calculations were inaccurate, [and testified that he] could not check the accuracy of the remaining numbers because the original data could not be retrieved.''[14] Based on these flaws, the court held that the study ''was not soundly and reliably generated,'' and therefore the expert could not rely on the study.[15]

While most scientific publications are not so fundamentally flawed, these examples should encourage counsel to look behind the publication when confronted with peer-reviewed, published medical literature. We discuss below some of the potential hot spots to be examined, as well as some procedures for doing so.

Questions That Should Be Asked About Peer-Reviewed Studies

- *Is the publication a bona-fide peer-reviewed scientific journal?*

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[2] *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 509 U.S. 579, 594 (1993) (citations omitted).

[3] Arnold S. Relman & Marcia Angell, *How Good Is Peer Review*, 321 New Eng. J. Med. 827, at 828 (1989).

[4] Drummond Rennie, *Guarding the Guardians: A Conference on Editorial Peer Review*, 256(7)J. Am. Med. Ass'n 2391 (1986).

[5] Andrew A. Skolnick, *The Maharishi Caper: Or How to Hoodwink Top Medical Journals*, Science Writers: The Newsletter of the National Association of Science Writers, (1991), *available at* http://www.aaskolnick.com/naswmav.htm (describing how the Journal of the American Medical Association was deceived in publishing an article about an alternative system of medical therapy known as Ayurveda).

[6] Bernard Fisher et al., *Five-Year Results of a Randomized Clinical Trial Comparing Total Mastectomy and Segmental Mastectomy With or Without Radiation in the Treatment of Breast Cancer*, 312 New. Eng. J. Med. 665 (1985).

[7] Marcia Angell & Jerome P. Kassirer, *Setting the record straight in the breast-cancer trials*, 330 New Eng. J. Med. 1448 (1994).

[8] A.J. Wakefield et al., *Ileal-lymphoid-nodular hyperplasia, non-specifi c colitis, and pervasive developmental disorder in children*, 351 Lancet 637 (1998).

[9] UK General Medical Council's Fitness to Practise Panel on Jan 28, 2010, available at http://www.scribd.com/doc/25983372/FACTS-WWSM-280110-Final-Complete-Corrected.

[10] Editors of the Lancet, *Retraction—Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children*, 375 Lancet 445 (2010).

[11] *In re Viagra Products Liab. Litig.*, 658 F. Supp. 2d 936, 945 (D. Minn. 2009).

[12] J. Douglas Bremner et al., *Functional Brain Imaging Alterations in Acne Patients Treated With Isotretinoin*, 162 Am. J. Psychiatry 983 (2005).

[13] *Palazzolo v. Hoffman-La Roche Inc.*, No. A-3789-07T3, slip op. at 10 (N.J. Super. App. Div. Feb. 3, 2010).

[14] *Id.* at 11-12.

[15] *Id.* at 12, The Appellate Division remanded the case to the trial court to consider whether the expert should be permitted to testify without the excluded study.

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Not all journals are created equal. Because journals range widely in quality, it is worth investigating the bona fides of the publication and the stringency of its peer-review process. ''Legitimate'' medical journals, including such leading journals as *Annals of Internal Medicine*, *BMJ*, *JAMA*, *The Lancet*, and *New England Journal of Medicine*, while not immune to fraudulent or improperly conducted studies, have medical doctors on their editorial board, are regularly indexed and cited, and conduct a rigorous peer-review of submitted articles. Their articles include new and original research, and vigorous scientific debate through correspondence is encouraged.

On the other hand, ''Supplements'' and ''Theme Issues'' or ''Special Series'' are ''collections of papers that deal with related issues or topics, are published as a separate issue of the journal or as part of a regular issue, and are usually funded by sources other than the journal's publisher.''[16] Articles in these special editions may not have been subjected to the journal's standard peer review process.

''Complimentary Journals'' are not real scientific journals but may be mistaken for such. The medical publisher Elsevier recently acknowledged that it had been paid to produce several volumes of the *Australasian Journal of Bone and Joint Medicine* and other similar ''journals.'' Although these journals had ''an honorary editorial board,'' they were not peer-reviewed, were not indexed in Medline, did not have a website, and did not disclose that publication was completely corporate funded.[17]

''Throwaway Journals'' are free publications that ''contain no original investigations . . . have a high advertisement-to-text ratio, and are nonsociety publications.''[18] While the content is sometimes disparaged as simplistic, practicing physicians often find these journals to be accessible and useful to clinical practice.[19] Yet, a throwaway journal may not use peer-review at all, or if it does, there may be questions about the stringency of the review. One study of peer-review at various medical journals reported that ''[i]n general the type of review to which articles in throwaways are subjected seems to be far different from the searching sort of peer-review used by the six legitimate journals cited.''[20]

■ *Does the article report research which has been replicated (''true peer review''), or research that has been published but not replicated (''editorial peer review''), or is it merely an opinion piece published in a peer-reviewed journal?*

There is an important difference between scientific research which has been replicated by other scientists, and research that has been published but not replicated. The case law refers to this as the distinction between ''editorial peer review'' (publication in a peer-reviewed journal) and ''true peer review'':

> True peer review means that a scientific hypothesis is subjected to independent evaluation by other scientists in that particular field, typically by independent testing and replication of the results. Pre-publication ''editorial peer review,'' on the other hand, usually consists of sending the proposed article to several outside reviewers who comment on its content and make a recommendation on publication. It is simply not feasible for the editorial staff or the outside reviewers to attempt to replicate the author's findings prior to publishing them. . . . Consequently, just because an article is published in a prestigious journal, or any journal at all, does not mean per se that it is scientifically valid.[21]

In the case of biomedical studies, which often involve large clinical trials or vast amounts of observational data, financial resources and time constraints make complete, independent, replication impractical. Nevertheless, true peer review is possible if the underlying data used in the study is made available to other scientists. Because ''[i]ndependent replication by independent scientists in independent settings provides the best assurance that a scientific finding is valid,'' medical journals increasingly are requiring authors to be prepared to share their raw, unprocessed data, including the study protocol, the electronic dataset used in the analysis, and the computer code used to analyze the data and generate the statistical results.[22]

Journals often publish – and experts often cite – review articles (summarizing a body of research), editorials, commentaries, viewpoints, or perspectives.[23] Such articles may or may not be subject to even editorial peer review. Even if they are peer-reviewed, because these types of articles are inherently opinion pieces, and may be intended to put forth controversial positions, publication in a peer-reviewed journal does not signify scientific validity.[24]

An understanding of the level of peer-review to which an article is subjected can be central to challenging its reliability.

■ *Has the author disclosed litigation consulting work?*

Virtually all journals require authors to disclose conflicting financial interests. Where an author has been retained by a party as a litigation expert, and for that reason has a financial interest in the outcome of the liti-

[16] International Committee of Medical Journal Editors, Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Publishing and Editorial Issues Related to Publication in Biomedical Journals: Supplements, Theme Issues, and Special Series, *available at* http://www.icmje.org/publishing_6supplement.html.

[17] Salamander Davoudi S & Andrew Jack, *Elsevier admits journal error*, Financial Times (London),May 6, 2009, *available at* http://www.ft.com/cms/s/0/c4a698ce-39d7-11de-b82d-00144feabdc0.html?nclick_check=1.

[18] Paula A. Rochon, et al, *Comparison of Review Articles Published in Peer-Reviewed and Throwaway Journals*, 287 J. Am. Med. Ass'n 2853 (2002).

[19] *Id.*

[20] Drummond Rennie, Lisa A. Bero, *Throw It Away Sam: The Controlled Circulation Journals*, 155 Am. J. Roentgenology 889, at 891 (1990).

[21] *Pick v. Amer. Med. Sys.*, 958 F. Supp. 1151, 1178 n.19 (E.D. La. 1997), *aff'd*, 198 F.3d 241 (5th Cir. 1999).

[22] Christine Laine et al., *Reproducible Research: Moving Toward Research the Public Can Really Trust*, 146 Annals Internal Med. 450, at 451 (2007). *See also* Roger D. Peng et al., *Reproducible Epidemiolgic Research*, 163 Am. J. Epidemiology 783 (2006).

[23] *See e.g.*, JAMA, Instructions for Authors (''*JAMA* publishes original contributions, reviews, brief reports, special communications, commentaries, and other categories of articles.'') http://jama.ama-assn.org/misc/ifora.dtl#Commentary.

[24] For example, the Journal of Applied Physiology advises that ''Viewpoint articles are a type of Perspective that are intended to present an insightful, thoroughly documented slant on a topic for which opinions are either controversial or undecided in the literature.'' http://www.the-aps.org/publications/specialcalls/jappl-pcp-instructions.htm.

gation, there is a disclosure obligation.[25] Nevertheless, litigation experts often fail to disclose such conflicts.

For example, in July 2008, *Lancet Oncology* published an article regarding smokeless tobacco and cancer in which the authors ''declare[d] no conflicts of interest.''[26] Shortly after publication, the journal learned that one of the authors, Dr. Steven Hecht, had been working as a plaintiffs' litigation expert. The journal promptly published a correction disclosing Dr. Hecht's expert role.[27] The Committee on Publication Ethics, which promulgates guidelines adopted by many scientific journals, has found the non-disclosure of litigation consulting to be ''a major conflict'' of interest. COPE recommends that journal editors investigate any alleged failure to disclose expert litigation work and that they either require disclosure or refuse to publish the manuscript.[28]

Thus, where a litigation expert has published on a topic pertinent to a case, the timing of the expert's retention and disclosure to the publication should be explored.

■ *Did the researcher actually follow the methods described in the published article?*

Articles reporting original scientific research are generally ''divided into the following sections: Introduction, Methods, Results, and Discussion. This so-called 'IMRAD' structure is not an arbitrary publication format but rather a direct reflection of the process of scientific discovery.''[29] The ''methods'' section is crucial because it permits readers to assess precisely how the investigator conducted the experiment and to assess the impact of any methodological flaws. Challenges to peer-reviewed studies often focus on the limitations inherent in the methods described in the published articles. However, recent cases have revealed instances where the researchers – either intentionally or unintentionally – have not followed their stated methodology.

Peer-reviewed scientific evidence is central—often outcome determinative—to product liability and mass tort litigation.

For example, in the recent Viagra litigation, the researcher represented in the published paper that he counted subjects as ''exposed'' to Viagra only if they used the medication before they developed NAION; the court found that the researcher did not adhere to this methodology and that a number of subjects who were counted as exposed had in fact been diagnosed with NAION *before* they first used the medication.[30] Similarly, in the Accutane case, the Court found that ''contrary to representations made in the article, [the researcher] did not get before-and-after . . . questionnaires from many of the subjects.''[31] Likewise, in the MMR vaccine case, the *Lancet's* retraction reports that the investigator did not adhere to the methods claimed in the study: ''In particular, the claims in the original paper that children were 'consecutively referred' and that investigations were 'approved' by the local ethics committee have been proven to be false.''[32]

Even where deviations from the published methodologies do not rise to the level necessary to undermine the reliability of the entire study, the information may be critical for the cross-examination of experts at trial. In the *PPA* litigation, the MDL court permitted plaintiffs' experts to rely on the central study demonstrating an association between PPA and stroke, recognizing that defendants were free to raise their challenges to the methodological deviations at trial. As courts have repeatedly stated, ''vigorous cross-examination of a study's inadequacies allows the jury to appropriately weigh the alleged defects and reduces the possibility of prejudice.''[33]

These examples demonstrate the need to investigate each and every step in the conduct of a published study. While the stated methods may appear valid on their face, discovery may demonstrate that the researchers did not actually follow the methods set forth in the published paper.

[25] The ''Uniform Requirements for Manuscripts Submitted to Biomedical Journals,'' promulgated by the International Committee of Medical Journal Editors specify that ''Financial relationships (such as employment, consultancies, stock ownership, honoraria, and *paid expert testimony*) are the most easily identifiable conflicts of interest and the most likely to undermine the credibility of the journal, the authors, and of science itself,'' and place responsibility on the author/litigation expert ''for disclosing all financial and personal relationships that might bias their work.'' Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Ethical Considerations in the Conduct and Reporting of Research: Conflicts of Interest, *available at* http://www.icmje.org/ethical_4conflicts.html (emphasis added). Some medical journal conflict-of-interest forms affirmatively require authors to disclose whether they ''Provide expert witness testimony for a commercial entity, or in any litigation related to the subject of the manuscript.'' CHEST Conflict of Interest Disclosure Form, *available at* http://chestjournal.chestpubs.org/site/misc/COI_CHEST.pdf

[26] Paolo Boffetta et al., *Smokeless tobacco and cancer*, 9 Lancet Oncology 667, at 673 (2008).

[27] Editors of Lancet Oncology, Errata, 9 Lancet Oncology 822 (2008) (Refers to: Paolo Boffetta et al., *Smokeless tobacco and cancer*, 9 Lancet Oncology 667 (2008)).

[28] Committee on Publication Ethics (COPE), Forum Agenda and Materials 2 December 2009, Case 09-19, Provenance of a correction: undisclosed court case involvement, *available at* http://publicationethics.org/files/u661/COPE_Forum_Agenda___materials_02_12.pdf; Committee on Publication Ethics (COPE), What to do if a reviewer suspects undisclosed conflict of interest (CoI) in a submitted manuscript, *available at* http://publicationethics.org/files/u2/05A_CoI_Submitted.pdf

[29] International Committee of Medical Journal Editors, Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Manuscript Preparation and Submission: Preparing a Manuscript for Submission to a Biomedical Journal, *available at* http://www.icmje.org/manuscript_1prepare.html.

[30] 658 F. Supp.2d 936, at 942-944.

[31] Accutane slip op. at 10-11.

[32] Editors of the Lancet, *Retraction—Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children*, 375 Lancet 445 (2010).

[33] *In re Phenylpropanolamine (PPA) Prods. Liab. Litig.*, 289 F. Supp. 2d 1230, 1240-41(W.D. Wash. 2003), *citing Hemmings v. Tidyman's Inc.*, 285 F.3d 1174, 1188 (9th Cir. 2002). *See also O'Neill v. Novartis Consumer Health, Inc.*, 147 Cal. App. 4th 1388, 55 Cal. Rptr. 3d 551 (2007) (affirming defense verdicts in PPA trials, and affirming admissibility of defendants' experts attack on study based on investigators' failure to follow study protocol).

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■ *Were the statistical calculations done properly?*

Statistical analysis is crucial to interpreting the results of a study, and to determining whether the results show a true association or are simply a function of chance. Journal peer reviewers do not ordinarily verify the statistical calculations reported in a study.[34] That failure leaves room for error. Recent cases show that it is not safe to assume that statistical calculations in published studies are valid.

In the Viagra case, the court found that the statistical ''methodologies described in the study were not the actual methodologies used.''[35] In addition, the computer programming ''code that [the researcher] wrote to produce the numbers in the [Study] contained errors that would affect the odds ratios and confidence intervals.''[36] Similarly, in the Accutane case, the investigator ''admitted that some of the statistical analysis was inaccurate.''[37]

Therefore, counsel should consider employing a statistician to review the raw data and verify the statistical calculations in key studies.[38] As discussed below, the data and computer programming underlying a key study is usually discoverable.

■ *Does the dataset that was analyzed accurately reflect the condition of the subjects?*

Before any statistical analysis can be performed, data needs to be collected and recorded. There is considerable opportunity for error at each step in that process. First, initial data collection often involves making entries on paper forms; such entries may be ambiguous or inconsistent (recall the highly contentious 2000 presidential election where hanging chads and other ambiguities made it difficult or impossible to assign certain ballots to a candidate). Second, the subsequent entry of the data into an electronic dataset provides opportunity for basic key punch errors. The occasional error in data recording is not unexpected. However, a well-done study will utilize various quality control procedures to minimize and correct such errors. The International Society for Pharmacoepidemiology has promulgated good practice guidelines to insure data quality and integrity. These guidelines include proper training, documentation of entry and any revisions, and verification.[39]

Peer-review does not guarantee that these good practices have been observed or that the electronic dataset accurately represents the study population. Even apart from intentional falsification of data, such as occurred in the breast cancer lumpectomy trials, studies published in peer-reviewed publications may contain serious data errors. In *In re Viagra*, the court found that there were ''discrepancies'' between the dates entered on the hard copy questionnaires and those used in the electronic dataset. These errors ''raise[d] serious concerns about the reliability of the'' published study.[40] Similarly, in the Accutane case the Court found that the researcher ''admitted that some of the [data] he used in his calculations were inaccurate, [but] could not check the accuracy of the remaining numbers because the original data could not be retrieved.''[41]

These examples highlight the importance of learning how data was collected for a study, as well as comparing the study's data collection forms to the electronic dataset to confirm the accuracy of the data used in the ultimate analysis.

Confronting Peer-Reviewed Articles Regarding Procedure

Knowing what questions to ask when investigating published articles, we now turn to how to get the information necessary to answer them.

■ *Are the underlying raw data, protocols and statistical calculations discoverable?*

It is a bedrock legal principal that a litigant '' 'has a right to every man's evidence,' except for those persons protected by a constitutional, common-law, or statutory privilege.''[42] Where a scientific study is central to the opinion of an expert in a product liability litigation, the law is well settled that the underlying study data is obtainable by subpoena served on the investigator. The seminal case is *Deitchman v. E.R. Squibb & Sons, Inc*.[43] In that case, Squibb and other pharmaceutical companies were defendants in actions alleging that diethylstilbestrol (DES) caused vaginal adenocarcinoma in the daughters of women who used the medication. Squibb served a document subpoena upon Dr. Arthur Herbst, a researcher who maintained a registry of vaginal adenocarcinoma cases and published more than a dozen articles regarding DES and adenocarcinoma.

Although Dr. Herbst was not engaged as an expert in the litigation, plaintiffs' experts relied on his studies in support of their product liability claims. Dr. Herbst moved to quash the subpoena on the grounds that it was burdensome and oppressive, and more importantly, that it would jeopardize patient confidentiality and deter patients and physicians from supplying the registry with data in the future. The Seventh Circuit reversed the trial court decision quashing the subpoena, finding that Squibb had a compelling need to examine

[34] Brief for Amici Curiae Daryl E. Chubin et al. at 10, *Daubert v. Merrell Dow Pharms. Inc*., 509 U.S. 579 (1993) (No. 92-102) (''peer review referees and editors limit their assessment of submitted articles to such matters as style, plausibility, and defensibility; they do not duplicate experiments from scratch or plow through reams of computer-generated data in order to guarantee accuracy or veracity or certainty''). The Annals of Internal Medicine, which has a rigorous editorial review process, may ''on occasion , perform [its] own analyses of the data with the authors' cooperation.'' Christine Laine et al., *Reproducible Research: Moving Toward Research the Public Can Really Trust*, 146 Annals Internal Med. 450, at 451 (2007).

[35] 658 F. Supp.2d 936, at 944.

[36] *Id.*

[37] Accutane Slip op. at 11.

[38] ''Many peer reviewed journals now require authors to be prepared to share their raw, unprocessed data with other scientists or state the availability of raw data in published articles.'' Iain Hrynaszkiewicz et al., *Research Methods & Reporting: Preparing raw clinical data for publication: guidance for journal editors, authors, and peer reviewers*, 340 Brit. Med. J. c181 (2010), *available at* http://www.bmj.com/cgi/content/full/340/jan28_1/c181.

[39] ISPE, *Guidelines for good pharmacoepidemiology practices (GPP)*, 17 Pharmacoepidemiology and Drug Safety 200 (2008).

[40] 658 F. Supp.2d 936, at 944.

[41] *Accutane* Slip op. at 12.

[42] *Branzburg v. Hayes*, 408 U.S. 665, 688 (1972).

[43] 740 F.2d 556 (7th Cir. 1984).

the underlying data in order to test the validity of the studies:

> The value of the conclusions turns on the quality of the data and the methods used by the researcher. . . . So if the conclusions or end product of a research effort is to be fairly tested, the underlying data must be available to others equally skilled and perceptive. . . . [A] study of this sort may have a number of different but inadvertent, biases present. . . . **For Squibb to prepare properly a defense on the causation issue, access to the Registry data to analyze its accuracy and methodology is absolutely essential.**[44]

The court ruled that a protective order could be fashioned to compensate Dr. Herbst for his time and to protect medical privacy.[45]

A similar result obtained in the multidistrict phenylpropanolamine (PPA) products liability litigation. Plaintiffs, claiming to have suffered strokes as a result of using various medications containing PPA, relied on an epidemiologic study, the Yale Hemorrhagic Stroke Project (HSP). Defendant pharmaceutical manufacturers first obtained underlying study documents from the Yale investigators, and later served ''a series of subpoenas . . . on hospitals possessing medical records for participants'' in the HSP so they could ''verify the accuracy of the data underlying the HSP and to clarify the extent to which the HSP participants were scrutinized for 'potential stroke risk confounders.' ''[46] The Court denied a motion to quash the subpoenas and directed the parties to work with the hospitals to establish a redaction protocol so the underlying data could be produced.

In the multidistrict hormone replacement therapy (HRT) litigation, defendants subpoenaed and obtained underlying data from the Women's Health Initiative study, which is the cornerstone of plaintiffs' claims that their use of HRT caused breast cancer. As in the DES and PPA cases, the MDL court supervising the HRT litigation entered orders directing the Fred Hutchinson Cancer Research Center to produce underlying data, subject to certain restrictions.[47]

As noted previously, peer reviewed medical journals are increasingly requiring authors to make available upon request their original unprocessed data, including the study protocol, the electronic dataset, and the computer code used to analyze the data and generate the statistical results. For example, the American College of Epidemiology has a published policy statement encouraging data sharing;[48] the *Annals of Internal Medicine* has adopted a ''reproducible research'' initiative that ''require[s] authors to state whether they are willing to share the protocol, data or statistical code;''[49] the National Institutes of Health require data sharing for all grants with funding in excess of $500,000;[50] and federal regulations provide that research data collected with federal funds must be made available under the Freedom of Information Act.[51] Procedures have been devised for researchers to prepare their underlying data in a format suitable for sharing that protects confidentiality and medical privacy (including compliance with the Health Insurance Portability and Accountability Act).[52] Accordingly, legitimate researchers already collect and maintain the data underlying their studies. Litigants should seek access to this information as well.

■ *Are peer reviewer comments, criticisms and related documents discoverable from scientific journals?*

The International Committee of Medical Journal Editors obligates medical journals to hold peer review communications confidential and to oppose requests for discovery:

> Editors must not disclose information about manuscripts (including their receipt, content, status in the reviewing process, criticism by reviewers, or ultimate fate) to anyone other than the authors and reviewers. This includes requests to use the materials for legal proceedings.[53]

In two recent decisions, district courts in Massachusetts and Illinois ruled that peer review communications are not discoverable, holding that editors and peer reviewers were entitled to the same type of confidentiality as journalists.[54] Whether other courts will recognize this new claim of privilege remains to be seen.

Remedies

Confronted with an article lacking scientific validity or, worse, intentionally or fraudulently misstating the scientific evidence, what options are available?

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[44] *Id.* at 562-563 (emphasis added).

[45] *Id.* at 564.

[46] *In Re: Phenylpropanolamine (PPA) Prods. Liab. Litig.*, MDL No. 1407, Order re: Motion to Quash Subpoenas re Yale Study's Hospital Records, at 1, 2 (W.D. Wash. Aug. 19, 2002), *available at* http://www.wawd.uscourts.gov/documents/SpecialCaseNotices/MDL1407/0819motion.pdf

[47] *In re: Prempro Prods. Liab. Litig.*, MDL No. 4:03-CV-1507-WRW, Order 509 (Feb. 1, 2005) ; *In re: Prempro Prods. Liab. Litig.*, MDL No. 4:03-CV-1507-WRW, Order 1077 (Mar. 20, 2006); *In re: Prempro Prods. Liab. Litig.*, MDL No. 4:03-CV-1507-WRW, Order 2106 (Jul. 13, 2009).

[48] American College of Epidemiology, Policy Statement on Sharing Data from Epidemiologic Studies, May 2002, *available at* http://www.acepidemiology.org/policystmts/DataSharing.pdf.

[49] Christine Laine et al., *Reproducible Research: Moving Toward Research the Public Can Really Trust*, 146 Annals Internal Med. 450, at 452 (2007).

[50] National Institutes of Health, Final NIH Statement On Sharing Research Data, Feb. 26, 2003, *available at* http://grants.nih.gov/grants/guide/notice-files/NOT-OD-03-032.html.

[51] Office of Management and Budget Circular A-110 § .36(d)(1) provides that ''in response to a Freedom of Information Act (FOIA) request for research data relating to published research findings produced under an award that were used by the Federal Government in developing an agency action that has the force and effect of law, the Federal awarding agency shall request, and the recipient shall provide, within a reasonable time, the research data so that they can be made available to the public through the procedures established under the FOIA.'' Executive Office of the President of the United States, Office of Management and Budget Circular A-110 § .36(d)(1), Amended Sept. 30, 1999, *available at* http://www.whitehouse.gov/omb/rewrite/circulars/a110/a110.html.

[52] Iain Hrynaszkiewicz et al., *Research Methods & Reporting: Preparing raw clinical data for publication: guidance for journal editors, authors, and peer reviewers*, 340 Brit. Med. J. c181 (2010), *available at* http://www.bmj.com/cgi/content/full/340/jan28_1/c181.

[53] International Committee of Medical Journal Editors, Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Ethical Considerations in the Conduct and Reporting of Research: Privacy and Confidentiality, *available at* http://www.icmje.org/ethical_5privacy.html.

[54] *In re Bextra & Celebrex Mktg. Sales Practices & Prod. Liab. Litig.*, 249 F.R.F. 8, 14 (D. Mass. 2008); *In re Bextra & Celebrex Mktg. Sales Practices & Prod. Liab. Litig.*, No. 08-cv-00402, 2008 U.S. Dist. LEXIS 21098 at *8, *9-10 (N.D. Ill. March 14, 2008).

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■ *Exclusion of the Study and/or the Expert*

First and foremost, in the underlying litigation, improprieties in the data or methodologies will likely give rise to a *Daubert* challenge. *Daubert* (or its state court counterparts) charges trial courts with the gatekeeping responsibility of keeping outside of the courtroom scientific evidence that is unreliable. If the crux of an expert's opinion is based on a peer-reviewed study that is found to be unreliable, the expert opinion will be excluded.

In the Viagra case, the court initially ruled that plaintiffs' general causation evidence was reliable, placing ''great weight on the fact that the McGwin Study had been peer-reviewed and published by the Journal, and that the study had not been produced using post-litigation data.'' However, after further discovery demonstrated that the study was critically flawed – as discussed above – the court reconsidered its earlier decision, and found that ''numerous miscodings and errors have rendered the McGwin Study as published unreliable.''[55] Absent that study, the court found there was no admissible basis for the expert's opinion.[56] In a companion opinion, the court granted summary judgment for Pfizer.[57]

On the other hand, if there is a reliable basis for the expert's opinion independent of the flawed study, then the opinion may still be admissible. Thus, in the Accutane case, the appellate court affirmed the lower court decision excluding the expert's study finding it to be ''not soundly and reliably generated,'' but nevertheless remanded the matter to the trial court ''to consider whether [the expert] should be permitted to testify as an expert on general causation without reference to the PET study.''[58]

■ *Correction or Retraction of the Study*

Many scientific journals are members of the Committee on Publication Ethics, an organization ''concerned with integrity of peer-reviewed publications in science, particularly biomedicine.''[59] COPE has promulgated a Code of Conduct which provides for correction or retraction of flawed studies:

> Whenever it is recognised that a significant inaccuracy, misleading statement or distorted report has been published, it must be corrected promptly and with due prominence.
>
> If, after an appropriate investigation, an item proves to be fraudulent, it should be retracted. The retraction should be clearly identifiable to readers and indexing systems.[60]

Consistent with the COPE guidelines, *Lancet* published a retraction of the MMR vaccine autism article, and *Lancet Oncology* published a correction of the smokeless tobacco article to disclose the author's work as a litigation expert. Thus, if discovery reveals significant flaws in a published study, the journal may be willing to correct or retract the publication.

■ *Scientific Integrity Investigations*

The Office of Research Integrity (ORI), part of the Department of Health and Human Services, promotes integrity in biomedical and behavioral research supported by the U.S. Public Health Service by defining research misconduct and overseeing institutional investigations of misconduct. ORI regulations identify three specific acts of ''research misconduct'' (fabrication, falsification and plagiarism), each of which requires intent as a necessary element of the offense:

> Research misconduct means fabrication, falsification, or plagiarism in proposing, performing, or reviewing research, or in reporting research results.
>
> (a) Fabrication is making up data or results and recording or reporting them.
>
> (b) Falsification is manipulating research materials, equipment, or processes, or changing or omitting data or results such that the research is not accurately represented in the research record.
>
> (c) Plagiarism is the appropriation of another person's ideas, processes, results, or words without giving appropriate credit.
>
> (d) Research misconduct does not include honest error or differences of opinion.[61]
>
> Besides federal regulations, individual institutions may have their own policies regarding scientific integrity and research misconduct that govern researchers affiliated with the institution.[62]

Thus, depending upon the degree of culpability, the source of funding, and the institutional affiliation of the researcher, a scientific integrity investigation may be initiated if there is serious misconduct in a study. Federal regulations and institutional policies have established procedures for a party to file a scientific misconduct complaint.

Conclusion

Peer-reviewed scientific evidence is central – often outcome determinative – to product liability and mass tort litigation.

Daubert views peer-review as an important component of the reliability analysis. But, just as the absence of peer review does not require exclusion of an expert's opinion, the fact of peer review does not equate to the study's validity or admissibility.[63]

Because peer review is far from perfect, such studies can be and should be vigorously challenged. Each step in the researcher's process merits scrutiny and verification. The effort may lead to surprising – and favorable – results.

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[55] 658 F. Supp.2d 936, at 945.

[56] *Id.* at 946.

[57] *In re Viagra Products Liab. Litig.*, 658 F. Supp.2d 950, 968 (D. Minn. 2009).

[58] *Accutane* Slip op. at 12, 20.

[59] Committee on Publication Ethics, About COPE, *available at* http://publicationethics.org/about.

[60] Committee on Publication Ethics, COPE Code of Conduct, at 2, *available at* http://publicationethics.org/files/u2/New_Code.pdf.

[61] 42 CFR 93.103.

[62] *See, e.g.*, University Of Alabama At Birmingham, Policy Concerning The Maintenance Of High Ethical Standards In Research And Other Scholarly Activities, Jan. 27, 1997 (editorial changes made Jun. 28, 2007), *available at* http://www.iss.uab.edu/Pol/HiEthicsMtab.pdf.

[63] *Daubert*, 509 U.S. at 593-94 (''Publication (which is but one element of peer review) is not a sine qua non of admissibility; it does not necessarily correlate with reliability'').