



## SCRATCHING SURFACE PLAUSIBILITY: ONE COURT'S TEXTBOOK SCRUTINY OF EXPERT TESTIMONY

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Rule 702 of the Federal Rules of Evidence requires that experts testify on the basis of “scientific, technical, or other specialized knowledge” based in “reliable principles and methods.” The rule is derived from several U.S. Supreme Court decisions, beginning with *Daubert v. Merrell Dow Pharmaceuticals*.<sup>1</sup> Under *Daubert*, a trial judge must examine the “scientific validity” and “reliability” of the “principles and methodology” underlying an expert’s opinion, considering such factors as whether the theory can be and has been tested, whether it has been subject to peer review and publication, any known or potential error rate, and general acceptance within the relevant scientific community.<sup>2</sup> A federal district court case decided earlier this year in the Southern District of Florida, *In re Denture Cream Products Liability Litigation*, illustrates how a judge applying these principles may look beneath surface plausibility to exclude what is in fact unreliable scientific expert testimony.<sup>3</sup>

### Case Background and Theory

The case arose as part of a multi-district litigation in which users of Fixodent® denture cream sued various Procter & Gamble entities, alleging Fixodent® had caused them to develop a neurological disorder known as copper deficiency myeloneuropathy (CDM). Plaintiffs argued their injuries were caused by zinc contained in Fixodent® that dissociated and became bioavailable in their intestines, where it caused a net body copper outflow leading to long-term copper deficiency and eventually CDM.

Defendants did not dispute that zinc can cause a temporary body copper outflow, although the exact mechanism by which this occurs is somewhat unclear. They did, however, dispute the reliability of plaintiffs’ proof of the other steps in the purported causal chain, *i.e.*, the dissociation and bioavailability of zinc, the temporary copper outflow’s developing into long-term copper deficiency, and that deficiency’s causing CDM. Although plaintiffs’ experts proffered various seemingly plausible pieces of evidence to support these steps, the court ultimately rejected nearly all of them as failing to meet the requirements of Rule 702.

### The Double-Blind Study

The first piece of evidence the court discussed in detail was a double-blind study designed by one of plaintiffs’ experts and conducted by a physician in India. The purpose of the Fixodent Blockade Study was to examine the short-term effect of Fixodent® on copper levels. In the 36-day trial, 12 subjects received pills containing Fixodent®, 6 received pills containing zinc acetate, and 6 received placebos. During days 3–5 and 31–33, each subject was given a dose of copper-65 and in days 31–33 the ratio in fecal samples of that isotope

<sup>1</sup> 509 U.S. 579 (1993).

<sup>2</sup> *Id.* at 593–595.

<sup>3</sup> 2015 WL 392021 (S.D. Fla. Jan. 28, 2015).

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to copper-63 was measured. A higher ratio would indicate that the substance the subject had taken had blocked the copper-65's absorption, so that it was then excreted. Since the blocking effect of zinc on copper absorption was well-accepted, the zinc acetate, a form of zinc known to be highly absorbable, served as a positive control for such blockage. When the study found that the copper-65-to-copper-63 ratio was significantly higher for both the Fixodent® and zinc acetate as compared to placebo subjects, plaintiffs' experts concluded this demonstrated the dissociation and bioavailability of the zinc in Fixodent® and resulting blockade of copper absorption.<sup>4</sup>

On examination, however, the judge found the study scientifically unreliable. Although the study protocol had been approved by an independent ethics committee, the study as conducted deviated from the protocol in several respects. The original protocol called for the measurement of copper-65 against its baseline levels, but the study instead measured copper-65 against copper-63. The original protocol also called for tracking copper ratios over the entire 36-day period, while the final results only measured ratios over days 31–33. This deviation was particularly suspect given that the results were not statistically significant over the whole study but were statistically significant over days 31–33. Additionally, plaintiffs' experts changed the study's definition of statistical significance. The protocol required that the probability that any observed differences could have occurred by chance (referred to as the "p-value") be less than five percent, *i.e.*,  $p < 0.05$ , but the testers only required that it be less than ten percent, *i.e.*,  $p < 0.1$ .

Although plaintiffs contended these changes simply reflected "clarifications" of the original protocol, the judge noted they demonstrated at best sloppy protocol draftsmanship or at worst deliberate manipulation of results, in either case inconsistent with reliable scientific methods.<sup>5</sup> Further, the study's administration was rife with careless errors. For instance, the zinc acetate capsules were a different size than the Fixodent® and placebo capsules, threatening the integrity of the blinding process, and the capsules were so large as to raise the specter of non-compliance by subjects. Fecal samples may also have been contaminated by improper storage. When these defects were considered together with the protocol deviations, the Fixodent Blockade Study was simply "not 'good science'" and not a reliable basis for expert testimony.<sup>6</sup>

### The *In Vitro* Studies

The court next turned to a different plaintiffs' expert's use of certain *in vitro* studies conducted by Procter & Gamble. According to the expert, the studies showed that when Super Poligrip® denture cream was exposed to stomach acid in a test tube, zinc would dissociate from the denture cream. The expert asserted that Fixodent® and Super Poligrip® were sufficiently similar chemically that the same results would apply to Fixodent®, and thus concluded that zinc in Fixodent® would dissociate, become bioavailable in the stomach, and block copper absorption as zinc is known to do.

The court noted, however, that the expert's opinion did not cite specific parts of the studies or provide significant analysis of his own. Accordingly, his conclusion that the study results were valid was a mere "conclusory statement[] devoid of factual or analytical support" and "simply not enough."<sup>7</sup>

Moreover, the expert failed to demonstrate that the studies were applicable to the issues in the case. First, the studies involved different denture creams, and the expert did not adequately explain why Fixodent® and Super Poligrip® should be considered equivalent when even small changes in chemical composition can make a significant difference in a substance's properties. Second, the expert did not explain why *in vitro* studies would accurately reflect what would transpire *in vivo* (in the body), a particularly glaring omission since the expert had criticized other Procter & Gamble studies (which showed that zinc did *not* dissociate in significant amounts) for improperly assuming that the results of *in vitro* studies were valid *in vivo*. Third, while citing *in vitro* studies

<sup>4</sup> *Id.* at \*8.

<sup>5</sup> *Id.* at \*9.

<sup>6</sup> *Id.* at \*11 (citing *Daubert*, 509 U.S. at 593).

<sup>7</sup> *Id.* at \*13.

showing dissociation in stomach fluids, he ignored other such studies which showed very little dissociation in *intestinal* fluids, and it is by intestinal presence that zinc appears to cause copper deficiency. Collectively, these “severe inadequacies” rendered the expert’s conclusions unreliable and hence inadmissible.<sup>8</sup>

## The Epidemiological Study

The court spent a considerable amount of time discussing the flaws of an epidemiological study conducted by another of plaintiffs’ experts. In that study, the expert performed a retrospective analysis of a previous Scottish study describing 16 patients with copper deficiency, as identified by a national reference laboratory based on serum copper levels, out of 22 total patients with this condition over a five-year period (the study authors had inadequate records to describe the 6 excluded patients). The study had found that 12 of the patients had high serum zinc concentrations, of which 9 had used “zinc-containing dental fixatives,” and 12 had certain neurological and hematological symptoms associated with copper deficiency. The study did not note the extent of overlap between the two groups of 12.

Based on his analysis, the expert opined a causal relationship existed between denture cream and CDM. He first estimated that the proportion of the Scottish population that wore dentures was identical to the known proportion for the U.K. as a whole, and then estimated the proportion of this group that used denture cream as between the known figures for the U.K. and U.S. As a result, he estimated that 270,000 Scots used denture cream and 4.93 million did not. Using the Scottish study results, he concluded that 12 Scots—the ones with neurological and hematological symptoms—had developed CDM over the study period. Since 9 of the 16 total study patients were denture-cream users, but their overlap with the 12 CDM patients was unspecified, this meant that no less than 6<sup>9</sup> and perhaps as many as all 9 of the CDM patients were denture-cream users. Comparing the estimated incidence of CDM in denture-cream users of between 6 and 9 per 270,000 to the estimated incidence among non-users of between 3 and 6 per 4.93 million, denture-cream users were between 18 and 55 times more likely to develop CDM than non-users.

The court, however, found the expert’s methodology suffered from numerous serious flaws. For starters, the expert offered no explanation as to why it was appropriate to apply the entire U.K. population’s denture-wearing proportion to Scotland, or how he applied the U.K. and U.S. denture cream usage proportions to come up with an estimate for Scotland that differed from both of those numbers. The court cited a previous Eleventh Circuit holding that this sort of “[t]ransposition of data based on such conjecture and rough approximation lacks the intellectual rigor required by *Daubert*.”<sup>10</sup>

In addition, the expert’s methodology was based on assumptions about the study’s conduct that had no demonstrable basis. For example, he assumed the study captured all copper deficiency cases in Scotland during the study period, yet the study had excluded 6 known patients, used a restrictive definition of copper deficiency, and explicitly acknowledged that the actual prevalence of such deficiency was likely to be greater than even the 22 initially identified patients.

Also, the study’s only stated purpose was to review copper deficiency cases to identify signs and symptoms to facilitate early treatment. While the study took note of patients’ denture cream use, it said nothing about the amounts, duration, or brands used, or the temporal relationship between usage and copper deficiency, yet the expert simply assumed the patients’ treating physicians would not have noted the use of denture cream unless it was used in sufficient amounts and duration before diagnosis to be relevant to causation. He also assumed all patients with the noted hematological and neurological features actually had CDM, while the study made no such statement and the expert himself did not review the patients’ records. Thus while the study may have been

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<sup>8</sup> *Id.* at \*14.

<sup>9</sup> Note that, barring information not disclosed in the opinion, the correct figure should be 5.

<sup>10</sup> *In re Denture Cream*, 2015 WL at \*25 (quoting *Rink v. Cheminova*, 400 F.3d 1286, 1292 (11th Cir. 2005)).

reliable in light of its stated purpose—to characterize the signs and symptoms of copper deficiency—that did not make it a reliable basis for the expert to testify to a causal link between denture cream and CDM.

### The Dose-Response Opinion

The plaintiffs also proffered expert testimony that there was a dose-response relationship between Fixodent® and the risk of CDM by which an increase in Fixodent® exposure increased the risk of CDM. One of the experts purported to opine as to a level of Fixodent® exposure above which there was an increased risk of copper deficiency, and hence CDM.

The expert began with the upper limit for regular intake of 40 mg/day recommended by the Institutes of Medicine. He then used data on bioavailability (from another report by the same expert), dissociation (from the above-described *in vitro* studies), denture cream ingestion (from Procter & Gamble internal studies), and zinc levels in denture cream to calculate the amount of denture cream that would need to be applied daily to exceed this limit. His calculation showed that if a denture-cream user applied between 2.44 and 3.56 grams per day (or higher), more than 40 mg of zinc would dissociate and become bioavailable from the portion of the cream that would be ingested. Based on other research not more specifically described by the court, the expert concluded that approximately 10% of Fixodent® users applied this level of denture cream daily.

The court noted, however, that both the bioavailability and dissociation calculations were based on other evidence already ruled inadmissible. While an expert may base an opinion on inadmissible evidence if it is of a type reasonably relied upon by experts in the field, here the evidence was inadmissible because it was unreliable, thus negating its use as a basis for expert opinion. Moreover, even if the underlying methods were reliable, merely exceeding the recommended zinc limit was not a reliable basis for concluding copper deficiency would result. The recommended limit was not meant to “establish a safety threshold above which clinical injury occurs”—while it was known that exceeding the limit led to a decrease in a specific biomarker of copper status, whether that decrease caused harmful consequences, much less CDM, had not been shown. The expert’s rejoinder that such a decrease “can’t be a good thing” hardly “reflect[ed] the intellectual rigor required under *Daubert*” for a causation opinion.<sup>11</sup>

### Lessons Learned

Plaintiffs in *In re Denture Cream Products Liability Litigation* sought to introduce numerous scientific studies and expert opinions addressing multiple aspects of a complicated chain of general medical causation. While the precise factual bases on which the court found the opinions unreliable and hence inadmissible may be unique to this case, the underlying reliability principles the court applied have universal import. Thus the court seemed particularly troubled by:

- The unjustified transposition of known information about one substance, population, or setting to another, such as from one brand of denture cream to another, the entire U.K. (or U.S. and U.K.) population to Scotland, or the *in vitro* to *in vivo* environments.
- Unjustified assumptions about studies conducted by others, such as that the Scottish copper deficiency study was actually comprehensive of all population cases, or that patients with certain symptoms actually had CDM when no such diagnosis was specified.
- Unjustified after-the-fact departures from a planned study protocol, such as the criterion for statistical significance, especially when they materially affect study results.

Accordingly, litigants should be alert to similar flaws in opposing experts’ testimony, and indeed in their own.

<sup>11</sup> *Id.* at \*31.