IN THE COURT OF COMMON PLEAS OF PHILADELPHIA COUNTY
FIRST JUDICIAL DISTRICT OF PENNSYLVANIA
CIVIL TRIAL DIVISION

IN RE: DENTURE ADHESIVE CREAM LITIGATION	:	**JUNE TERM, 2009**
	:	**NO. 4534**
	:	**CONTROL NO.: 13092505**

OPINION

New, J. **February 7th, 2014**

For the reasons set forth below, the Court grants the Global Motion to Exclude General Causation Expert Testimony filed by Defendants The Procter & Gamble Manufacturing Company, Procter & Gamble Distributing, LLC, and Rite-Aid Corporation (hereinafter "Moving Defendants").

FACTUAL AND PROCEDURAL HISTORY

On July 2, 2009, the coordinating judge of the Complex Litigation Center created the In re Denture Adhesive Cream mass tort master-docket. The Third Amended Master Long Form Complaint contains allegata against eight defendants, which can easily be distilled into three groups – 1) The Procter & Gamble Manufacturing Company and its subsidiaries, which manufacture and distribute Fixodent, 2) GlaxoSmithKline and its subsidiaries, which manufactured and distributed Super Poligrip, and 3) Defendant Rite-Aid Corporation, which sold both Fixodent and Super Poligrip. See Third Amended Master Long Form Complaint at ¶¶ 17-52.

By September 2013, only twelve cases, all filed by the law firm of Chaffin and Luhana LLP, remained in the In re Denture Cream mass tort program, and GlaxoSmithKline and its

subsidiaries were no longer defendants in these cases. On September 17, 2013, Moving Defendants filed an omnibus Motion to Exclude all of Plaintiff's general causation experts in these remaining cases. Following extensive briefing by the parties and the reception of live testimony from Dr. Lautenbach, the Court heard oral argument on the Motion.

In these cases, the individual plaintiffs allege their use of zinc containing denture adhesive creams manufactured by Procter & Gamble caused them to develop an irreversible neurologic condition known as "copper deficiency myeloneuropathy.[1]" The parties agree each gram of Fixodent contains approximately 17 milligrams of zinc bound within a Gantrez polymer. From this starting point, the plaintiffs allege the following causal chain: 1) Fixodent contains zinc, 2) some zinc from Fixodent is absorbed into the blood, 3) excessive zinc in the blood blocks copper absorption, causing copper deficiency, 4) sustained copper deficiency for a prolonged period of time results in copper deficiency myeloneuropathy.

The plaintiffs identified eight causation experts, Martyn T. Smith, PhD, Frederick K. Askari, M.D., PhD, Ebbing Lautenbach, M.D., M.P.H., Carl F. Cranor, PhD, M.S.L., David Grainger, PhD, Steven A. Greenberg, M.D., M.S., Joseph R. Prohaska, PhD, and Elizabeth A. Shuster, M.D. Although Plaintiffs offer eight experts to support their theory of causation, only four experts, Dr. Smith, Dr. Lautenbach, Dr. Askari, and Dr. Greenberg, submitted opinions linking Fixodent to copper deficiency myeloneuropathy. Three of the remaining experts, Dr. Cranor, Dr. Grainger, and Dr. Prohaska authored expert reports which buttress the conclusions of those experts who do link Fixodent to copper deficiency myeloneuropathy. For example, Dr.

[1] The Court notes the parties and witnesses use a number of distinct, yet related, medical terms to describe the neurological injuries suffered by Plaintiffs. These terms include 1) myelopathy – a spinal cord disease; 2) neuropathy – a peripheral nerve disease; 3) myeloneuropathy – a combination of spinal cord disease and peripheral nerve disease; and 4) copper deficiency myeloneuropathy – a type of myeloneuropathy caused by copper deficiency. For ease of reference, the Court refers to the constellation of neurological injuries plaintiffs allege as "copper deficiency myeloneuropathy."

Prohaska's report discusses how excess zinc ingestion can lead to copper deficiency; however, Dr. Prohaska's report does not link Fixodent to excessive zinc ingestion. Since their opinions do not link Fixodent to copper deficiency myeloneuropathy, but serve only to bolster the testimony of the experts who do make such a link, this opinion will not address the testimony of Dr. Cranor, Dr. Grainger, and Dr. Prohaska.

Plaintiffs' also present the testimony of Dr. Shuster, who treated one of the patients in the contemporaneous Federal Multi-District Litigation, In re Denture Cream Products Liability Litigation, 795 F.Supp.2d 1345 (S.D.F.L. 2011). In the Multi-District Litigation, Dr. Shuster opined Fixodent caused her patient to develop copper deficiency myeloneuropathy. Notably, Dr. Shuster did not file an expert report offering an opinion as to general causation in these cases; rather, Plaintiff attaches excerpts of her deposition transcript from the Multi-District Litigation. See Moving Defendants Motion at Ex. 13. The fact Dr. Shuster did not author a general causation expert report is hardly surprising in light of the fact Plaintiffs' candidly admit Dr. Shuster's employment contract prohibits her from serving as a general causation expert. See Plaintiff's Response in Opposition at p. 103 n.33. Nonetheless Plaintiffs' argue Dr. Shuster's prior testimony supports general causation because it logically follows if Fixodent caused Dr. Shuster's patient to develop copper deficiency myeloneuropathy, then Fixodent must cause copper deficiency myeloneuropathy generally. In light of the fact Dr. Shuster did not author a report offering an opinion as to general causation in any of the cases currently pending before this Court, Dr. Shuster's opinions will not be addressed. Accordingly, this Opinion only addresses the expert opinions of Dr. Lautenbach, Dr. Askari, Dr. Smith, and Dr. Greenberg.

This is not the first time the Philadelphia Court of Common Pleas has been asked to consider the expert testimony of some of these experts as it relates to the denture cream litigation. In the matter of Mark Jacoby v. Rite Aid Corp., et al., February Term 2011 No. 24,

the Honorable Sandra Moss granted the defendants' Frye motion and corresponding motion for summary judgment. The Court struck the reports of the plaintiff's causation experts, Dr. Lautenbach, Dr. Askari, and Dr. Smith. The Court found the opinions expressed by Dr. Lautenbach, Dr. Askari, and Dr. Smith to be novel science and therefore subject to Frye inquiry. Jacoby, February Term 2011 No. 24, opinion at pp. 7-8 (Ct. Com. Pl. April 12, 2012). After the Frye inquiry, the Court found Dr. Smith's "Weight of the Evidence" methodology to be unreliable because analytical gaps existed in the underlying data; specifically, it was uncertain 1) how much zinc is absorbed by the body as a result of Fixodent ingestion, 2) how much zinc is required to cause copper deficiency, and 3) how low a person's copper level must be or for how long a duration before it potentially results in copper deficiency myeloneuropathy. Id. at 8-9. The Court found Dr. Askari's "Totality of Evidence" methodology to be unreliable because it relied on the same data Dr. Smith relied on. Id. at pp. 10-11. Finally, the Court found Dr. Lautenbach's epidemiologic analysis to be insufficient because 1) he relied exclusively on case reports and case series, which are disfavored by the appellate courts in this Commonwealth, and 2) his use of the Naranjo scale in a non-clinical context was unreliable since he relied on the same flawed data as Dr. Smith and Dr. Askari. Id. at pp. 11-12. On December 9, 2013, the Superior Court affirmed Judge Moss' decision in an unpublished memorandum opinion. See Jacoby v. Rite Aid Corp., et al., 1508 EDA 2012, 2013 WL 6556773 (Pa. Super. Dec. 9, 2013).

In light of the analytical gaps found in Jacoby, Plaintiffs produced supplemental evidence which they argue cures the deficiencies. This supplemental evidence falls into two categories: 1) Dr. Lautenbach's cohort study based on data he mined from the "Gabreyes article,"[2] and 2) the

[2] In January 2013, Scottish haematologist Alemayehu Gabreyes, along with four colleagues, published an article in the European Journal of Haematology. See Alemayehu A. Gabreyes, et al., Hypocupremia associated cytopenia and myelopathy: a national retrospective review, 90 European Journal of Haematology, 1-9 (2013). For tactical reasons, Plaintiffs refer to this

Fixodent Copper Blockade Study, or "India Study."

In the Gabreyes article, the authors undertook a 5 year retrospective review of copper deficiency in Scotland, using information received from the Scottish Trace Element and Micronutrient Reference Laboratory. Gabreyes, et al., Hypocupremia associated cytopenia and myelopathy: a national retrospective review, 90 European Journal of Haematology, 1, 1-2 (2013). The Gabreyes article's authors identified twenty-two individuals who did not have pre-existing cytopenia and who suffered from copper deficiency; of these twenty-two individuals identified, sixteen patients were included in the final analysis. Id. at p. 2. Twelve of the sixteen patients suffered from neurological symptoms. Id. at p. 5. Additionally, twelve of the sixteen patients had high levels of zinc in their blood and nine of those twelve patients used zinc-containing denture creams. Id. at p. 2. Importantly, the Gabreyes article does not indicate how many of denture cream users also suffered neurological symptoms, nor does it contain any information regarding the amount of denture cream used, the frequency with which the denture cream was used, the time-frame between use of the denture cream and onset of the symptoms, or whether the use of denture cream preceded the neurological symptoms. The Gabreyes article's authors concluded 1) copper deficiency is an under-recognized cause of several types of cytopenia, which can progress to significant neurological injury if left untreated, and 2) physicians should closely look for copper deficiency because some neurological injuries can be reversed if the copper deficiency is diagnosed and treated early. Id. at 8.

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article as the "Gabreyes national retrospective study," see e.g. Plaintiffs' Response at p. 28, while Defendants refer to the article as the "Gabreyes case series." See e.g. Moving Defendants' Motion at p. 14. While the Court appreciates the legal, and epidemiological, significance of the distinction between a study and a case series, the Court notes neither of the names used by the parties appropriately describe the Gabreyes article, which was described by its authors as "a retrospective audit of clinical practice [and not] clinical research." See Response of Gabreyes Case Series Authors, Moving Defendants' Ex. 59 at Bates Stamp PG 001113778. Accordingly, the Court shall refer to article as the "Gabreyes article."

Following the release of the Gabreyes article, Dr. Lautenbach generated a new cohort study, which is contained exclusively within in his expert report. Dr. Lautenbach's cohort study purports to show denture cream users are at least eighteen times[3] more likely to suffer from copper deficiency myeloneuropathy than non-denture cream users. See Lautenbach Expert Report, Moving Defendants' Motion at Ex. 11, ¶¶ 40-55. To arrive at this conclusion, Dr. Lautenbach synthesized information from the Gabreyes article with publicly available information. See id. at ¶ 48 (using publicly available census data to determine the population of Scotland during the five years covered by the Gabreyes article). When no information was available, Dr. Lautenbach made estimates based on available data. See e.g. id. at ¶ 50 (estimating the percentage of the Scottish population who wear dentures based on the percentage of the population of the United Kingdom who wear dentures), ¶ 51 (estimating the percentage of the Scottish population who use denture cream based on the percentages of the United States and United Kingdom populations that use denture cream).

The Fixodent Copper Blockade Study, or "India Study," was a thirty-day study, designed by Dr. Askari and administered by a third-party, to study the effects of Fixodent on copper absorption in the human body. See Askari Expert Report, Moving Defendants' Motion at Ex. 3, p. 12. Specifically, the study hypothesized Fixodent would block copper absorption, thereby resulting in decreased copper levels in the study participants' blood (serum) and increased copper levels in the study participants' urine and feces. Id. at pp. 11-13. A total of 24 subjects participated in the India Study. Id. at p. 12. Each participant was fed a controlled diet to ensure

[3] Dr. Lautenbach's conclusion denture cream users are at eighteen times more likely to suffer from copper deficiency myeloneuropathy than denture users who do not use denture cream is based on his use of the most conservative variables possible. Ex. 11 at ¶ 55. When the most liberal variables are used, Dr. Lautenbach concludes a denture cream user is more than fifty times more likely to suffer from copper deficiency myeloneuropathy than denture users who do not use denture cream. Id. at ¶ 54.

any variations in the participant's levels of zinc and copper could not be attributed to diet. Id. Twelve randomly-selected participants ingested encapsulated Fixodent three times a day, six participants ingested encapsulated zinc acetate three times a day, and six participants ingested an encapsulated placebo three times a day during the study. Id. Dr. Hongkun Wang, a biostatistician who is not named as an expert in these cases, interpreted the data and concluded there was not a statistically significant difference between the serum (blood) zinc or serum (blood) copper levels of participants taking Fixodent and those taking placebo-sugar pills. See Fixodent Copper Blockade Study, Plaintiff's Response Ex. 29 at ASKARI-000014; see also Defendant's Ex. 65, Dr. Wang Dep. at 66:24-67:4 (August 13, 2013). Similarly, Dr. Wang concluded the urine copper levels showed no significant difference between the participants who ingested the Fixodent and the participants who ingested the placebo. Defendant's Ex. 65, Dr. Wang Dep. at 63:2-64:24. However, Dr. Askari and Dr. Wang concluded the participants' fecal excretions at days 31-33 showed a statistically significant difference in the amount of copper contained in the fecal excretions between the participants who ingested the Fixodent and the participants who ingested the placebo. Askari Expert Report at p. 13; Fixodent Copper Blockade Study at ASKARI-000014.

Plaintiffs argue they have met their burden under Frye when this new evidence – the Gabreyes article, Dr. Lautenbach's cohort study based on the Gabreyes article, and the Fixodent Copper Blockade Study – is viewed in totality with 1) the prior expert reports of Dr. Lautenbach, Dr. Askari, and Dr. Smith and 2) the newly produced expert reports of Dr. Cranor, Dr. Grainger, Dr. Prohaska, Dr. Greenburg, and Dr. Shuster. For the reasons set forth below, this Court disagrees.

ANALYSIS

Rule 702 of the Pennsylvania Rules of Evidence controls the admissibility of expert

testimony on scientific knowledge, and states as follows:

> If scientific, technical or other specialized knowledge beyond that possessed by a layperson will assist the trier of fact to understand the evidence or to determine a fact in issue, a witness qualified as an expert by knowledge, skill, experience, training or education may testify thereto in the form of an opinion or otherwise.

Pa.R.E. 702. The Frye test, first announced in Frye v. United States, 293 F. 1013 (D.C. Cir. 1923), and adopted in Pennsylvania in Commonwealth v. Topa, 369 A.2d 1277 (Pa.1977), is part of Rule 702. Grady v. Frito-Lay, Inc., 839 A.2d 1038, 1043-44 (Pa. 2003). Under Frye, novel scientific evidence is admissible if the methodology that underlies the evidence has general acceptance in the relevant scientific community. Id. A trial court must first determine whether the science being offered has been developed through a "novel" methodology. If the science being offered is no longer considered novel, then a Frye inquiry is not required. Id., see also Commonwealth v. Delbridge, 859 A.2d 1254, 1260 (Pa. 2004).

Novel Science

The proponents of novel scientific evidence bear the burden of proving general acceptance in the relevant scientific community of the methodologies they are promoting. Grady, 839 A.2d at 1044. In Betz v. Pneumo Abex, 44 A.3d 27 (Pa. 2012), the Supreme Court stated:

> A reasonably broad meaning should be ascribed to the term "novel." Furthermore, we conclude that a Frye hearing is warranted when a trial judge has articulable grounds to believe that an expert witness has not applied accepted scientific methodology in a conventional fashion in reaching his or her conclusions. We believe a narrower approach would unduly constrain trial courts in the appropriate exercise of their discretion in determining the admissibility of evidence.

Betz, 44 A.3d at 53.

Plaintiffs argue the science espoused by their experts is not novel because twenty-three medical textbooks and multiple peer-reviewed journal articles mention the link between zinc-

containing denture creams and copper deficiency myeloneuropathy. See Response Brief at pp. 13-24. This Court concludes otherwise.

Although the link between copper deficiency and neurological injuries has been established for over eighty years, and the link between zinc and copper deficiency has been established for over forty years, any mention of a link between zinc-containing denture creams and neurological injuries is relatively recent. According to Dr. Lautenbach, scientists first postulated a link between zinc-containing denture cream and neurological injuries in 2005. Lautenbach Expert Report at ¶ 28. The two most influential journal articles addressing the link between zinc-containing denture creams and neurological injuries were not published until 2008 and 2009, respectively. See Nations et al., Denture Cream: An Unusual Source of Excess Zinc, Leading to Hypocupremia and Neurologic Disease, 71 Neurology 639–643 (June 2008) (the "Nations Article"); Hedera et al., Myelopolyneuropathy and Pancytopenia Due to Copper Deficiency and High Zinc Levels of Unknown Origin II, Neurotoxicology (2009) (the "Hedera Article"). The experts on both sides of this case acknowledge the Nations Article and the Hedera Article have been criticized within the medical community. See Smith Expert Report, Moving Defendant's Motion Ex. 14, at ¶ 136 (stating "Some of these case reports have come in for criticism, especially the 2008 article by Nations et al. and the 2009 report by Hedera et al.); Nelson Expert Report, Moving Defendants' Ex. 26, at pp. 84-85. These facts alone suggest any link between zinc-containing denture cream and neurological injuries is based on science that is novel.

Additionally, scientists genuinely dispute whether zinc-containing denture creams cause neurological injuries. See e.g. Defense expert reports; Jacoby, February Term 2011 No. 24, opinion at pp. 7-8, aff'd 1508 EDA 2012 (Pa. Super. Dec. 9, 2013)(unpublished); In re Denture Cream Products Liability Litigation, 795 F.Supp.2d 1345 (S.D. F.L. 2011)(Altonaga, J.).

Finally, the methodologies utilized by Dr. Smith, Dr. Askari, and Dr. Lautenbach in this matter - the "Weight of the Evidence" test, the "Totality of the Evidence" test, and the Naranjo scale in a non-clinical context, respectively – are the same methodologies the Court found to be novel in Jacoby. See Jacoby, February Term 2011 No. 24, opinion at pp. 7-8, aff'd 1508 EDA 2012 (Pa. Super. Dec. 9, 2013)(unpublished). For all of these reasons, this Court concludes Plaintiffs' experts rely on novel science and are therefore subject to Frye inquiry.

Frye inquiry

Since Plaintiffs' experts rely on novel science, this Court must perform its function as gatekeeper and evaluate the methodologies employed by Dr. Lautenbach, Dr. Askari, Dr. Smith, and Dr. Greenberg to ensure those methodologies are generally accepted by practitioners in the respective scientific fields. See Grady, *supra*. In Jacoby, the Court identified three fatal analytical gaps in the plaintiff's proposed expert testimony; those analytical gaps consist of the uncertainty of 1) how much zinc is absorbed by the body as a result of Fixodent ingestion, 2) how much zinc is required to cause copper deficiency, and 3) how low a person's copper level must be or for how long a duration before it potentially results in copper deficiency myeloneuropathy. Jacoby, February Term 2011 No. 24, opinion at pp. 7-8, aff'd 1508 EDA 2012 (Pa. Super. Dec. 9, 2013)(unpublished). Here, Plaintiffs argue they have produced sufficient evidence to fill all of these analytical gaps; accordingly, the Court will focus its attention on these areas to determine whether such gaps continue to exist.

Furthermore, the Court is mindful that the question before it is whether a specific zinc-containing denture cream, Fixodent, causes copper deficiency myeloneuropathy; the question is not whether zinc-containing denture creams in general cause copper deficiency myeloneuropathy. This distinction is crucial because not all zinc-containing denture creams are created equal. The evidence shows, at the relevant time period to these cases, two products,

Fixodent and Super PoliGrip, controlled the market share of zinc-containing denture creams. See Moving Defendants' Motion at p. 20; Plaintiffs' Response at p. 41. Fixodent contained 17 milligrams of zinc per gram, while Super PoliGrip contained double that amount, 34 milligrams of zinc per gram. Smith Expert Report at ¶ 93. In light of these differences in the zinc concentration of Fixodent and Super PoliGrip, the Court must also focus on whether Plaintiffs' experts linked any neurological injuries to Fixodent specifically, and not to the more generic category of zinc-containing denture creams which encompasses denture creams with a higher zinc concentration like Super PoliGrip.

First, Plaintiffs' attempt to fill the analytical gaps, identified in Jacoby, through the supplemental evidence and research from Dr. Lautenbach, an epidemiologist. Dr. Lautenbach authored a report dated April 15, 2013 and produced on July 3, 2013, in which he concludes there is an epidemiological association between Fixodent and copper deficiency myeloneuropathy. See e.g. Lautenbach Expert Report at ¶ 16. In his report, Dr. Lautenbach makes the following conclusions to a reasonable degree of scientific certainty:

> 15) . . . One of the most common causes of acquired copper deficiency is excessive zinc ingestion. Zinc causes an upregulation of metallothionein production in the enterocytes. Copper has a higher binding affinity for metallothionein than zinc. Thus, copper displaces zinc from metallothionein, remains in the enterocytes and it is then lost in the stool as intestinal cells are sloughed off. Thus, there is a clear biological mechanism for excessive zinc ingestion causing copper deficiency. Moreover the ability of zinc to induce changes in copper levels and cause certain hematologic abnormalities (i.e., anemia and neutropenia) has been long understood.
>
> 16) I have conducted a comparative epidemiological study using data from the population based Gabreyes study and from other available population demographic data. In this analysis, I compared the incidence of [copper deficiency myeloneuropathy (CDM)] in denture cream users vs. the incidence of CDM in non denture cream users. As discussed in detail below, even with the most conservative assumptions, the incidence of CDM is significantly greater (up to 50-fold higher) in denture cream users compared to non-users.

17) Moreover, numerous case reports and case series have described patients in which denture cream use has been linked to CDM. Patients' histories often revealed poorly fitting dentures and ingestion of excessive amounts of denture adhesives.

18) Case reports and case series hold an important place in the epidemiologic armamentarium. In evaluating a case report or case series of an adverse event, the Naranjo scale is a widely used and accepted epidemiologic approach to classifying the probability that an adverse event is related to drug/product exposure.

19) In many of the published case reports and case series, there was substantial evidence that the use of zinc-containing denture adhesives, such as Fixodent and Poligrip, contributed to CDM and associated hematologic abnormalities. . . .

. . .

22) Indeed, the Gabreyes study, my own epidemiological study, the peer-reviewed denture cream case reports and case series with Naranjo analysis, P&G's own confirmation of events reported with Fixodent use causing/contributing neurological conditions, . . . the compelling biological plausibility regarding zinc and its impact on copper, the existing scientific literature and the spontaneous adverse events strongly support the causal link between Fixodent use and CDM and resulting hematological injuries.

See Lautenbach Expert Report at ¶¶ 15-22. The Court finds Dr. Lautenbach's methodology to be fatally flawed in a number of ways.

The primary piece of evidence Dr. Lautenbach relies on to support his conclusions is the cohort study contained within his expert report. This cohort study, in turn, was based on data contained within the Gabreyes article. While the Court recognizes the general acceptance of cohort studies within the epidemiological community, see e.g. Jennifer L. Kelsey et al., Methods in Observational Epidemiology 86-129 (2d ed. 1996), the Court will not rubber stamp Dr. Lautenbach's analysis and allow it to be presented to a jury simply because it carries the label "cohort study." See Betz, 44 A.3d at 58 (an expert cannot evade a Frye inquiry "merely by making reference to accepted methodologies in the abstract"). Rather, the Court must look at the

underlying factual basis of the cohort study to ensure Dr. Lautenbach's methodology is sound. A review of Dr. Lautenbach's cohort study shows it does not conform to generally accepted epidemiological methodologies.

When performing a retrospective cohort study, there must be an accurate measure of exposure. Kelsey et al., Methods in Observational Epidemiology at p. 118. This is because errors in the measurement of exposure skew the magnitude of the corresponding epidemiological association. Id. Furthermore, without a refined measure of exposure, "it is impossible to assess whether a dose-response relationship between the exposure and the disease exists." Id.

In his cohort study, Dr. Lautenbach, concludes that of the twelve people identified as having copper deficiency myeloneuropathy, at least six, and as many as nine, of these individuals were users of denture cream. Lautenbach Expert Report at ¶¶ 54-55. Absent from Dr. Lautenbach's analysis was the type of denture cream used by these six, or nine, individuals. A review of the Gabreyes article shows the article does not mention the type of denture cream used by these individuals. This information is critical because, as noted above, Super PoliGrip contains twice the amount of zinc as Fixodent.[4] Furthermore, the Gabreyes article does not contain, and Dr. Lautenbach did not otherwise obtain, any information regarding the amount of denture cream used, the frequency with which the denture cream was used, the time-frame between use of the denture cream and onset of the symptoms, or whether the use of denture

[4] Plaintiffs argue the difference in zinc concentration between Fixodent and Super PoliGrip is of no consequence because the zinc polymer in each denture cream dissociates in the same manner. This argument is inconsistent with their expert's testimony. Dr. Grainger opines the zinc polymer in Fixodent and the zinc polymer in Super PoliGrip dissociate the same; however, Dr. Grainger also opines Super PoliGrip will result in a greater zinc delivery to the body because all zinc in both products will be absorbed by the body and Super PoliGrip contains twice the amount of zinc than Fixodent. Grainger Expert Report, Moving Defendants' Motion at Ex. 7, p. 9. Thus, even Plaintiffs' expert agrees the effect of Super PoliGrip on the body will be different than the effect of Fixodent on the body because Super PoliGrip contains double the amount of zinc.

cream preceded the neurological symptoms. Without this information, an accurate measure of the exposure cannot be achieved; therefore, it is impossible to assess whether a dose-response relationship exists between Fixodent and copper deficiency myeloneuropathy. See Methods of Observational Epidemiology, *supra*. Accordingly, Dr. Lautenbach's cohort study, which purports to show an epidemiological association between Fixodent and copper deficiency myeloneuropathy, is based on a scientific methodology that is not generally accepted.

The veracity of Dr. Lautenbach's cohort study is further undermined by faulty logic and clear litigation driven bias. Dr. Lautenbach's cohort study relies on the following faulty logical premise: since Fixodent controlled 45% of the denture cream market share, then 45% of denture cream-related neurological injuries can be attributed to Fixodent. Lautenbach Testimony 26:5-21 (November 12, 2013). This premise is faulty because, as noted above, the amount of zinc in Super PoliGrip is not the same as the amount of zinc in Fixodent; in order for Dr. Lautenbach's premise to be valid, the amount of zinc in Fixodent must be the same as the amount of zinc in the other zinc-containing denture creams on the market. Additionally, the Court has concerns as to Dr. Lautenbach's estimates of population of denture wearers and denture cream users. Dr. Lautenbach estimates the percentage of the Scottish population who wear dentures is the same as the percentage of the United Kingdom population who wear dentures; however, Dr. Lautenbach's estimate does not account for variables, such as regional variations in diet and access to dental care, which may affect both the number of denture users and the number of denture cream users. The failure to account for such variable undermines Dr. Lautenbach's ultimate conclusion that denture cream users face an increased risk of developing copper deficiency myeloneuropathy. Finally, the fact Dr. Lautenbach's cohort study has not been subject to peer review nor has it been published in any academic journals also concerns this Court. While the lack of peer review will not categorically doom a study as unreliable, the

Court, viewing the totality of the circumstances, finds Dr. Lautenbach's cohort study unreliable because it is a blatant, litigation driven, attempt to remediate the analytical deficiencies identified in Jacoby.

In addition to his cohort study, Dr. Lautenbach also relies on case reports and case series which he analyzed through the lens of the Naranjo scale.[5] Once again, while the Court recognizes the Naranjo scale is commonly used within the medical community, the mere mention of the Naranjo scale cannot be used to evade a Frye inquiry. See Betz, 44 A.3d at 58. Rather, the Court must look at the underlying evidence, the case reports, to determine whether they are a methodologically sound source of information.

> A case report is the clinical description of a single patient . . . . A case series is simply a report of more than 1 patient with the disease of interest. One advantage of a case report or case series is its relative ease of preparation. In addition, a case report or case series may serve as a clinical or therapeutic example for other healthcare epidemiologists who may be faced with similar cases. Perhaps most importantly, a case report or series can serve to generate hypotheses that may be tested in future analytic studies.... The primary limitation of a case report or case series is that it describes, at most, a few patients and may not be generalizable. In addition, since a case report or case series does not include a comparison group, one cannot determine which characteristics in the description of the cases are unique to the illness. While the reports are thus usually of limited interest, there are exceptions, particularly when they identify a disease or describe the index case of a new disease.

Ebbing Lautenbach, Practical Healthcare Epidemiology 33 (3d ed. 2010). "One of the characteristics of case reports and case series that dictate their rejection as scientific proof is the fact they are usually not planned ahead of time with a sound scientific protocol." Nelson Expert Report, Ex. 26, at p. 12. As illustrated below, the case reports and case series relied upon by Dr. Lautenbach do not provide a sound basis for Dr. Lautenbach's conclusions.

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[5] The Naranjo adverse drug reaction probability scale classifies the likelihood an adverse event is related to drug therapy as definite, probable, possible or doubtful. See Lautenbach Expert Report at ¶66

Only one case report, contained within the Hedera article, identifies Fixodent as the exclusive zinc-containing denture cream taken by the patient. There are multiple reasons this case report is unreliable. First, like the Gabreyes article, the case report in the Hedera article contains insufficient information to support Dr. Lautenbach's conclusion because "the case report does not identify how much Fixodent that patient used, but only states he, along with the other subjects, 'reported applying large amounts of the denture creams.'" In re Denture Cream Products Liability Litigation, 795 F.Supp.2d at 1363. Second, the result of the case report does not support the Plaintiffs' hypothesis that the zinc in Fixodent causes excessive zinc in the blood, which blocks copper absorption, because "this single Fixodent user had near-normal zinc levels before stopping use of the product, and his copper level remained abnormally low after cessation . . . ." Id. Third, the patient who used exclusively Fixodent did not develop copper deficiency myeloneuropathy; he had "Axonal Polyneuropathy." "Case reports suggesting a link between denture cream and 'axonal polyneuropathy' cannot act as reliable evidence of an association between Fixodent use and [copper deficiency myeloneuropathy.]" Id. Finally, the Hedera article "mischaracterizes the results to make it appear that all the patients' blood zinc and copper levels returned to the normal range when the patients stopped using denture cream. In fact, even after cessation of denture cream, seven of eight patients still had high urine zinc and six of eleven continued to have high plasma zinc." Id. For all of these reasons, this single case report is unreliable and cannot serve as the basis for Dr. Lautenbach's conclusion that Fixodent causes copper deficiency myeloneuropathy.

Even if these factual inaccuracies did not exist, the Hedera article and the other case reports contain numerous methodological deficiencies. These methodological deficiencies include the authors' failure to 1) establish a case definition or set of diagnostic criteria, 2) follow a written protocol, 3) discern the amount of denture cream the patients used or how long the

patients had used denture cream, and 4) take the subjects' complete medical histories to exclude potential alternative causes for their neurological symptoms. See In re Denture Cream Products Liability Litigation, 795 F.Supp.2d at 1364 (internal citations omitted). For all of these reasons, Dr. Lautenbach's reliance on case reports and case series cannot serve as the basis for his opinion there is an epidemiological link between Fixodent and copper deficiency myeloneuropathy. Thus, Dr. Lautenbach's testimony does not fill any of the analytical gaps previously identified in Jacoby.

Next, Plaintiffs attempt to fill the analytical gaps identified in Jacoby through the expanded research and testimony of Dr. Askari, a gastroenterologist and pharmacologist. Dr. Askari authored a report dated June 3, 2013 and produced on July 3, 2013 in which he concludes there is a link between Fixodent usage and copper deficiency myeloneuropathy. See Askari Expert Report at p. 29. In his report, Dr. Askari makes the following conclusions to a reasonable degree of medical and scientific certainty:

1. Zinc-induced copper deficiency and resulting hematological and neurological injuries are well-recognized in the medical and scientific communities.

2. Fixodent can and has been shown to cause zinc-induced copper deficiency and resulting hematological and neurological injuries.

3. The [pharmokinetics] and Fixodent Copper Blockade Study show that biologically available zinc is being released from Fixodent *in vivo* in humans and that Fixodent can block copper absorption in human subjects in as little as thirty days of exposure.

4. Exposure to as little as 25 mg of zinc in a single repeated daily doses has been shown to be sufficient to cause suppression of copper in some humans.

5. That copper blockage caused from zinc overload from a product like Fixodent, left untreated, will result in copper deficiency and resulting hematological and/or neurological injuries.

6. The constellation of symptoms reported in the denture cream case reports, including elevated blood zinc, suppressed blood copper, anemia, neutropenia, neurological injury, histories of significant Fixodent usage over many years, the resolving or stabilization of symptoms when patients stopped using Fixodent and/or were copper supplemented corroborates the other evidence of causation described herein.

Id. To support his conclusions, Dr. Askari relies on three main classifications of materials: 1) the same case reports and case series relied on by Dr. Lautenbach, 2) Wilson's Disease research and studies, and 3) the results of the Fixodent Copper Blockade Study, which Dr. Askari designed. For the reasons set forth above in the analysis of Dr. Lautenbach's testimony, the case reports and case series are methodologically flawed and cannot serve as a base for Dr. Askari's opinions.

Dr. Askari also relies on Wilson's Disease research and studies to support his conclusion Fixodent causes copper deficiency myeloneuropathy. Specifically, Dr. Askari refers to studies conducted on Wilson's Disease patients which show the ingestion of 25mg of zinc acetate results in a temporary negative copper balance in some individuals. See Askari Expert Report at pp. 8-9. The Wilson's Disease research does not support Dr. Askari's conclusions. That research involves a negative copper balance, which refers to a temporary period of time during which the body excretes more copper than it takes in. Here, Plaintiffs do not complain of neurological injuries caused by negative copper balance; rather, they complain of neurological injuries caused by *copper deficiency*, which occurs when copper stores are depleted throughout the body. There is a large analytical gap between the proposition that a 25 mg dose of zinc may place a particular person into a temporary negative copper balance and the proposition that people who ingest zinc from denture cream daily for many years will develop a severe copper deficiency with neurological symptoms. See In re Denture Cream Products Liability Litigation, 795 F.Supp.2d at 1353. While there may be a link between negative copper balance and severe copper deficiency,

neither Dr. Askari nor any of Plaintiffs' other experts establish such a link.[6]

Finally, Dr. Askari relies on the results of the Fixodent Copper Blockade Study to support his conclusion. According to Dr. Askari, the Fixodent Copper Blockade Study shows a statistically significant difference in the amount of copper contained in the fecal excretions between the participants who ingested the Fixodent and the participants who ingested the placebo. Askari Expert Report at p. 13; Fixodent Copper Blockade Study at ASKARI-000014. The Moving Defendants vigorously object to this conclusion for a variety of reasons.[7] See Moving Defendants' Motion at pp. 42-50. The Court will not address these arguments because, at best, the Fixodent Copper Blockade Study shows exposure to Fixodent could result in loss of copper. Just as with the Wilson's Disease studies, there is an analytical gap between the proposition that zinc from Fixodent may place a particular person into a temporary negative

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[6] Plaintiffs argue they have established such a link through extrapolation. This argument is unpersuasive. The appellate courts have recognized extrapolation satisfies a Frye inquiry only if the extrapolation is based on methodologically sound evidence. See Trach v. Fellin, 817 A.2d 1102 (Pa. Super. 2003). In Trach, the Superior Court approved of the plaintiff's expert's use of extrapolation to conclude the plaintiff's ingestion of 1800 mg of Doxepin daily for seven days caused the plaintiff's eye injuries, which included glaucoma and partial blindness, based on the fact studies showed ingestion of 300 mg of Doxepin daily could cause blurred vision. Id. at 1105-06. Thus, in Trach, the expert started from the proposition 'ingestion of Doxepin at a low dose could cause mild eye injury' and extrapolated to conclude ingestion of Doxepin at high dose caused more severe eye injuries. In contrast, Plaintiffs' here ask the Court to allow their experts to start with the proposition 'short term ingestion of zinc acetate leads to temporary negative copper balance without neurological injury' and extrapolate to conclude long term ingestion of a different substance, denture cream zinc polymer, leads to copper deficiency with neurological injury. This extrapolation is not logically sound and will not be sanctioned by this Court.

[7] Moving Defendants argue the Fixodent Copper Blockade study must be rejected because 1) the data does not support Dr. Askari and Dr. Wang's conclusions, 2) the final statistical analysis examined different endpoints than were initially identified in the study protocol developed before commencement of the study, 3) the threshold for statistical significance used by Dr. Wang in his final statistical analysis was changed from the threshold contained in the initial study protocol, 4) no statistician was consulted when crafting the initial study protocols, 5) the study was not balanced, rather more participants ingested Fixodent than ingested zinc acetate or placebo, and 6) there are significant questions regarding the integrity of the data collected.

copper balance and the proposition that people who ingest zinc from Fixodent daily for many years will develop a severe copper deficiency with neurological symptoms. Furthermore, the Court finds the Fixodent Copper blockade study unreliable because, like Dr. Lautenbach's cohort report, the Fixodent Copper blockade study is nothing more than a blatant, litigation driven, attempt to remediate the analytical deficiencies identified in Jacoby. Accordingly, the Court concludes the Fixodent Copper Blockade Study does not provide a reliable base for Dr. Askari's conclusions.

Plaintiffs also attempt to fill the analytical gaps identified in Jacoby through the testimony of Dr. Smith, a toxicologist. Dr. Smith authored a report dated May 31, 2013 and produced on July 3, 2013, in which he states he applied a "Weight of the Evidence" methodology to a wide body of evidence and concluded Fixodent can cause copper deficiency myeloneuropathy. Smith Expert Report at ¶ 14. According to Dr. Smith's report, he reached the following conclusions to a reasonable degree of medical certainty:

1) Excess zinc intake is toxic to the blood and nervous system.
2) Copper deficiency can be induced by chronic zinc exposure and can produce serious hematological and neurological changes, including myelopathy.
3) The U.S recommended daily intake of zinc is 11mg for adult men and 8 mg for adult women. Normal daily intake is estimated to be 5-16 mg. The Institute of Medicine, a branch of the National Academy of Sciences, set the tolerable intake upper limit of zinc is 40 mg per day from all sources.
4) Fixodent contains approximately 17 mg of zinc per gram of adhesive.
5) If a consumer applied approximately 2.44 – 3.56 g of Fixodent to the dentures per day and had otherwise normal daily intake of zinc, the possibility exists for the consumer to exceed the tolerable daily intake upper limit at 40 mg/day.

6) The manufacturer of Fixodent was aware of the potential dangers of incorporating zinc into denture cream and failed to adequately evaluate its safety prior to going to market.

7) The available medical and scientific literature regarding the association between zinc-containing denture cream and neurological injuries, as well as Dr. Lautenbach's cohort study and Dr. Askari's Fixodent Copper Blockade Study supports the conclusion that high-end users of Fixodent denture cream are susceptible to zinc-induced copper deficiency leading to myelopathy.

8) In the field of toxicology, a well-accepted methodology that is regularly employed to evaluate whether a chemical is capable of causing particular injuries is the weight-of-the-evidence methodology.

See Smith Expert Report at ¶ 13. The Court finds three deficiencies with the methodology used by Dr. Smith to arrive at these conclusions.

First, the body of evidence examined by Dr. Smith included, *inter alia*, 1) dose-response relationship evidence, 2) available epidemiological evidence, 3) clinical studies involving Fixodent and Super PoliGrip, 4) the opinions of Plaintiffs' other experts and 5) various internal documents made available by the defendants in this action. Smith Expert Report at ¶ 16. The majority of this evidence has already been discussed, and rejected above; therefore, this evidence cannot serve as a valid base upon which Dr. Smith's opinions rest.

Second, Dr. Smith's "weight of the evidence" test fails to conform to even the most basic definition of scientific methodology since there is no way for other scientists to test or replicate Dr. Smith's "weight of the evidence" analysis. As the Superior Court has noted, a key component of any scientific methodology is the ability to test a hypothesis through replicated experimentation. Trach v. Fellin, 817 A.2d at 1113 (stating "Key aspects of the scientific method

include the ability to test or verify a scientific experiment by a parallel experiment . . . and to replicate the experiment to expose or reduce error"). Here, Dr. Smith's "weight of the evidence" methodology does not have any predetermined standard for weighing the evidence. Dr. Smith Deposition, Moving Defendants' Motion at Ex. 51, 81:4-12 (September 25, 2012). It is axiomatic that if there is not a predetermined standard for weighing evidence, then another scientist will not be able to replicate Dr. Smith's analysis because the other scientist will not know how to weigh certain evidence. Dr. Smith admitted the same in his deposition. Id. at 83:9-11. Accordingly, Dr. Smith's methodology cannot be replicated to expose or reduce error. For this reason, Dr. Smith's "weight of the evidence" methodology must be rejected because Plaintiffs have not produced any evidence to show general acceptance of a methodology that cannot be tested or replicated.

Third, even if it could be tested and replicated by other scientists, Dr. Smith's "weight of the evidence" methodology contains a fatal methodological defect. The only recognized standard Dr. Smith mentions he employed is he "[kept] in mind the list of considerations first proposed by Sir Austin Bradford Hill for inferring general causation . . . ." Id. at ¶ 19. The Bradford-Hill criteria are used by epidemiologists to assess whether an established epidemiological association reflects a causal relationship. See In re Avandia Mktg., Sales Practices and Prods. Liab. Litig., 2011 WL 13576, *3 (E.D.Pa. Jan. 4, 2011)(Rufe, J.). Importantly, the Bradford-Hill criteria are to be applied only after an epidemiological association has been established. See id. As is noted above, Dr. Lautenbach's expert report does not provide a sound epidemiological basis from which to conclude there is an association between Fixodent and copper deficiency myeloneuropathy. Similarly, Dr. Smith's report does not contain any

other source from which to conclude such an association exists.[8] Thus, the Court is left to conclude Dr. Smith applied the Bradford-Hill criteria without first having an epidemiological association. Plaintiffs' have not provided any evidence to suggest the application of the Bradford-Hill criteria in the absence of an epidemiological association has been generally accepted by the scientific community. Since it is based on a scientific methodology that has not been generally accepted by the scientific community, Dr. Smith's testimony must be precluded.

Finally, Dr. Greenberg, a neurologist, concludes within a reasonable degree of medical and scientific certainty there is a link between Fixodent and copper deficiency myeloneuropathy. Greenberg Expert Report, Moving Defendants' Motion at Ex. 9. A review of Dr. Greenberg's report shows it is based on the same case studies and case reports relied upon by Dr. Lautenbach and Dr. Askari. For the reasons stated in the above discussion, these case studies and case reports do not provide a methodologically sound basis to support the conclusion Fixodent causes copper deficiency myeloneuropathy. Furthermore, Dr. Greenberg does not point to a single case linking Fixodent specifically to copper deficiency myeloneuropathy. For these reasons, Dr. Greenberg's testimony must be excluded.

In conclusion, the addition of Dr. Lautenbach's "cohort study" and Dr. Askari's Fixodent Copper Blockade Study to the evidence previously adduced by the parties in Jacoby is insufficient for the Plaintiffs to meet their burden under Frye. Plaintiffs' experts have failed to establish in a methodologically sound manner that denture cream use, in general, results in copper deficiency myeloneuropathy. Furthermore, Plaintiffs' experts have failed to utilize sound methodology to establish a link between Fixodent and copper deficiency myeloneuropathy. For

[8] This Court notes in Jacoby, Dr. Smith admitted at his deposition he did not have any evidence to show a statistical association between neurological injuries in Fixodent users and neurological injuries in non-Fixodent users. See Jacoby v. Rite Aid Corp, et al., 1508 EDA 2012, p. 13 (Pa. Super. Dec. 9, 2013)(unpublished).

these reasons, the opinions of Drs. Lautenbach, Askari, Smith, Greenberg, Cranor, Grainger, Prohaska, and Shuster must be excluded.

An appropriate Order granting Moving Defendants' Motion is attached hereto.

BY THE COURT:

ARNOLD L. NEW, J.