UNITED STATES DISTRICT COURT

NORTHERN DISTRICT OF CALIFORNIA

IN RE: VIAGRA (SILDENAFIL CITRATE) AND CIALIS (TADALAFIL) PRODUCTS LIABILITY LITIGATION

This Document Relates to: ALL ACTIONS

Case No. 16-md-02691-RS

ORDER GRANTING IN PART AND DENYING IN PART MOTIONS TO EXCLUDE EXPERT TESTIMONY

I. INTRODUCTION

In 2014 the Li study was published in JAMA Internal Medicine, a journal of the American Medical Association, concluding that "[s]ildenafil use may be associated with an increased risk of developing melanoma." The study cautioned its findings were insufficient to require altering clinical recommendations at that time, but acknowledged a need for continued investigation of the observed association between sildenafil use and melanoma. The first of the lawsuits now pending in this Multi District Litigation were filed in response to that study. Plaintiffs allege they have suffered from melanoma exacerbated by their use of sildenafil (sold under the brand name Viagra) and/or the similar drug tadalafil (sold under the brand name Cialis). They contend the results of multiple studies following up on Li 2014 are now sufficient to support a scientific conclusion that sildenafil and tadalafil use causes melanoma progression in some instances, and they proffer expert witnesses who are prepared to testify accordingly.

Defendant Pfizer, the maker of Viagra, and defendant Eli Lilly, the maker of Cialis, present

experts who dispute the opinions of plaintiffs' experts, and who opine that the body of scientific evidence that has emerged following the Li 2014 study does *not* support a conclusion that sildenafil or tadalafil causes melanoma progression. Each side now moves to exclude significant portions of the expert opinions offered by the other side, under the standards articulated in *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 509 U.S. 579 (1993) and its progeny, and as reflected in Rule 702 of the Federal Rules of Evidence.

Over the course of four days the parties presented live testimony from a subset of their respective expert witnesses. Plaintiffs called four experts, two testifying it is "biologically plausible" that the drugs could cause melanoma progression, and two testifying the epidemiological research shows use of the drugs in fact does cause melanoma progression in some cases. Defendants presented three experts, essentially in rebuttal to the testimony of plaintiffs' experts. For the reasons explained below, while the opinions of plaintiffs' experts regarding "biological plausibility" are admissible, their experts' opinions as to causation are not. The opinions offered by defendants' experts in turn represent admissible rebuttal. Accordingly, defendants' motion to exclude the testimony of plaintiffs' experts will be granted in part, and denied in part. Plaintiffs' motion to exclude the testimony of defendants' witnesses will be denied.

II. BACKGROUND

A. *Melanoma*

Melanoma is the most serious form of skin cancer, causing the majority of skin cancer deaths. Rates of the disease have been rising in recent decades. Melanoma, however, remains less common than other skin cancers, such as basal cell carcinoma and squamous cell carcinoma. Melanoma arises in melanocytes—cells at the bottom of the epidermis that are present in normal skin. Melanocytes are the cells that produce melanin, the pigment responsible for skin color. Upon undergoing certain genetic mutations, melanocytes gain the ability to grow more rapidly and invade into deeper parts of the skin and beyond. Melanomas are characterized by growth and invasion—they typically begin in nevi (commonly referred to as moles), then grow larger and

move (invade) over time.

Melanoma ordinarily takes many years to develop from premalignant nevi into identifiable and diagnosable tumors. Even after a tumor develops, it can lie dormant for decades, or progress only slowly within the skin or in the lymph nodes. There appears to be no dispute that early stage or dormant melanomas may sometimes be reactivated to grow by an environmental trigger or a pharmacologic stimulus. The question is whether tadalafil and sildenafil have that capacity to cause melanoma progression. Because the survival rate for melanoma patients significantly declines as the disease progresses, any agent that promotes rapid progression carries severe consequences.

B. *PDE5 inhibitors*

Phosphodiesterases (PDEs) are a family of enzymes that play a role in signaling between cells. The particular PDE relevant here is PDE5.[1] Sildenafil and tadalafil both act as "inhibitors" of PDE5, in that they slow or stop the normal activity of the enzyme. Plaintiffs have offered detailed explanations as to how PDE5 inhibitors affect erectile dysfunction. That science, however, does not appear directly relevant to the issue of whether PDE5 inhibitors might contribute to melanoma progression and will not be recounted here. The possible effects of PDE5 inhibitors on a variety of other medical conditions are the subject of ongoing investigation. Indeed, some research is exploring PDE5 inhibitors as a treatment for certain cancers other than melanoma.[2]

[1] The parties use "PDE5" and "PDE5A" interchangeably.

[2] Defendants also point to a clinical trial currently underway at the University of Heidelberg involving giving Cialis to patients who have already experienced melanoma progression and for whom other treatments have not proved effective. While the existence of that trial does not conclusively establish PDE5 inhibitor use cannot contribute to melanoma progression, it does support defendants' argument that the medical community does not believe there is evidence of such a causal link.

C. *The studies*

Epidemiology is "the field of public health and medicine that studies the incidence, distribution, and etiology of disease in human populations." Michael D. Green et al., Reference Guide on Epidemiology, in Reference Manual on Scientific Evidence 551, 551 (3d ed. 2011). Epidemiological observational studies compare the risk of disease between patients exposed to a given substance and patients who were not exposed. Such studies may be prospective, identifying patients and then following them for a period of time, or retrospective, identifying patients and then performing a review to determine what took place during the period they did or did not take the drug. There are two types of observational studies: cohort studies and case control studies.

A cohort study identifies patients who are taking the drug and then follows them for a certain amount of time to determine if they experience the alleged negative outcome. The cohort study also identifies people *not* taking the drug and follows them. The study then compares the rate of the negative outcomes in the first group with the rate in the second group to compute the "relative risk."

A case-control study identifies persons who had a negative outcome (the cases), and reviews their medical records to determine how many of those persons used the studied drug. The study then identifies an equal number of people who did not have the negative event (the controls) and determines how many of them were taking the drug. From those figures an "odds ratio" is computed.

The parties also rely on several meta-analyses, which pool the results of various studies and arrive at a single figure intended to represent the totality of the studies reviewed. Meta-analysis has the advantage of pooling more data so that the results are less likely to be misleading solely due to chance.

When reviewing the results of a study it is important to consider the confidence interval, which, in simple terms, is the "margin of error." For example, a given study could calculate a relative risk of 1.4 (a 40 percent increased risk of adverse events), but show a 95 percent "confidence interval" of .8 to 1.9. That confidence interval means there is 95 percent chance that

the true value—the actual relative risk—is between .8 and 1.9. Because the confidence interval includes numbers that do not show any increased risk, and indeed, show the possibility of a decreased risk, such study results do not demonstrate a "statistically significant" increased risk of an adverse outcome. Confidence intervals are calculated, in part, based on the number of people and events included in the study. The larger the sample size in a study, all other things being equal, the narrower the confidence boundaries will be.

All of the experts, on both sides, report that they reviewed *all* of the available scientific literature on the relationship between PDE5 inhibitors and melanoma, including peer-reviewed articles and "abstracts" submitted in advance of potential future publication of articles describing the results obtained in research studies. The following epidemiological studies feature most prominently in the various expert reports:

(1) The seminal observational study, mentioned above, is known as Li 2014. It found a "significantly elevated risk of invasive melanoma" in patients who had recently used sildenafil. The study reported a risk factor of 1.84, with a confidence interval of 1.04-3.22.

(2) Loeb 2015 found an increased risk of melanoma in men with filled PDE5 prescriptions. The risk factor was 1.21, with a confidence interval of 1.08-1.36.

(3) Matthews 2016 reported a positive association between PDE5 inhibitor use and melanoma, with a risk factor of 1.14 and a confidence interval of 1.01-1.29.

(4) Lian 2016 identified a positive overall association with an increased risk for melanoma among those who had received seven or more prescriptions. The risk factor was 1.3, with a confidence interval of 1.01-1.69. Among those who had greater than twenty-five pills the risk factor was 1.34 with a confidence interval of 1.04-1.72.

(5) Pottegård 2016 observed an association in patients reporting a "high use" of PDE5 inhibitors. The risk factor was 1.28, with a confidence interval of 1.05-1.56.

(6) Shkolyar 2018 found an association between higher volume PDE5 inhibitor use and development of melanoma.

(7) A set of three abstracts presented to the American Academy of Dermatology all found

increased risks of melanoma following sildenafil and tadalafil use—the Boor 2016, Ma 2017, and Nardone 2018 studies.

(8) Six meta-analyses have reported an association between PDE5 inhibitor use and an increased risk of melanoma: Loeb 2017; Tang 2017; Wang 2017; Deng 2018; Han 2018; Feng 2018. The risk estimates in these studies ranged from 1.11-1.13.

Separately from these epidemiological studies, plaintiffs rely on two laboratory studies to support their contention that it is biologically plausible that sildenafil and tadalafil can cause melanoma progression. Arozarena 2011 investigated whether the PDE5 gene (which makes the PDE5 enzyme) plays a role in melanoma. The study reported the findings of more than 50 cell and animal experiments, but because the main focus of the study was understanding the role of the PDE5 gene itself, only a handful of those experiments involved PDE5 inhibitors.

The Dhayade 2016 study proposed that PDE5 inhibition results in increased melanoma cell growth in laboratory experiments conducted in petri dishes (known as "in vitro" experiments). Dhayade also reported increased tumor growth in mice as shown by "in vivo" experiments (testing conducted on living organisms). The majority of the experiments in the Dhayade study involved a mouse melanoma cells line known as B16. Unlike most human melanomas, B16 cells lack the so-called BRAF or NRAS mutations. Those mutations are present in more than 75% of all human melanomas.

III. LEGAL STANDARDS

As an initial matter, the customary label attached to motions of this nature is "*Daubert*." Indeed, the parties and the court both have generally referred to the evidentiary hearings and the underlying motions in this case as *Daubert* proceedings. Strictly speaking, however, the governing rule is set out in Rule 702 of the Federal Rules of Civil Procedure, as opposed to *Daubert* itself. *Daubert* expressly held that the version of Rule 702 then in effect had superseded the prior common law test articulated in *Frye v. United States*, 293 F. 1013, 1014 (D.C. Cir. 1923). Rule

702 was amended in 2000, seven years after *Daubert* was decided. Amendment of the rule required approval by the Supreme Court and acceptance by Congress under the Rules Enabling Act, and the amended rule superseded any other law. *See* 28 U.S.C. § 2072(b) ("All laws in conflict with such rules shall be of no further force or effect after such rules have taken effect."). Thus, Rule 702 provides the governing law.

That said, no obvious conflict arises between the Rule as amended and *Daubert*, at least as relevant to the issues in this case. While the advisory committee's note to the 2000 amendment specifically states it was not intended to "codify" the specific factors identified in *Daubert*, it is clear that revisions to the Rule were designed to be generally consistent with both *Daubert* and its progeny. *See* Rule 702 advisory committee note to 2000 amendment (reviewing *Daubert* and subsequent case law and concluding "[a]ll of these factors remain relevant to the determination of the reliability of expert testimony under the Rule as amended.").

Rule 702 provides that expert opinion testimony is admissible if: (1) the witness is qualified to testify about the topics she intends to address; (2) the expert's specialized knowledge will help the jury "to understand the evidence or to determine a fact in issue"; (3) "the testimony is based on sufficient facts or data"; (4) "the testimony is the product of reliable principles and methods"; and (5) "the expert has reliably applied the principles and methods to the facts of the case." To be qualified, the expert must have sufficient "knowledge, skill, experience, training, or education" to offer the opinion. Fed. R. Evid. 702. So long as the expert's testimony is "within the reasonable confines of his subject area," a lack of particularized expertise generally goes to the weight of the testimony, not its admissibility. *D.F. ex rel. Amador v. Sikorsky Aircraft Corp.*, 2017 WL 4922814 at *14 (S.D. Cal. Oct. 30, 2017) (quoting *Avila v. Willits Environmental Remediation Trust*, 633 F.3d 828, 839 (9th Cir. 2011) and citing *United States v. Garcia*, 7 F.3d 885, 889-90 (9th Cir. 1993)); *see also Hopkins v. Dow Corning Corp.*, 33 F.3d 1116, 1124 (9th Cir. 1994).

Aside from the qualification requirement, there are two questions at the heart of the admissibility determination: whether the testimony is relevant and whether it is reliable. *See City*

of Pomona v. SQM North America Corp., 750 F.3d 1036, 1043 (9th Cir. 2014). "Expert opinion testimony is relevant if the knowledge underlying it has a valid connection to the pertinent inquiry." *Id*. at 1044 (citation omitted). In other words, the expert testimony must "fit" the question the jury must answer. *Daubert v. Merrell Dow Pharmaceuticals, Inc*. (*Daubert II*), 43 F.3d 1311, 1321 n.17 (9th Cir. 1995). This bar is cleared where the evidence "logically advances a material aspect of the proposing party's case." *Messick v. Novartis Pharmaceuticals Corp*., 747 F.3d 1193, 1196 (9th Cir. 2014) (citation omitted).

Expert evidence "is reliable if the knowledge underlying it has a reliable basis in the knowledge and experience of the relevant discipline." *City of Pomona*, 750 F.3d at 1044 (citation omitted). In deciding whether to permit an expert to testify, courts face the difficult task of "determin[ing] whether the analysis undergirding the experts' testimony falls within the range of accepted standards governing how scientists conduct their research and reach their conclusions." *Daubert v. Merrell Dow Pharm., Inc*. (*Daubert II*), 43 F.3d 1311, 1317 (9th Cir. 1995). Among the factors courts consider in making this determination are: (1) whether the expert's theory or method is generally accepted in the scientific community; (2) whether the expert's methodology can be or has been tested; (3) the known or potential error rate of the technique; and (4) whether the method has been subjected to peer review and publication. *Id*. at 1316 (citing *Daubert*, 509 U.S. at 593-94). Consideration should also be given to whether the expert's testimony springs from research independent of the litigation. *Id*. at 1317. If not, the expert should point to other indicia of reliability, such as peer-reviewed studies or a reputable source showing that the expert "followed the scientific method, as it is practiced by (at least) a recognized minority of scientists in their field." *Id*. at 1317-19. These factors are not a mandatory or inflexible checklist, and a court has broad discretion to determine which factors are most informative in assessing reliability in the context of a given case. *See Kumho Tire Co. v. Carmichael*, 526 U.S. 137, 141-42 (1999); *United States v. Alatorre*, 222 F.3d 1098, 1102 (9th Cir. 2000).

The focus of the reliability inquiry is on the principles and methodology an expert uses in forming the opinions rather than the expert's conclusions. In conducting the reliability analysis,

the court must also consider whether, for a given conclusion, "there is simply too great an analytical gap between the data and the opinion proffered." *General Electric Co. v. Joiner*, 522 U.S. 136, 146 (1997). In short, both unsound methods and unjustified extrapolations from existing data can require exclusion of an expert's testimony.

The Ninth Circuit has placed great emphasis on *Daubert's* admonition that a district court should conduct the analysis "with a 'liberal thrust' favoring admission." *Messick*, 747 F.3d at 1196 (quoting *Daubert*, 509 U.S. at 588). Accordingly, the Ninth Circuit has emphasized that the gatekeeping function is meant to "screen the jury from unreliable nonsense opinions, but not to exclude opinions merely because they are impeachable." *Alaska Rent-A-Car, Inc. v. Avis Budget Group, Inc.*, 738 F.3d 960, 969 (9th Cir. 2013). "Vigorous cross-examination, presentation of contrary evidence, and careful instruction on the burden of proof are the traditional and appropriate means of attacking shaky but admissible evidence." *Daubert*, 509 U.S. at 596; *see also Murray v. Southern Route Maritime SA*, 870 F.3d 915, 925 (9th Cir. 2017); *Wendell v. GlaxoSmithKline LLC*, 858 F.3d 1227, 1237 (9th Cir. 2017).

IV. DISCUSSION

A. Plaintiffs' experts

1. General Issues

All of plaintiffs' experts have shown they are generally qualified to render expert opinions in their respective fields. Although defendants impugn each expert in various indirect ways—for example, pointing out that one is on a "non-tenure track"—they do not suggest the witnesses lack the requisite specialized training, knowledge, and experience to testify as experts. Defendants do fault plaintiffs and their experts for having taken differing positions over time as to what "progression" means with respect to melanoma. Defendants understandably point out inconsistencies in the record as to whether the witnesses are referring to "growth" or "invasion" or both, when contending sildenafil and tadalafil contribute to the progression of melanoma. Those apparent inconsistencies, however, do not rise to a level that would warrant excluding the experts

as unreliable on that basis. Rather, those matters would properly be explored through cross-examination at trial.

Defendants also point to the fact that none of plaintiffs' experts developed his or her opinions independently of this litigation or have sought to publish any of his or her research or conclusions. As noted, a relevant factor in assessing reliability of a scientific expert opinion is "whether the method has been subjected to peer review and publication." *Daubert II*, *supra*, 43 F.3d at 1316 (citing *Daubert*, 509 U.S. at 593-94). Nevertheless, the Ninth Circuit has made clear that "[w]hile independent research into the topic at issue is helpful to establish reliability, its absence does not mean the experts' methods were unreliable." *Wendell*, *supra*, 858 F.3d at 1235. Likewise, expert testimony may still be reliable and admissible without peer review and publication. *Id.*

Here, one of plaintiffs' experts, Dr. Ahmed-Saucedo, testified she believed that she had an obligation to keep her work in this matter confidential, which of course would preclude her from seeking to publish her findings and conclusions. More fundamentally, the very nature of the research conducted here by plaintiffs' experts would not appear to lead naturally to publication. *See Wendell*, 858 F.3d at 1236 (quoting an experts' explanation for why he had not published, "[o]pinions are not publishable. Data is publishable. What I'm reporting here is my opinion.") Accordingly, while the fact that the experts presented by plaintiffs reached their conclusions only in the context of this litigation and only from a review of the work of others may weigh slightly against a finding of sufficient reliability, it does not tip the balance in favor of exclusion.

2. Biological plausibility

In the abstract, there is no independent requirement that a plaintiff establish it to be biologically plausible that exposure to a particular drug or substance could cause the disease or condition at issue. If, for example, a plaintiff showed that exposure to a particular substance always leads to a specific outcome, and that all other possible causes could be eliminated, it would be of no moment if the science were unable to provide any explanation as to how the substance

could cause that effect. *See Daubert II*, 43 F.3d at 1314 ("Not knowing the mechanism whereby a particular agent causes a particular effect is not always fatal to a plaintiff's claim. Causation can be proved even when we don't know precisely *how* the damage occurred, if there is sufficiently compelling proof that the agent must have caused the damage *somehow*.") (emphasis in original).

In this case, however, plaintiffs have taken on the task of showing biological plausibility because it is an available factor to support a conclusion that an observed statistical association between exposure to a substance and a particular effect is causal, as opposed to random, or the result of something else. "Biological plausibility" thus is only a subsidiary consideration in the larger question of general causation. Here, though, it appropriately is the first question because plaintiffs have presented experts who are offering opinions specifically on that narrower issue, and because plaintiffs' general causation experts in turn rely on biological plausibility as part of their own analyses.

At the hearing, plaintiffs offered two experts to testify it is "biologically plausible" that use of PDE5 inhibitors can cause melanoma progression. Dr. Rizwan Haq testified regarding sildenafil. Dr. Anand Ganesan focused on tadalafil. Plaintiffs also offer, and defendants also move to exclude, the testimony of Dr. Gary Piazza, who did not testify at the hearing but who offers an opinion that a plausible biological mechanism exists by which PDE5 inhibitors can "enhance or accelerate the growth or the invasiveness" of pre-existing melanoma cells.

Defendants' principal challenge to Drs. Haq, Ganesan, and Piazza rests on arguments that the underlying Arozarena 2011 and Dhayade 2016 studies are not sufficient to show biological plausibility. In the case of Arozarena 2011, defendants have presented as their own expert Dr. Richard Marais, one of the study authors, who expressly rejects the conclusions plaintiffs' experts attempt to draw from the study.

As noted above, the Arozarena 2011 study investigated whether the PDE5 gene (which makes the PDE5 enzyme) plays a role in melanoma. While the study involved more than 50 cell and animal experiments designed to explore the role of the PDE5 gene itself, only a few of them involved PDE5 inhibitors. Among those, one in vitro experiment used melanoma cells with a

mutated BRAF gene, and appeared to show that the cells became more "invasive" when treated with Viagra, Cialis, or another PDE5 inhibitor that is not the subject of plaintiffs' claims in this litigation. "Invasion," however, was a measure of cell movement; the results were limited to melanoma cells from a single patient who already had advanced, metastatic disease; and the study did not replicate the results in several other experiments using melanoma cells from other patients, including those with and without the BRAF mutation.

Ultimately, the Arozarena 2011 authors conclude that they did not perceive the use of PDE5 inhibitors "to be a problem." They cautioned that their "data should be interpreted with care," and that it did "not immediately suggest that PDE5A inhibitors will drive melanoma metastasis."

Defendants similarly attack Dhayade 2016 on various grounds, including the fact that its experiments involved B16 mouse cells, which may not be representative of human melanomas, and the fact that the cells were treated with Viagra in combination with another substance called c-type natriuretic peptide ("CNP"). Defendants contend the study does not permit a conclusion to be drawn as to the effect of Viagra alone.

The "methodology" Drs. Haq, Ganesan, and Piazza employed in reaching their opinions was to apply their education, training and experience to a comprehensive review of the available medical literature on the topic. Such an approach is appropriate. *See Wendell*, at 858 F.3d 1234. ("The doctors employed sound methodologies to reach their conclusions. Dr. Shustov based his opinions on medical records as well as his education, training and experience, knowledge of the pertinent medical literature . . . ."). Although defendants vigorously dispute the notion that Arozarena 2011 or Dhayade 2016 *should* be interpreted to show biological plausibility, they concede that plaintiffs' experts are not alone in reaching that conclusion.

Thus, in the final analysis, plaintiffs have adequately shown that their biological plausibility experts have reliably applied accepted scientific methods in reaching their conclusions. Defendants' challenges to the experts' opinions are appropriately presented through cross-examination and rebuttal experts. *See Wendell*, 858 F.3d at 1237-38 ("That defendants may be

able to offer other equally qualified medical opinion[s] . . . does not support the idea that *Daubert* should bar the admission of the testimony of the doctors offered as experts by Plaintiffs.")

3. General causation

Causation in toxic tort and pharmaceutical personal injury cases "is typically discussed in terms of generic and specific causation." *In re Hanford Nuclear Reservation Lit.*, 292 F.3d 1124, 1133 (9th Cir. 2002). The general causation question asks "whether the substance at issue had the capacity to cause the harm alleged." *Id*. Thus, in *Hanford* the Ninth Circuit explained the general causation inquiry is "whether exposure to a substance for which a defendant is responsible, such as radiation at the level of exposure alleged by plaintiffs, is capable of causing a particular injury or condition in the general population." *Id.* Specific causation, in contrast, refers to whether a particular individual suffers from a particular ailment as a result of exposure to a substance. *Id*. At this stage of the present litigation, specific causation is not yet at issue.

Plaintiffs' experts rely on epidemiology in their attempt to prove general causation. As alluded to above, "[t]he field of epidemiology addresses the incidence, distribution and etiology (causation) of disease in human populations by comparing individuals exposed to a particular agent to unexposed individuals to determine whether exposure increases the risk of disease." *In re Silicone Gel Breast Implants Prod. Liab. Litig*., 318 F. Supp. 2d 879, 892 (C.D. Cal. 2004). Scientists use "relative risk" to identify an association between exposure to the substance at issue and a disease.

> For example, if a study found that 10 out of 1000 women with breast implants were diagnosed with breast cancer and 5 out of 1000 women without implants (the "control" group) were diagnosed with breast cancer, the relative risk of implants is 2.0, or twice as great as the risk of breast cancer without implants. This is so, because the proportion of women in the implant group with breast cancer is 0.1 (10/1000) and the proportion of women in the non-implant group with breast cancer is 0.05 (5/1000). And 0.1 divided by 0.05 is 2.0.

Id. A relative risk of 1.0 suggests that there is no association between the product and the disease,

that is, the same percentage of people using the product are diagnosed with the disease as those who do not. Thus, a relative risk of less than 1.0 suggests that the product might actually be "protective" against the disease—i.e., fewer people using the product contract the disease than those who do not use the product. *Id.* at n. 5.

In general, epidemiology studies are probative of general causation. Where a relative risk greater than 1.0 appears, it suggests the product has the capacity to cause the disease, if other factors are adequately addressed. "Where the study properly accounts for potential confounding factors and concludes that exposure to the agent is what increases the probability of contracting the disease, the study has demonstrated general causation—that exposure to the agent is capable of causing [the illness at issue] in the general population." *Id*. at 893 (internal quotation marks and citation omitted).[3] There is no requirement to show that exposure to a substance will *always* cause the disease, or even that it will most often cause the disease. At the general causation stage of litigation, plaintiffs need only show that exposure can be a contributing factor to development of the disease in some instances.

Additionally, notwithstanding any suggestion in *Silicone Gel* that epidemiological studies may sometimes demonstrate causation, plaintiffs are not to be faulted for the fact that they can point to no published studies expressly *concluding* that sildenafil or tadalafil use causes melanoma progression. Epidemiology studies typically only expressly address whether an *association* exists between agents such as sildenafil and tadalafil and outcomes like melanoma progression. As explained in *In re Roundup Prod. Liab. Litig*., 390 F. Supp. 3d 1102, 1116 (N.D. Cal. 2018), "[w]hether the agents cause the outcomes, however, ordinarily cannot be proven by epidemiological studies alone; an evaluation of causation requires epidemiologists to exercise judgment about the import of those studies and to consider them in context." To that end, "[o]nce

[3] Here, as noted, plaintiffs are not actually contending exposure to sildenafil and tadalafil causes melanoma to arise in the first instance. Rather, they argue the exposure causes the disease to progress more quickly. References in this order to causing disease should be understood to encompass plaintiffs' progression theory.

epidemiologists have concluded from the studies that there is an association between an agent and an outcome, they often assess causation through a framework called the "Bradford Hill criteria," named for Sir Austin Bradford Hill, who wrote a 1965 article[4] that articulated nine "viewpoints" now generally accepted to be relevant to assessing causation. *Id.* Broadly, these factors are: (1) the strength of the association; (2) consistency; (3) specificity; (4) temporality; (5) biological gradient or dose response; (6) biological plausibility; (7) coherence with other scientific knowledge; (8) experimental evidence; and (9) analogy. *Id.*

Here, plaintiffs proffer experts who have reviewed the published studies reporting an association between sildenafil or tadalafil use and melanoma progression, and who then purport to conduct Bradford Hill analyses to evaluate whether the observed association is causal. Defendants contend the opinions of plaintiffs' experts are reliable neither with respect to the association between sildenafil and tadalafil and melanoma progression, nor with respect to their Bradford Hill analyses. The proffered opinions of plaintiffs' three "general causation" experts will be considered in turn.

a. *Dr. Rehana Ahmed-Saucedo*

Dr. Ahmed-Saucedo, referred to by the parties as "Dr. Ahmed," testified in the hearings and generally presented as a learned and credible witness. Since 2011, Dr. Ahmed has been an Assistant Professor of Dermatology at the University of Minnesota, and is a practicing dermatologist at Lakes Dermatology in Minnesota where she also serves as president of the company. Dr. Ahmed received a Ph.D. in cancer epidemiology in 2006 and an MD in 2007, both from the University of Minnesota. She then completed a residency in dermatology in 2011 at the University of Minnesota, Department of Dermatology. Dr. Ahmed is an author on more than two dozen peer-reviewed journal articles, many of which involve epidemiological research. Dr. Ahmed

[4] Austin Bradford Hill, The Environment and Disease: Association or Causation?, 58 Proceedings of the Royal Society of Medicine 295 (1965)

also currently serves as a peer-reviewer for fifteen scientific publications, including journals involving topics such as epidemiology, dermatology, oncology, and cancer etiology. In addition, Dr. Ahmed has given presentations on both epidemiology and dermatology.

Dr. Ahmed relies on the epidemiological studies cited above to conclude that there is an *association* between use of PDE5 inhibitors and melanoma progression. Defendants strenuously argue that conclusion is not reliable because none of the studies adequately account for possible confounding. Confounding arises where a factor not addressed by the study wholly or partially explains an apparent association between the agent under study and the outcome. A factor is a confounder where it is independently related to both the exposure and the disease of interest. Failure to control for true confounding variables can skew the results of a study, producing an observed association where none exists or an observed association that is stronger or weaker than the actual association.

Here, defendants contend, among other things, that the increased rates of melanoma observed in users of PDE5 inhibitors is virtually identical to the increased rate of basal cell carcinoma in the same groups. Because there is no suggestion that PDE5 inhibitors contribute to basal cell carcinoma, defendants argue the studies support a conclusion that something other than sildenafil and tadalafil must be driving the observed increases in melanoma progression among users of those drugs.

The question of whether an epidemiological study adequately considered confounding variables and possible sources of bias is central to assessing whether the study can form a reliable basis for an expert's opinion. *See Roundup*, *supra*, 390 F. Supp. 3d at 1117. Nevertheless, the ultimate question that must be answered at this juncture is whether Dr. Ahmed (and plaintiffs' other experts) have performed a review and analysis of the studies that "falls within the range of accepted standards governing how scientists conduct their research and reach their conclusions." *Daubert II*, 43 F.3d at 1317. Defendants have offered numerous arguments from which a trier of fact could reasonably conclude that Dr. Ahmed has reached an incorrect *conclusion* that there is an actual association between PDE5 inhibitor use and melanoma progression. Again, however, "the

question at this phase is not whether the plaintiffs' experts are right." *Roundup*, 390 F. Supp. 3d at 1109. Defendants' challenges to Dr. Ahmed's conclusion that there is an actual association between PDE5 inhibitor use and melanoma progression do not warrant exclusion of her testimony under Rule 702 and *Daubert* jurisprudence. Rather, they represent matters that may be raised on cross-examination and in rebuttal testimony.

Dr. Ahmed's application of the Bradford Hill criteria, however, is a different matter. There is no dispute that, as a general proposition, Bradford Hill analysis is a reliable and accepted method for determining causation. *See, e.g., Wendell*, 858 F.3d at 1235 n.4 ("The Bradford Hill methodology refers to a set of criteria that are well accepted in the medical field for making causal judgments.") Although Bradford Hill analysis is not the sort of scientific process that is amenable to objective testing, or that has a known or potential error rate, its general acceptance in the field of epidemiology makes it an appropriate basis for expert opinion, and defendants do not contend otherwise. *See Daubert II*, 43 F.3d at 1316 (in assessing reliability of derivative analytical work, "it makes little sense to ask whether the technique employed 'can be (and has been) tested'. . . or what its 'known or potential rate of error' might be"); *Lust By & Through Lust v. Merrell Dow Pharmaceuticals, Inc.*, 89 F.3d 594, 597 (9th Cir. 1996) (noting that "testing and rate of error . . . do not apply, however, when the expert has not done original research, but rather has surveyed available literature and drawn conclusions that differ from those presented by the scientists who performed the original work"). The question, therefore, is whether the way Dr. Ahmed assessed each of the Bradford Hill factors is reliable in light the underlying evidence. It is not.

The very first Bradford Hill factor is "the strength of the association." It is self-evident that the stronger the association between exposure to a substance and a particular outcome, the more likely it is that the relationship is causal. Indeed, when reliable studies show a risk factor higher than 2, that can support not just general causation, but specific causation as well. *See Silicone Gel*, *supra*, 318 F. Supp. 2d at 893 ("[A] relative risk of 2.0 implies a 50% probability that the agent at issue was responsible for a particular individual's disease. This means that a relative risk that is greater than 2.0 permits the conclusion that the agent was more likely than not responsible for a

particular individual's disease.")

Here, the risk factor that emerged across all the studies was somewhere around 1.2. Although a risk factor in that range would not necessarily preclude a conclusion that causation exists, it undeniably is not a strong association. Dr. Ahmed nevertheless testified that she assigned significant weight to the "strength of association" factor of Bradford Hill. Dr. Ahmed, however, was unwilling to identify what she perceived the strength of association to be, instead testifying that she found it in the "totality" of the evidence. Dr. Ahmed pointed to the fact that a positive association was shown in all the studies mentioned above. That, however, would at most go to the "consistency" factor under Bradford Hill, not strength of association.

Additionally, Dr. Ahmed's dismissal of the importance of dose response evidence calls into further question the reliability of her Bradford Hill analysis. There is no dispute that none of the studies established a relationship between the amount of exposure to PDE5 inhibitors and melanoma progression. Although the lack of such evidence may not automatically preclude a finding of causation, the fact that Dr. Ahmed assigned virtually no weight to that factor further supports a finding that her Bradford Hill analysis was unduly results-driven.[5]

b. *Dr. Sonal Singh*

Like Dr. Ahmed, Dr. Singh was a generally credible witness, who appeared highly qualified in his field. Dr. Singh is currently an Associate Professor in the University of Massachusetts Medical School's Department of Family Medicine & Community Health and is also a clinician at the university's Meyers Primary Care Institute. Dr. Singh received an MD from

[5] It is also worth noting Dr. Ahmed testified that the only warning she had ever given to a patient of her own was that there is evidence of an association between PDE5 inhibitor use and melanoma progression. The contrast between that limited warning and Dr. Ahmed's proffered opinion that there is *causation* is troubling. Standing alone, it would only go to credibility that would have to be tested through cross-examination at trial. It does, however, further buttress the conclusion that Dr. Ahmed's opinion on causation is not sufficiently reliable for admission. In a sense, it could be said that Dr. Ahmed in her role *outside* this litigation represents yet one more professional who has never concluded sildenafil or tadalafil causes melanoma progression.

Patna Medical College in India in 1999 before completing a residency in internal medicine at the University of Rochester in New York in 2005. Dr. Singh went on to train in epidemiology and received a Master's in Public Health in 2008. Since that time, he has been employed as a clinician and investigator in epidemiological research, first at Johns Hopkins University and now at the University of Massachusetts.

Dr. Singh has taught courses in clinical epidemiology and pharmacoepidemiology, and is the recipient of numerous grants supporting his clinical and epidemiological research, including from the FDA and NIH. Dr. Singh devotes the majority of his professional time to such research. He has published more than 150 peer-reviewed scientific journal articles. He has also served as an editor and peer reviewer for dozens of journals. Dr. Singh's expertise is generally in evidence-based medicine, pharmacoepidemiology, drug safety, evidence synthesis, meta-analysis, and cancer epidemiology. Dr. Singh also has clinical expertise in melanoma, and as a medical doctor, sees patients with melanoma.

At the hearing, Dr. Singh candidly admitted that the Bradford Hill criteria are susceptible to an outcome-driven analysis, though he contends he did not take such an approach here. Notably, however, Dr. Singh testified that the criteria are not ranked in any order of importance, which is contrary to the position he has taken in prior litigation, and contrary to how it appears they are usually applied. While Dr. Singh stopped short of opining that a *strong* association between sildenafil and tadalafil melanoma progression exists, he gave particular emphasis to the higher association observed in Li 2014, on grounds that it purportedly controlled for sun exposure as a potential confounding factor. As Li 2014 was one of the smallest studies, and its results have not been duplicated, Dr. Singh has not provided a persuasive reason to rely more heavily on it.

Furthermore, even with Li 2014 emphasized, Dr. Singh could not reasonably conclude, and did not conclude, that the association was strong. His decision to weigh that factor relatively heavily in support of the existence of causality therefore appears untethered to the evidence. *See Joiner*, *supra*, 522 U.S. at 146 ("[T]here is simply too great an analytical gap between the data and

the opinion proffered."). Accordingly, as with Dr. Ahmed, the conclusion must be that Dr. Singh's Bradford Hill analysis was unduly results-driven.

c. *Dr. Feng Liu-Smith*

Dr. Liu-Smith is an Assistant Professor in the Department of Epidemiology at the University of California Irvine School of Medicine. In addition to her epidemiology degree, Dr. Liu Smith also holds a master's degree in biology and a Ph.D. in genetics. She has extensive experience in melanoma research, both as an epidemiologist and biologist. Dr. Liu-Smith has also previously conducted research on the major pathways leading to melanoma progression.

Dr. Liu-Smith serves as the sole Principal Investigator for two epidemiology studies, supported by NIH and Melanoma Research Alliance, investigating the impact of genetic background on melanoma risk. Dr. Liu-Smith teaches graduate courses including Principles of Epidemiology, Cancer Epidemiology, Cancer Biology, and Chronic Disease Epidemiology. Additionally, she has published more than 30 peer-reviewed manuscripts and serves as a grant and journal reviewer.

Dr. Liu-Smith did not testify at the hearings. In her Bradford Hill analysis, Dr. Liu-Smith first purported to evaluate the strength of the association and consistency. She found that several statistically significant increases in melanoma among PDE5 users were reflected in the data and "all but one of the tadalafil-specific odds ratios are greater than one." Noting the consistency of the data as a whole, she found that the increased risk is "observed across different patient populations with different characteristics," "from different regions," and "using different observational databases."

It is apparent that Dr. Liu-Smith, similarly to Dr. Ahmed, conflates strength of association with consistency, as a means of downplaying the undeniable fact that the evidence does not support a finding of a strong association. Again, while a weak association may not rule out causation, Dr. Liu-Smith's application of the Bradford Hill factors appears result-driven.

In sum, while plaintiffs' causation experts would be entitled to opine that there is an association between PDE5 use and melanoma progression, they have not reliably applied a Bradford Hill analysis to make the requisite leap from correlation to causation. Plaintiffs insist that defendants are quarreling with the *conclusions* reached by plaintiffs' experts, rather than the soundness of their methodology. Plaintiffs are correct that "a trial judge should not exclude an expert opinion merely because he thinks it's shaky, or because he thinks the jury will have cause to question the expert's credibility." *Roundup*, *supra*, 390 F. Supp. 3d at 1109. Indeed, it is for that reason plaintiffs' biological plausibility experts are not subject to exclusion.

The opinions of causation experts, however, fall outside that category. The Advisory Committee Notes provided when Rule 702 was amended to reflect *Daubert* observe:

> The Court in *Daubert* declared that the "focus, of course, must be solely on principles and methodology, not on the conclusions they generate." 509 U.S. at 595. Yet as the Court later recognized, "conclusions and methodology are not entirely distinct from one another." *General Elec. Co. v. Joiner*, 522 U.S. 136, 146 (1997). Under the amendment, as under *Daubert*, when an expert purports to apply principles and methods in accordance with professional standards, and yet reaches a conclusion that other experts in the field would not reach, the trial court may fairly suspect that the principles and methods have not been faithfully applied. *See Lust v. Merrell Dow Pharmaceuticals, Inc.*, 89 F.3d 594, 598 (9th Cir. 1996). The amendment specifically provides that the trial court must scrutinize not only the principles and methods used by the expert, but also whether those principles and methods have been properly applied to the facts of the case.

(emphasis added).

Plaintiffs have been unable to point to *any* conclusion reached by any scientist, researcher, regulatory agency, or other qualified person or group apart from their experts in this litigation that use of PDE5 inhibitors causes melanoma progression. That fact alone puts this case in stark contrast to *Roundup*, where the International Agency for Research on Cancer ("IARC"), which is the specialized cancer agency of the World Health Organization, had classified the substance at

issue as "probably carcinogenic to humans." *See Roundup*, 390 F. Supp. 3d at 1110. Although the *Roundup* court explained in detail why the IARC's conclusion was not dispositive or even as helpful to the plaintiffs as they might have believed, it did represent a conclusion reached outside the context of litigation that served to buttress the plaintiffs' experts in a way nothing does here.[6] In the end, the *Roundup* court was able to conclude that "[t]he upshot of all this is that the epidemiology evidence is open to different interpretations." *Id.* at 1126.

While the studies here likewise may be subject to differing interpretations as to biological plausibility, or as to how strong the evidence is for an actual association, there simply is no interpretation by anyone other than plaintiffs experts that supports general causation. On that critical question, despite substantial research on the issue over many years, plaintiffs' experts apparently stand alone.[7] The unavoidable conclusion is that their weighing of the Bradford Hill factors does not represent a faithful application of an accepted methodology. The opinions must be excluded.

---

[6] In contrast in this instance, the most recent review of the evidence conducted within the FDA found no support for a conclusion of causation. Although plaintiffs dispute the admissibility and import of that finding, it certainly does not support their case.

[7] Plaintiffs insist that even to the degree the existing science is insufficient to support an admissible opinion that general causation exists, their experts nonetheless should be permitted to testify because "[t]he first several victims of a new toxic tort should not be barred from having their day in court simply because the medical literature, which will eventually show the connection between the victims' condition and the toxic substance, has not yet been completed." *Wendell*, *supra*, 858 F.3d at 1237 (citations omitted). The length of time since the question was raised as to a possible link between PDE5 inhibitors and melanoma progression, and the number of studies to have investigated the issue, ameliorate any such concern in this particular case.

B. Defendants' experts

In light of the conclusion above that plaintiffs lack admissible testimony to show general causation, the question of whether the testimony offered by defendants' experts is admissible under Rule 702 and *Daubert* likely is moot. While the testimony of defendants' experts may have helped elucidate the issues, nothing in this order is premised on accepting the opinions those experts offered. The opinions of Drs. Singh, Liu-Smith, and Ahmed have been excluded not on the basis that any of the opinions offered by defendants' experts are more persuasive, but because they fail to pass the admissibility test under Rule 702.

Nevertheless, to ensure a complete record, plaintiffs' motion to exclude the opinions of defendant's expert witnesses is denied on the merits. Defendants' witnesses are primarily offered to explain what they believe are the flaws in the analyses of plaintiffs' witnesses, and there is no basis to contend they lack the expertise or have applied flawed methodology in doing so. To the extent that defendants' experts are presenting affirmative opinions of their own, they likewise have demonstrated those opinions to be adequately grounded.

V. CONCLUSION

Plaintiffs insist that as the research has unfolded—from the earliest laboratory studies suggesting a possible biological mechanism by which PDE5 inhibitors might contribute to melanoma progression through an ever-increasing number of epidemiological studies and meta-studies finding an association—it has become clear that "the science is heading towards causation." They have failed to show, however, how the evidence supports that characterization.

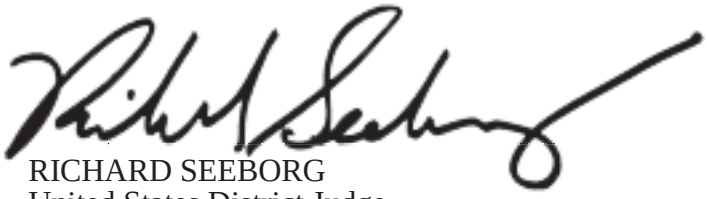
Instead, defendants' theme that "science has worked the way it is supposed to" is compelling. The Arozarena 2011 laboratory experiments suggested there could be an issue worth studying. Li 2014 took up the challenge in an epidemiological study. While it found an association, it cautioned that further research would have to be done before anyone should reach a conclusion that PDE5 inhibitor use does or could contribute to melanoma progression, such that a change in prescribing practices would be warranted. In the ensuing years numerous other

researchers have followed up, with studies that have been more robust in many ways. Those studies have consistently found an apparent association much smaller than that observed in Li 2014, and none of them has produced results that any person or organization other than plaintiffs' experts have believed support a conclusion of causation, or even of a degree of uncertainty that warrants additional precautions to be taken regarding PDE5 inhibitor use.

Defendants' motion is granted to the extent set out above. Plaintiffs' motion is denied. Within 20 days of the date of this order, the parties shall file a joint statement setting out their views as to what steps should now follow in this litigation.

IT IS SO ORDERED.

Dated: January 13, 2020



RICHARD SEEBORG
United States District Judge

United States District Court
Northern District of California