IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF SOUTH CAROLINA
CHARLESTON DIVISION

IN RE: LIPITOR (ATORVASTATIN CALCIUM) MARKETING, SALES PRACTICES AND PRODUCTS LIABILITY LITIGATION	**MDL No. 2:14-mn-02502-RMG** **CASE MANAGEMENT ORDER NO. 49** **This Order relates to all cases.**

General Causation and Dosage

In this MDL, Plaintiffs allege that Lipitor caused their Type 2 diabetes. Pfizer has moved to exclude all of Plaintiffs' general causation opinions. (Dkt. No. 972). In its motion, Pfizer argues, among other things, that "[d]ose is critical to proving general causation," and that Plaintiffs lack reliable evidence that Lipitor causes diabetes at doses less than 80 mg. (*Id.* at 49). While Plaintiffs claim that evidence of causation at doses less than 80 mg exists, they admit that their experts "offer causation opinions that are not dose-specific." (Dkt. No. 1159 at 26). As Plaintiffs' state in briefing, their experts "opine that Lipitor can cause diabetes, without specifying the precise dose at which this effect begins." (*Id.* (emphasis added)).

For example, Dr. Singh testified that he did not analyze the Lipitor data by dose. (Dkt. No. 972 at 269). If studies suggested an increased risk of diabetes, he "ascribe[d] the risk to all doses." (*Id.*). Plaintiffs argue that they are not required to put forward general causation testimony of the doses at which Lipitor is capable of causing diabetes but "need only show that Lipitor is causally related to diabetes to prevail on general causation." (Dkt. No. 1159 at 21). For the reasons stated below, the Court finds that, under the facts presented in this case, Plaintiffs

must demonstrate, at general causation, that particular doses of Lipitor are capable of causing diabetes.

A. General Causation versus Specific Causation

In order to carry the burden of proving a plaintiff's injury was caused by exposure to a specified substance, a plaintiff must demonstrate general and specific causation. *Westberry v. Gislaved Gummi AB*, 178 F.3d 257, 263 (4th Cir. 1999) (internal quotations omitted); *Zellers v. NexTech Ne., LLC*, 533 F. App'x 192, 196 (4th Cir. 2013) *cert. denied*, 134 S. Ct. 911 (2014). "General causation is whether a substance is capable of causing a particular injury or condition in the general population and specific causation is whether a substance caused a particular individual's injury." *Norris v. Baxter Healthcare Corp.*, 397 F.3d 878, 881 (10th Cir. 2005). "Plaintiff must first demonstrate general causation because without general causation, there can be no specific causation." *Id.* Here, if Lipitor is not capable of causing diabetes, then it did not cause a particular plaintiff's diabetes.

B. Dosages and Levels of Exposure

The parties agree that in toxic tort cases, "the plaintiff must demonstrate the levels of exposure that are hazardous to human beings generally" at the general causation stage. *Westberry v. Gislaved Gummi AB*, 178 F.3d 257, 263 (4th Cir. 1999) (internal quotations omitted); *Zellers v. NexTech Ne., LLC*, 533 F. App'x 192, 196 (4th Cir. 2013) *cert. denied*, 134 S. Ct. 911 (2014). While Plaintiffs admit that such evidence is required in toxic tort cases, they argue it is not required it in pharmaceutical cases. (Dkt. No. 1159 at 23). The Court disagrees.

In a case particularly on point, *In re Bextra & Celebrex Mktg. Sales Practices & Prod. Liab. Litig.*, the district court held "that dose matters" and considered whether the plaintiffs' general causation opinions were sufficiently supported at various dosages. 524 F. Supp. 2d

1166, 1174 (N.D. Cal. 2007). In *Celebrex*, the general causation issue was whether Celebrex was capable of causing heart attacks and strokes. Pfizer moved to exclude general causation opinions at 200 mg/d and 400 mg/d but not 800 md/d. *Id.* The court analyzed the "plaintiffs' experts' opinions as to causation at 200 md/d separate from their opinions as to 400 mg/d." *Id.* at 1175.

With regard to the 200 mg/d dosage, "there [were] no randomized controlled trials or meta-analyses of such trials or meta-analyses of observational studies that found an association between Celebrex 200 mg/d and a risk of heart attack or stroke." *Id.* The court excluded expert testimony on causation at this lower dosage because the experts who so opined "reache[d] his opinion first . . . and then cherry-pick[ed] observational studies that support his conclusion and rejecting or ignoring the great weight of the evidence that contradicts his conclusion." *Id.* at 1176. The court also rejected attempts by the experts to extrapolate causation at 200 mg/d from studies at 400 mg/d. *Id.* at 1180; *see also* Reference Manual on Scientific Evidence 613 n.196 (3d ed. 2011) ("[A] risk estimate from a study that involved a greater exposure is not applicable to an individual exposed to a lower dose.")

The court denied Pfizer's motion as to 400 mg/d because there was "a large, long-term, randomized placebo-controlled, double-blind, multi-center clinical trial [at this dosage] that was halted after 33 months because it demonstrated a statistically significant risk of heart attack, stroke, and heart failure." *Id.* at 1181.

In holding that "dose matters," the court noted that "[a]ll of plaintiffs' experts, with perhaps a single exception, agree that there is a dose effect with Celebrex; that is, that it is more toxic, and is therefore more likely to cause an adverse side effect, when taken at greater doses." *Id.* The same is true here. Plaintiffs argue emphatically that their "experts *did* find a dose-

response relationship." (Dkt. No. 1159 at 26 (emphasis in original); *see also* Dkt. No. 972-6 at 38-39). In other words, the greater a patient's dose of Lipitor, the greater the risk that they develop diabetes. *See* Reference Manual on Scientific Evidence 603 (3d ed. 2011) ("A dose-response relationship means that the greater the exposure, the greater the risk of disease.").

Also, as in *Celebrex*, multiple studies have found *no* statistically significant association between the lowest prescribed dose of Lipitor (10 mg) and diabetes, including the randomized controlled trial ASCOT (2003), the Naverese meta-analysis (2013), and Cederberg observational study (2015). These two factors—(1) that the experts agree that there is a dose-response relationship and (2) that studies have not found an association at lower dosages—suggest that Lipitor may not cause diabetes at lower dosages and warrant the question of whether Plaintiffs can demonstrate that Lipitor is capable of causing diabetes at lower dosages. *See, e.g., McClain v. Metabolife Int'l, Inc.*, 401 F.3d 1233, 1241 (11th Cir. 2005) (reversing District Court's allowance of testimony because, among other things, "[a]lthough he agreed that a drug's effect is dose-driven, [the expert] offered no testimony about the dose of Metabolife required to injure Plaintiffs or anyone else. He could not say how much is too much").

This "question of whether there is a no-effect threshold dose" is raised in a variety of toxic substance areas. Reference Manual on Scientific Evidence 603 n.160 (3d ed. 2011). Indeed, "[t]he idea that the 'dose makes the poison,'" in other words that "there is a safe dose below which an agent does not cause any toxic effect," is a "central tenet of toxicology." *Id.* "For agents that produce effects other than through [genetic] mutation, it is assumed that there is some level that is incapable of causing harm." *Id.* at 669. Even Plaintiffs admit that they do not claim Lipitor causes diabetes in very small doses but only at therapeutic doses. (Dkt. No. 1170 at 23). Thus, it is not surprising that the question of a threshold amount is also raised in the

context of pharmaceutical drugs, particularly where the experts agree there is a dose-response relationship and studies at low therapeutic doses of the drug do *not* show an association.

Plaintiffs rely heavily on *In re Seroquel Products Liab. Litig.*, No. 6:06-MD-1769-ORL-22D, 2009 WL 3806434, at *2 (M.D. Fla. June 18, 2009). However, the Court does not find this case as supportive of Plaintiffs' position as they suggest. In *Seroquel*, the defendant argued that the plaintiffs' expert had offered a "no threshold" opinion, and the court disagreed noting that the expert would not opine or "speculate" as to causation at lower dose levels. The *Seroquel* court refused to exclude the testimony "simply because it does not cover all possible dosing regimens in the thousands of cases in this MDL." *Id.* at * 18. This Court agrees with this holding in *Seroquel* and finds the situation markedly different from the one here, where plaintiffs' experts are apparently willing to speculate that studies at high doses apply to all doses or simply fail to consider dosage at all.

In *Seroquel*, plaintiffs alleged that Seroquel caused weight gain, diabetes and other related metabolic disorders. AstraZeneca attacked the expert's testimony on several grounds, one of which was that she "failed to come forward with reliable evidence of a dose-response relationship." *Id.* at *16. The court noted that "'[t]he expert who avoids or neglects the dose-response relationship] without justification casts suspicion on the reliability of his methodology,'" *id.* (quoting *McClain*, 401 F.3d at 1242), but held the expert "neither avoided nor neglected the dose-response relationship between Seroquel and weight gain and diabetes." *Id.* at 18. Among other things, data "showed a more than two-fold increased risk of weight gain across ***all five doses studied***" and "AstraZeneca itself concluded . . . that the percentage of Seroquel patients who experienced clinically significant weight gain increased with increasing Seroquel dose." *Id.* at 17 (emphasis added).

More to the point, AstraZeneca also argued that the expert's opinion was an impermissible "no-threshold" opinion. *Id.* at 18. In other words, the expert impermissibly opines that the drug can cause injury at any level. The court disagreed:

> She has not offered testimony that Seroquel is harmful in *any* amount. Indeed, when asked at her deposition whether Seroquel was harmful to patients at doses of 12.5 and 25 milligrams, ***Dr. Arnett declined even to speculate because she had not seen any studies evaluating doses that low***. . . Dr. Arnett's inability to reliably establish a dose-response curve for the metabolic effects of Seroquel does not render her methodology irreparably flawed, as AstraZeneca charges; it simply reflects the limitations of the existing data. Moreover, Dr. Arnett's testimony should not be excluded simply because it does not cover all possible dosing regimens in the thousands of cases in this MDL. Effective cross-examination is the more appropriate method to test the limitations of Dr. Arnett's opinions on dose.

Id. at *18 (emphasis added). The Court agrees with *Seroquel* in so far as it holds that Dr. Arnett's refusal to opine as to causation at low doses does not warrant excluding her opinions as to higher doses. Indeed, this fact indicates the reliability of Dr. Arnett's opinion. In accord with Rule 702, she would only opine as to causation when she had "sufficient facts or data" to support such an opinion.[1] Here, unlike in *Seroquel*, Plaintiffs experts did not consider whether there were sufficient facts or data to support a general causation opinion at various doses but "ascribe[d] the risk" found in studies at *any* dose "to all doses." (Dkt. No. 972 at 269).

Plaintiffs also rely on *In re: Zicam Cold Remedy Mktg., Sales Practices, & Products Liab. Litig.*, which allowed an expert to establish general causation without stating a minimum dosage that causes the adverse effect at issue.[2] 797 F. Supp. 2d 940, 946 (D. Ariz. 2011). In

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[1] Dr. Arnett's refusal to offer a general causation opinion at 12.5 and 25 milligram doses may indicate that summary judgment is warranted at these dosages but does not provide a reason for excluding her opinion under *Daubert*.

[2] One case cited but not discussed by Plaintiffs, *McClellan v. I-Flow Corp.*, 710 F. Supp. 2d 1092 (D. Or. 2010), is inapposite. *McClellan* was a medical device case, not a pharmaceutical case. At issue was whether the medical devices known as "pain pumps" that were used to continuously administer local anesthetics during arthroscopic surgery caused "the

Zicam, the issue was whether a nasal gel spray caused plaintiffs to lose their sense of smell. As an initial matter, *Zicam* is distinguishable because, in that case, "[t]he level of exposure will be mostly the same for all plaintiffs." 797 F. Supp. 2d at 946. The prescribed doses of Lipitor vary by a factor of 8. Also notably, unlike in *Celebrex* and the situation here, there were no studies showing the association with injury was *not* present in lower doses. However, apart from these factual distinctions, the Court disagrees with *Zicam*'s reasoning.

The *Zicam* court was concerned about the "challenge of determining a toxic dose" in pharmaceutical cases, noting that it would be unethical to run a study for the purpose of determining a toxic level. *Id.* at 943. However, it is also unethical to run studies to determine toxic levels of environmental agents. It is indeed *more* difficult to establish toxic levels of environmental agents because while researchers do not run randomized controlled trials exposing participants to potentially harmful environmental agents, such randomized controlled trials exposing patients to particular pharmaceutical drugs take place regularly. *See* Reference Manual on Scientific Evidence 658 (3d ed. 2011) ("Although [randomized controlled studies are] appropriate and very informative for the testing of pharmaceutical agents, it is generally unethical for chemicals used for other purposes.").

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rapid and permanent loss of cartilage in the shoulder joint." *McClellan*, 710 F. Supp. 2d 1092 at 1094-95. The expert's general causation opinion was based on a differential diagnosis and, while the court noted this would be inappropriate in some cases, the court found it acceptable under the unique circumstances there. *See id.* at 1103 ("Unlike the majority of cases in which differential diagnosis was held insufficient to rule in a potential causative factor, plaintiffs here do not allege toxic exposure through air, water, or groundwater contamination, ***or through the ingestion of a pharmaceutical drug***.") (emphasis added). The condition was a "very rare" one and "[v]ery few cases . . . were reported" until patients receiving very specific treatments were reported as having the condition. *Id.* at 1096. Physicians noted that healthy athletes were developing this "very rare" condition after arthroscopic surgery when pain pumps were used. In this context the court allowed the expert testimony even though "plaintiffs' experts cannot identify the precise threshold dose of bupivacaine or the length of exposure that triggers irreparable chondrocyte damage." *Id.* at 1111. This quote in the context of a rare disease with no other obvious explanation is not apposite here.

However, despite the challenge of determining a toxic dose in environmental exposure cases, it is undisputed that the law still generally requires establishing a minimum exposure in such cases. The Fourth Circuit's decision in *Westberry v. Gislaved Gummi AB*, 178 F.3d 257 (4th Cir. 1999), is instructive on this point.

In *Westberry,* while reiterating the well-established standard of having to show both a minimum level of exposure that is capable of causing injury and the plaintiff's level of exposure, the Fourth Circuit went on to recognize that it is often difficult to establish with quantitative precision the specific level of exposure (e.g., how many grams of asbestos did plaintiff inhale), and stated that "[c]onsequently, while precise information concerning the exposure necessary to cause specific harm to humans and exact details pertaining to the plaintiff's exposure are beneficial, such evidence is not ***always*** available, or necessary, to demonstrate that a substance is toxic to humans given substantial exposure and need not ***invariably*** provide the basis for an expert's opinion on causation." *Westberry*, 178 F.3d at 264 (emphasis added).

At issue in *Westberry* was a differential diagnosis opining that plaintiff's inhalation of talcum powder at his work caused his sinus condition. Upholding the District Court's allowance of the testimony, the Fourth Circuit held that "it was undisputed that inhalation of high levels of talc irritates mucous membranes," and that "there was evidence of substantial exposure," noting that the talc was "so thick that one could see footprints in it on the floor" and that "it covered him and his clothes." *Id.*

In *Zellers*, the plaintiff attempted to rely on *Westberry* when she could not show her level of exposure to a refrigerant gas at her place of employment. 533 F. App'x 192 (4th Cir. 2013). The Fourth Circuit, upholding the District Court's exclusion of expert testimony, stated, "[w]hile it is true, as Ms. Zellars argues, that precise information regarding a plaintiff's level of exposure

'is not always available, or necessary[,]' . . . it is also true that a 'plaintiff must demonstrate the levels of exposure that are hazardous to human beings generally as well as the plaintiff's actual level of exposure.'" *Id.* at 198 (quoting *Westberry*, 178 F.3d at 264, 263). The panel explained *Westberry* as follows:

> Ms. Zellars's reliance on *Westberry* on this point is inapposite. Specifically, in *Westberry*, we held that the plaintiff's expert did not need to cite specific quantitative evidence regarding the plaintiff's level of exposure because the record in that case clearly established that the plaintiff had been substantially exposed to the allegedly harmful substance in such a way that specific evidence was unnecessary. *Westberry*, 178 F.3d at 263. In particular, the allegedly harmful substance in that case was talc powder, and the record was replete with evidence of the plaintiff's substantial exposure to talc. . . . Here, there is no evidence of such substantial exposure. Thus, *Westberry* does not support Ms. Zellars's claim that she need not put forth specific evidence regarding her level of exposure.

Id. at 198 n.8.

In sum, *Westberry* stands for the proposition that generally, a plaintiff must show the minimum level of exposure that is capable of causing injury (general causation) and that any opinion on specific causation must state that plaintiff's level of exposure met this minimum. However, in obvious cases of substantial exposure, the expert need not state a particular quantitative amount for her causation testimony to be admissible; opining that a "substance is toxic to humans given substantial exposure" is sufficient. *Westberry*, 178 F.3d at 264.

Westberry's recognition that showing precise quantitative amounts is difficult in environmental cases suggests that pharmaceutical cases are ***more***, not less, amenable to the general standard announced in *Westberry*. Despite the difficulty in establishing precise minimum levels of exposure in environmental cases, *Westberry* held that it was still the general rule. This difficulty is not present in the same way in drug cases. In pharmaceutical cases, the parties know a plaintiff's dosage level and know the dosage levels at issue in particular studies.

The precision problem at play in *Westberry* is simply absent in a pharmaceutical case. Therefore, it makes more sense, not less, to apply the general standard stated in *Westberry*.[3]

The *Zicam* court also reasoned that the potential for *de minimis* exposure present in toxic tort cases is not present in pharmaceutical cases and that the standard in toxic tort cases exists to screen out "meritless claims based on generally harmless levels of exposure." 797 F. Supp. 2d at 945-46. However, especially in cases like this one where studies have found no association between low doses of a drug and a particular adverse effect, the requirement of stating whether the drug is capable of causing the adverse effect at particular dosages serves the same purpose of weeding out meritless claims.

Finally, most of the opinions cited by Plaintiffs simply do not address the issue. *See, e.g., Bartlett v. Mut. Pharm. Co., Inc.*, 760 F. Supp. 2d 220 (D.N.H. 2011), *aff'd* 678 F.3d 30 (1st Cir. 2012), *rev'd on other grounds*, 133 S. Ct. 2466 (2013); *In re Chantix (Varenicline) Products Liab. Litig.*, 889 F. Supp. 2d 1272, 1283 (N.D. Ala. 2012) *In re Avandia Mktg., Sales Practices & Products Liab. Litig.*, No. 2007-MD-1871, 2011 WL 13576 (E.D. Pa. Jan. 4, 2011); *In re Fosamax Products Liab. Litig.*, 645 F. Supp. 2d 164 (S.D.N.Y. 2009); *In re Neurontin Mktg., Sales Practices, & Products Liab. Litig.*, 612 F. Supp. 2d 116, 159 (D. Mass. 2009). These cases do not discuss whether dosage should be considered at the general causation stage because the argument was never raised. These cases consider issues such as whether an expert's causation opinion is admissible in the absence of evidence from controlled studies. *See, e.g., In re Fosamax*, 645 F. Supp. 2d at 176-77. However, they do not address the question currently before the Court.

[3] Because the prescribed dosages are known for a particular drug, the general causation question can be reframed from "what is the minimum level or threshold exposure that causes harm" to "has the specified dose been shown to cause harm."

In sum, at least where the experts agree that there is a dose-response relationship and where there is evidence that an association no longer holds at low doses, dose certainly matters, and Plaintiffs must have expert testimony that Lipitor causes, or is capable of causing, diabetes at particular dosages. The Court will allow Plaintiffs' expert(s) to submit supplemental reports addressing whether Lipitor causes diabetes at particular dosages but with specific parameters discussed below. The Court will then allow, after depositions, briefing on whether these opinions are reliable and based on sufficient facts or data as required by Rule 702.

THEREFORE, for the reasons stated above, the Court finds that Plaintiffs must demonstrate, with general causation testimony, that particular doses of Lipitor are capable of causing diabetes. Therefore, the Court will allow supplemental reports offering opinions as to whether Lipitor causes diabetes at dosages of 10 mg, 20 mg, 40 mg, and 80 mg. However, the Court imposes the following parameters on these supplemental reports:

(A) Plaintiffs may not retain new experts. Plaintiffs may seek supplemental reports from their current general causation experts Sonal Singh, Michael Quon, Barbara Roberts, and/or Edwin Gale.

(B) The purpose of these supplemental report(s) is not to amend or add justification for the experts' original report or opinions. These report(s) may only address the issue of whether Lipitor causes diabetes at dosages of 10 mg, 20 mg, 40 mg, and/or 80 mg. For each dosage level on which the expert opines, the report must set forth the facts and data that form the basis for the expert's opinion(s) that Lipitor causes diabetes at particular dosages and describe the methodology used to reach her opinion(s).

(C) No such supplemental report may rely on Dr. Jewell's "re-analysis" of the ASCOT data or analysis of the NDA data. The Court intends to exclude this testimony under Rule 702 by separate order.

(D) An expert may only consider and rely on studies or data submitted to the Court in response to its September 28, 2015 text order, (*see* Dkt. Nos. 1153, 1159), or specifically cited in an expert's prior report.

The Court enters the following amended scheduling order:

1. Plaintiffs' Supplemental General Causation Reports: Plaintiffs supplemental reports issued in accordance with the Court's above instructions must be served on or before **November 23, 2015**. On November 23, 2015, the PSC shall also provide two (2) deposition dates for each expert between **November 30, 2015 and December 18, 2015**.
2. Defendant's Supplemental Reports: If Pfizer wishes to serve supplemental report(s) in accordance with the Court's above instructions or in rebuttal to Plaintiffs' supplemental reports, these reports must be served on or before **December 18, 2015**. Pfizer shall also provide two (2) deposition dates for each expert between **January 4, 2016, and January 15, 2016**.
3. Briefing: Both parties shall file supplemental briefing on the motion to exclude Plaintiffs' general causation testimony by **January 29, 2016**. Any reply briefs must be filed by **February 5, 2016**.
4. In light of the Court's ruling, oral argument on Pfizer's Motion for Summary Judgment in *Daniels v. Pfizer*, Case No. 2:14-cv-1400 is cancelled and will be rescheduled for a later date.

5. The Court will hear oral argument on the motions to exclude case-specific expert testimony in *Hempstead v. Pfizer*, 2:14-cv-1879 (Dkt. Nos. 1004, 1006) on **December 3, 2015**, at 10 A.M.

6. In light of the Court's ruling, Jury Selection and trial in *Daniels v. Pfizer*, Case No. 2:14-cv-1400, is continued to the Court's March-April, 2016 trial term.

AND IT IS SO ORDERED.

Richard Mark Gergel
United States District Court Judge

October 22, 2015
Charleston, South Carolina