UNITED STATES DISTRICT COURT
WESTERN DISTRICT OF LOUISIANA
LAFAYETTE DIVISION

IN RE: ACTOS® (PIOGLITAZONE) PRODUCTS LIABILITY LITIGATION

MDL No. 6:11-md-2299

JUDGE DOHERTY

MAGISTRATE JUDGE HANNA

This Document Applies To:
Allen, et. al. v. Takeda Pharmaceuticals North America, Inc., et al.
(Case No. 12-cv-00064)

MEMORANDUM RULING: JENNIFER SOUTHGATE, PH.D.

This multidistrict litigation arises from product liability claims against the manufacturer and marketer of Actos® and other drugs containing pioglitazone. Pending before this Court is the Defendants' Motion to Exclude Testimony of Plaintiffs' Expert, Jennifer Southgate , Ph.D.[1] For the following reasons, the Defendants' Motion will be denied.

EVIDENCE AT ISSUE

Dr. Southgate is a molecular biologist whose specialty includes epithelial cancer cells, molecular carcinogenesis, bladder tissue (specifically including PPARs, or peroxisome proliferator-activated receptors). She is the Chair of Molecular Carcinogenesis at the University of York and the Director of the Jack Birch Unit of Molecular Carcinogenesis. She has been designated by the Plaintiffs as an expert with the following areas of expertise: molecular biology/biologic oncology, epithelial cell biology, bladder carcinogenesis and mechanisms of

[1] Rec. Doc. 3468. This motion has been urged on behalf of all named defendants in this matter. The Memorandum in Support of Defendants' Motion to Exclude Testimony of Plaintiffs' Expert Jennifer Southgate, Ph.D. is found at Rec. Doc. 3468-1 ["Memorandum"]; the Plaintiffs' Memorandum of Law in Opposition to Defendants' Motion to Exclude Testimony of Plaintiffs' Expert Jennifer Southgate, Ph.D. is found at Rec. Doc. 3611 ["Opposition"]; and the Defendants' Reply in Support of Defendants' Motion to Exclude Testimony of Plaintiffs' Expert Jennifer Southgate, Ph.D. is found at Rec. Doc. 3667 ["Reply"]. For these purposes only, the Court will make no distinction between and among defendants as, for these purposes, there is no legal distinction.

action with particular expertise in peroxisome proliferator-activated receptors (PPARs), experimental animal studies and human relevance.

Her Report[2] presents the following conclusions (which this Court interprets as her opinions):

> Pioglitazone is a dual agonist and functions to derail the normal homeostatic balance of proliferation and differentiation in urothelium by interfering with the PPAR-gamma regulated differentiation. Whereas PPAR-gamma activation can function to promote tumour development in genotoxic carcinogenesis, the cumulative evidence indicates that as a dual agonist pioglitazone has a far more sinister role as a non-genotoxic or epigenetic modifier. Thus, by activating PPAR-alpha+gamma simultaneously, it rebalances the tumour suppressive differentiated environment of the urothelium towards a tumour-conducive regenerative environment.
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> This leaves important implications for the interpretation of the clinical trials. In particular, given that patients were randomised into the different treatment arms of Takeda's clinical trials, there is no justification in excluding less than one-year exposure urothelial cancer cases on the basis of biological implausibility. This is not a classic genotoxic agent and its receptor-mediated effects mean that the classical dormancy period associated with other cancers (*e.g.*, smoking related cancers), is not relevant here.
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> Because the nature of the epigenetic changes associated with non-genotoxic carcinogenesis is that it involves reprogramming of gene expression, it is possible that any changes to the urothelium are not simply reversed upon withdrawal of the drug. The implications that this carries for the future risk of developing urothelial cancer remain to be determined.
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> In sum, and on the basis of the evidence discussed above, it is my opinion with a reasonable degree of scientific certainty that pioglitazone causes bladder cancer in rats and humans. It is also my opinion that there are biologically plausible mechanisms by which pioglitazone exerts carcinogenic effects on the urothelium chiefly through receptor-mediated effects that are relevant in humans. None of the mechanisms discussed has anything to do

[2] "The Southgate Report" was submitted by the Plaintiffs as Exhibit 1 to the Opposition, and was submitted by the Defendants as Omnibus Exhibit C13.

> with the rat phenomenon known as the "crystal hypothesis." The lack of scientific rigor and diligence with which Takeda addressed the issue when brought to their attention by regulators on both sides of the Atlantic is apparent. The ready acceptance of the crystal hypothesis and the claim of selective PPAR gamma activity (as opposed to dual agonism) have in fact blinded investigation from other, scientifically valid pathways to bladder cancer in rats and in humans.[3]

The Defendants do not challenge, in any way, Dr. Southgate's expertise in the areas for which she has been tendered as an expert. Furthermore, they do not challenge her qualifications to opine within the scope of her proffered expertise. Finally, they do not challenge the relevance of her opinions. Rather the Defendants have challenged Dr. Southgate's qualifications and expertise to proffer only one, specific opinion: that "epidemiologic and randomized clinical data demonstrate that Actos causes bladder cancer in humans."[4]

LAW AND ANALYSIS

I. APPLICABLE LAW

While state law governs the Plaintiffs' claims in this matter, the Federal Rules of Evidence control the admission of expert testimony.[5] Under the Federal Rules of Evidence, "relevant" evidence is admissible, while irrelevant evidence not admissible.[6] Evidence is "relevant" if it has any tendency to make a fact more or less probable than it would be without the evidence, and the fact being proven or disproven is of consequence in determining the action.[7] The party seeking to have expert opinion testimony admitted into evidence bears the

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[3] Southgate Report, at 23.

[4] Memorandum, at 1.

[5] Huss v. Gayden, 571 F.3d 442, 452 (5th Cir. 2009), *citing* Mathis v. Exxon Corp., 302 F.3d 448, 459 (5th Cir. 2002).

[6] F.R.E. 402.

[7] F.R.E. 401.

burden of demonstrating, by a preponderance of the evidence, that the expert's findings and conclusions are based on the scientific method and, therefore, are reliable.[8]

The Federal Rules of Evidence require that a judge, faced with a proffer of expert scientific testimony, must begin by determining, pursuant to Rule 104(a), whether the expert is proposing to (i) testify to scientific knowledge (ii) that will assist the trier of fact to understand or determine fact in issue.[9] This will require a preliminary assessment of whether the reasoning or methodology underlying the testimony is scientifically valid and of whether that reasoning or methodology properly can be applied to the facts in issue.[10] This requirement is found in Rule 702 of the Federal Rules of Evidence, which reads as follows in its entirety:

> A witness who is qualified as an expert by knowledge, skill, experience, training, or education may testify in the form of an opinion or otherwise if:
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> (a) the expert's scientific, technical, or other specialized knowledge will help the trier of fact to understand the evidence or to determine a fact in issue;
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> (b) the testimony is based on sufficient facts or data;
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> (c) the testimony is the product of reliable principles and methods; and
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> (d) the expert has reliably applied the principles and methods to the facts of the case.

In the United States Supreme Court's landmark decision in Daubert v. Merrell Dow Pharmaceuticals, Inc., the Court acknowledged the existence of a federal court's gatekeeping role with regard to expert scientific opinion testimony, characterizing that role as one ensuring

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[8] Moore v. Ashland Chemical, Inc., 151 F.3d 269, 276 (5th Cir. 1998) (*en banc*).

[9] Daubert v. Merrell Dow Pharmaceuticals, Inc., 509 U.S. 579, 592, 113 S.Ct. 2786, 2796, 125 L.Ed.2d 469 (1993).

[10] Id., 509 U.S. at 592-93; Moore, 151 F.3d at 276.

that such evidence meet the requirements of both reliability and relevance.[11] "Reliability" as discussed in Daubert refers to *evidentiary* reliability, *i.e.*, trustworthiness, rather than *scientific* reliability, which asks whether application of the principle produces consistent results, a distinction often blurred by Defendants' arguments. In a case involving scientific evidence, evidentiary reliability is based upon scientific validity, which asks whether the principle supports what it purports to show.[12]

The objective of this requirement is to make sure that an expert, whether basing testimony upon professional studies or personal experience, employs in the courtroom the same level of intellectual rigor that characterizes the practice of an expert in the relevant field.[13] The Supreme Court identified several non-exclusive factors a court should consider in determining whether proffered scientific opinion testimony is sufficiently reliable to permit admission into the record.[14] Those factors are:

- whether the expert's theory can be or has been tested;
- whether the theory has been subject to peer review and publication;
- the known or potential rate of error of a technique or theory when applied;
- the existence and maintenance of standards and controls; and
- the degree to which the technique or theory has been generally accepted in the scientific community.[15]

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[11] Moore, 151 F.3d at 275.

[12] Daubert, 509 U.S. at 590 n.9.

[13] Kumho Tire Company, Ltd. v. Carmichael, 526 U.S. 137, 152, 199 S.Ct. 1176, 143 L.Ed.2d 238 (1999). *See also* Brown v. Illinois Central Railroad Co., 705 F.3d 531, 535 (5th Cir. 2013).

[14] *See* discussion, 509 U.S. at 594-595.

[15] Moore, 151 F.3d at 275.

Several years later, the Supreme Court clarified when it held the gatekeeping role applied to all types of expert opinion testimony, not just scientific evidence, and revisited the reliability analysis.[16] Moreover, the Supreme Court reiterated that a court must have considerable leeway in deciding, in a particular case, how to go about determining whether particular expert testimony is reliable.[17] Therefore, the test of reliability is flexible and there is no necessary or exclusive list of factors that must exist in order for a particular opinion to be admissible.[18]

> Daubert makes clear that the factors it mentions do not constitute a definitive checklist or test. Daubert adds that the gatekeeping inquiry must be tied to the facts of a particular case. We agree with the Solicitor General that the facts identified in Daubert may or may not be pertinent in assessing reliability, depending on the nature of the issue, the expert's particular expertise, and the subject of his testimony. The conclusion, in our view, is that we can neither rule out, nor rule in, for all cases and for all time the applicability of the factors mentioned in Daubert, nor can we now do so for subsets of cases categorized by category of expert or by kind of evidence. Too much depends upon the particular circumstances of the particular case at issue.[19]

In the Fifth Circuit, "[t]o determine whether proffered testimony is reliable, the trial court must make 'a preliminary assessment of whether the reasoning or methodology underlying the testimony is . . . valid and of whether that reasoning or methodology properly can be applied to the facts in issue.'"[20] Further, "[t]o establish reliability under Daubert, an expert bears the burden of furnishing 'some objective, independent validation of [his] methodology.'"[21] In doing

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[16] Kumho Tire, 526 U.S. at 141-142.

[17] Id. at 152.

[18] Id., at 141-142, 149.

[19] Id., at 150 (citations and quotation marks omitted).

[20] Brown v. Illinois Central Railroad Co., 705 F.3d 531, 535 (5th Cir. 2013) (*quoting* Daubert, 509 U.S. at 592–93).

[21] Brown, 705 F.3d at 536 (*quoting* Moore, 151 F.3d at 276).

so, "[t]he expert's assurances that he has utilized generally accepted [principles] is insufficient."[22]

In Brown the Fifth Circuit held that the trial court did not abuse its discretion where an expert testified that offered opinions were reliable merely upon and because of "education and experience" and did not engage in or rely upon a credible methodology, particularly in the face of evidence in opposition to those opinions. Standing alone then, it is insufficient for an expert to base his or her opinion on education and experience alone, especially in the face of evidence to the contrary.

II. ANALYSIS

Plaintiffs bear the ultimate burden on this issue, thus, this Court will first look to Plaintiffs' *prima facie* showing. The task for this Court within this Motion, as the gatekeeper, is to determine whether the Plaintiffs' experts will have the necessary qualifications, employed a required process, methodology, rely upon sufficiently sound scientific evidence and comport with the inquiry and factors identified in Daubert, within their respective areas of expertise so as to be allowed to pass the gatekeeper inquiry. The specific analysis of this issue will begin with consideration of the Plaintiffs' evidence in support of their *prima facie* case, and then proceed to consideration of the Defendants' specific challenges.

A. Dr. Southgate's Report, Opinions, and Supporting Evidence

The body of the Southgate Report is 23 pages in length, with an attached list of the 57 references to published studies and reports upon which she relied in developing her opinions. She also submitted a separate list of the case materials she reviewed in developing her opinions and producing her report. The Southgate Report contains:

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[22] Id. (*quoting* Moore, 151 F.3d at 276).

- a description of her qualifications;[23]
- a brief introduction to the basic facts of the urothelium;[24]
- a description of the methodology she used in developing her opinions;[25]
- her consideration of the published evidence;[26]
- a discussion of other relevant issues, including the route of exposure, receptor-mediated effects of pioglitazone, dual agonism of pioglitazone, how the body uses pioglitazone, gender-related differences, and mutagenicity studies;[27]
- a description of the biologically-plausible mechanisms that pioglitazone might use to promote tumor growth; and[28]
- her conclusions.[29]

This Court has conducted an exhaustive review of the briefs, the exhibits submitted in support of both parties' arguments, and all studies and reports, including those of Dr. Southgate that are under challenge through the current motion. This Court finds, as a threshold matter, that Dr. Southgate is qualified to develop the opinions she has reached in this case, that as a threshold matter, she relied on standards and accepted scientific methods in formulating those opinions and again, as a threshold matter, the studies, publications and data which she relied upon were sufficiently reliable as to overcome the Defendant's threshold challenge. In making this determination, this Court has considered the five illustrative factors noted below and identified in

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[23] Southgate Report at 1-4.

[24] Id. at 2.

[25] Id. at 5.

[26] Id. at 6-14.

[27] Id. at 14-18.

[28] Id. at 18-22.

[29] Id. at 23.

Daubert and concluded that they either weigh in favor of the admissibility of Dr. Southgate's opinions and foundational underpinnings, or, alternatively, do not weigh in favor of the exclusion of the challenged opinions and foundational underpinnings.

B. Rule 702/Daubert Factors

After full review of all argument, evidence and supporting documentation, this Court finds the five factors identified in Daubert, either weigh in favor of admissibility of Dr. Southgate's causation opinions or do not weigh in favor of exclusion of the challenged evidence.

- ***Testability***. Dr. Southgate relies heavily on studies that have been published in peer-reviewed literature. As a threshold matter, the testability of the foundational underpinnings of her theory supports a finding of admissibility. The fact that Dr. Southgate has not engaged in independent testing of pioglitazone in humans, but relies on published studies, is not fatal under the circumstances of this case because she has used an acceptable methodology of review of otherwise tested and testable studies, and the underlying foundational underpinnings have been tested.

- ***Peer Review***. Dr. Southgate has cited a great many peer-reviewed publications that provide scientific support for her opinions. While it does not appear that Dr. Southgate's specific opinions in this case have been subjected to peer review, this Court finds the *underlying studies* relied upon, incorporated, and used as foundational support for her conclusions, are and have been sufficiently subject to peer review and are accepted within the relevant scientific community. The absence of peer review for Dr. Southgate's opinions, in and of itself, does not invalidate those opinions when otherwise accepted methodology has been employed to extrapolate information and analysis from peer-review publications. Dr. Southgate's heavy reliance on identified *peer-reviewed publications*, studies, and information lend strong support for the argument in favor of admissibility of her opinion and foundational support for her conclusions, as a threshold matter.

- ***Rate of Error***. The published studies relied upon by Dr. Southgate have error rates attached to them and are readily available for review and cross examination. The absence of a rate of error as to her specific opinions should not be fatal in light of the availability of such error rates for the underlying studies on which she relies.

- ***Standards and Controls***. Dr. Southgate is a highly-qualified molecular biologist who has conducted her investigation and developed her opinions, in this matter, in compliance with the standards and controls under which she normally operates in her professional life. This Court finds that those standards and controls lend strong support for the argument of/for reliability of Dr. Southgate's opinions, as a threshold matter.

- ***General Acceptance.*** The Southgate Report provides ample evidence that her methodology is generally-accepted in the scientific community and that her investigation (while it hasn't been conducted or replicated by any third party) is consistent with those generally-accepted principles. Dr. Southgate's process employed, conclusions reached, and opinions posited have been guided by scientifically-accepted processes found within the accepted scientific method, and stand upon a foundation of independent peer-reviewed studies and articles. Consequently, this factor argues for allowing presentation of Dr. Southgate's opinions to the trier of fact.

This Court notes, that the Defendants have raised an *ipse dixit* challenge similar to the one discussed in Brown. This challenge will be discussed *supra*. For present purposes, this Court would simply note that the Southgate Report reveals that Dr. Southgate relies on many studies and publications, as well as extensive data, in reaching each of opinions. This Court finds that the Plaintiffs have met their *prima facie* burden of demonstrating, as a threshold matter, that Dr. Southgate's opinions are admissible.

C. The Defendants' Challenges

As noted above, the Defendants argument is clear that they do not intend to challenge Dr. Southgate, her *qualifications*, or her *methodology* with regard to any opinion that falls *within the scope of her expertise for which the Plaintiffs have proffered her*. Rather, they seek to preclude her from testifying *that epidemiological data demonstrate Actos causes bladder cancer in humans*. This Court has very carefully reviewed both the Southgate Report and the Southgate Deposition[30] and has concluded that neither the report nor the deposition establish reason to believe that either Dr. Southgate or the Plaintiffs have intention of eliciting testimony from Dr. Southgate about *epidemiological data* and what it does or doesn't show *as her opinion*. While this conclusion raises a distinction which might not be an obvious one, this Court directs the parties' attention to the fact that all of Dr. Southgate's discussions are of epidemiological *studies*

[30] Submitted by the Defendants as Omnibus Exhibit B11.

not created by her and their findings, while the Defendants' motion discusses epidemiological *data* and what it does or doesn't prove within those studies. A close reading of the briefing on the current motion makes it rather clear the Defendants want to preclude Dr. Southgate from serving as, in effect, a surrogate expert epidemiologist, and equally clear that the Plaintiffs do not intend to use Dr. Southgate as a surrogate epidemiologist, having epidemiologist for that purpose. Plaintiffs do not, from their briefing, in any way, indicate Plaintiffs will elicit testimony from Dr. Southgate *as to epidemiological data and its meaning*. Rather, Dr. Southgate might refer to and *incorporate* epidemiological studies and publications within her overall opinion – an accepted practice by experts.

Both Dr. Southgate and the Plaintiffs' counsel have been clear Dr. Southgate is not an epidemiologist and neither intends to have her testify as though she had such expertise.[31] This Court agrees that, were any effort made to proffer Dr. Southgate as an epidemiologist, or have her testify as to the underlying epidemiological validity or lack thereof, of the epidemiological studies she might reference, this Court likely would sustain an objection and preclude Dr. Southgate from presenting such testimony. The Southgate Report and the Southgate Deposition, however, demonstrate that epidemiological studies play only two, limited roles in Dr. Southgate's opinions:

- First, Dr. Southgate includes, in the section of her Report where she provides the Court with a general introduction to PPARs, a description of the findings from four epidemiological studies/clinical trials not conducted by her. The discussion of these studies seems to illustrate, in part, the role that PPARs play in bladder cancer in animals and in humans. In this discussion, Dr. Southgate *does not discuss the underlying epidemiological data produced by the authors of the cited studies*; *she does not conduct an independent evaluation of the data*; and *she does not offer an opinion as to the quality of those studies*. Rather, she reports that she conducted some research *in the literature*, *reports on the existence of the studies*

[31] *See* Southgate Deposition, at 23, 215.

that she located, and *reports the findings in those studies*. The Defendants have not sought to exclude such evidence or testimony by Dr. Southgate.

- Second, Dr. Southgate's conclusions contain a brief discussion of the impact that her findings could be expected to have on clinical studies of pioglitazone. Dr. Southgate opined that, as a result of her demonstration of a different mechanism by which tumor development could occur – suggesting that the classical assumptions about bladder cancer no longer necessarily hold true – the interpretation of clinical trials would, necessarily, be impacted. Again, the discussion does not suggest Dr. Southgate intends to opine *as to the proper interpretation or creation of epidemiological data*. Her opinion is, rather, that such interpretations would, in future, necessarily be impacted by her recent discovery of this alternative mechanism by which bladder tumors can develop. Again, the Defendants have not sought to exclude this evidence and testimony.

Thus, neither of the discussions of epidemiological studies found in the Southgate Report fall within the scope of the Defendants' motion, nor do they suggest that the Plaintiffs intend to present the testimony that the Defendants have challenged. Consequently, the Court is once again perplexed as to the purpose and argument of Defendants' motion.

Additionally, Dr. Southgate's deposition testimony demonstrates:

- she isn't an epidemiologist and can't perform like one;[32]
- she is "fairly certain" that the authors of epidemiological studies don't declare causation on the basis of one study, no matter how strong the evidence;[33]
- she has been reviewing epidemiological studies for over 30 years as part of her normal research process, and so is well-trained by long experience to read, understand, and interpret study findings such as the ones at issue in this case;[34] and
- she read studies and took information from them in the form of their findings and results, but did not conduct any analysis of the underlying data to reach any independent conclusions about what those data prove or do not prove.[35]

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[32] Southgate Deposition, at 23-24, 147-49, 215.

[33] Id. at 216-17.

[34] Id. at 23-24.

[35] *See, e.g.*, id. at 148-49, 215.

The record establishes that Dr. Southgate has reviewed published reports of several epidemiological studies and that she considered those findings as an important part of the total package of evidence upon which her opinions are based. It is without dispute experts have the right to consider all different types of facts or data that might impact their opinions, and Dr. Southgate, in particular as a molecular biologists when exploring causation, certainly may and likely should rely on or consider all such data other molecular biologists reasonably would rely upon in these circumstances.[36] Her descriptions of the role that the epidemiological data played, on their face, demonstrate that her consideration of that data falls soundly into the accepted role of consideration of data reasonably relied upon pursuant to F.R.E. 703. The Defendants' arguments have not suggested otherwise, and the Court is perplexed as to the true challenge and nature of Defendants' objection to Dr. Southgate's *actual opinions rendered.*

Dr. Southgate will, therefore, be free to testify as to her research, the findings that she considered, the impact of those findings on her analysis and her conclusions, and similar explanations of the role of the epidemiological studies in assisting her to reach her conclusions. However, Plaintiffs' counsel are cautioned that they are to limit their questioning *to the role that the studies and the study findings played in her analysis and conclusions and not a discussion of the proper interpretation of the epidemiological data upon which those findings are based.* The *Defendants are similarly counseled that, if they attempt to use the questioning of Dr. Southgate as an method of attack on the Plaintiffs' epidemiological evidence generally, they likely will have opened the door to precisely the type of questioning that they seek to exclude in the current motion.*

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[36] F.R.E. 703.

III. EVIDENTIARY HEARING

The Defendants requested this Court agree to hear live testimony from the experts prior to ruling on the instant motion; this Court carefully considered the Defendants' request. The decision of how to go about ruling on the instant motion is squarely within this Court's discretion.

> The trial court must have the same kind of latitude in deciding *how* to test an expert's reliability, and to decide whether and when special briefing or other proceedings are needed to investigate reliability, as it enjoys when it decides whether or not that expert's relevant testimony is reliable. Our opinion in Joiner makes clear that a court of appeals is to apply an abuse-of-discretion standard when it reviews a trial court's decision to admit or exclude expert testimony. That standard applies as much to the trial court's decisions about how to determine reliability as to its ultimate conclusion. Otherwise, the trial judge would lack the discretionary authority needed both to avoid unnecessary "reliability" proceedings in ordinary cases where the liability of an expert's methods is properly taken for granted, and to require appropriate proceedings in the less usual or more complex cases where cause for questioning the expert's reliability arises. Indeed, the Rules seek to avoid unjustifiable expense and delay as part of their search for truth and the just determination of proceedings.[37]

This Court reviewed the extensive briefing provided by both parties, as well as the large number of exhibits, including expert reports, depositions, and other documents, and concluded the nature of the challenges presented and the arguments made did not illustrate a need for live testimony. Live testimony would not be likely to contribute to any greater understanding of the nature of the dispute than can be and has been found in a careful reading and analysis of the briefs and accompanying evidence and documentation. The request for an opportunity to present live testimony in an evidentiary hearing is DENIED.

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[37] Kumho Tire, 526 U.S. at 152-53 (emphasis in original) (citations and quotations omitted).

CONCLUSION

For the foregoing reasons, the Defendants' Motion to Exclude Testimony of Plaintiffs' Expert, Jennifer Southgate , Ph.D., shall be DENIED.

THUS DONE AND SIGNED this 6 day of January, 2014.

REBECCA F. DOHERTY
UNITED STATES DISTRICT JUDGE