UNITED STATES DISTRICT COURT

EASTERN DISTRICT OF LOUISIANA

	:	**MDL NO. 1355**
IN RE: PROPULSID	:	
PRODUCTS LIABILITY LITIGATION	:	**SECTION "L"**
	:	
	:	**JUDGE FALLON**
.. .. ..	:	

THIS DOCUMENT RELATES TO THE FOLLOWING CASES:
***Dorita Black, et al. v. Johnson & Johnson, et al., and only regarding Plaintiff, Ernestine Brock,* Civil Action No. 00-2497**

ORDER & REASONS

Before the Court is the Defendants' Motion to Exclude Opinions of Dwain L. Eckberg, M.D. and William E. Shell, M.D. in the case of Ernestine Brock ("Brock"), a plaintiff in Civil Action No. 00-2497. The defendants challenge these experts' opinions as unreliable under the standards set forth in Federal Rule of Evidence 702, which in essence codified the Supreme Court's opinion in *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 509 U.S. 579 (1995). For the following reasons, the motion is GRANTED.

The defendants have also moved for summary judgment in Brock's case, arguing that if the only evidence relating to the causation of her injuries fails, then the plaintiff cannot carry her burden of proof as a matter of law. Since the Court grants the defendants' motion to exclude evidence, the motion for summary judgment will also be GRANTED. Defendants further move for partial summary judgment on

the plaintiff's composition, express warranty, and design claims. Since the Court finds that the plaintiffs case fails because she cannot prove causation, it will DISMISS AS MOOT the defendants' motion for partial summary judgmnent.

I. Procedural History

Plaintiff Brock used Propulsid from January, 1996 to May, 1997 pursuant to the instructions of her treating physician, Dr. George Howard. Dr. Howard prescribed Propulsid to treat Brock's severe esophagitis.[1] During the course of her treatment with Propulsid, Brock suffered no apparent cardiac incidents. In August, 2000, Brock was one of several plaintiffs who filed suit in the Eastern District of Louisiana alleging causes of action against Johnson & Johnson and Janssen Pharmaceutica for damages under the Louisiana Products Liability Act ("LPLA"), LA. REV. STAT. ann. § 9:2800.51-2800.60. The main basis of her complaint is that Propulsid was defective because it caused her to have a sustained prolonged QT interval,[2] which places her at risk for sudden death. Her case was consolidated with MDL-1355 for which this Court was designated the transferee court.[3] After several years of discovery, the Court exercised its role as the original trial court in the Brock case, and, after consulting with all parties, set the matter for trial. Defendants now move to exclude the opinions of Dr. Dwain Eckberg and Dr. William Shell, Brock's two expert physicians on the issue of Propulsid's sustained effects on Brock's QT interval.

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[1]Inflamation of the esophagus.

[2]The unit of measurement for a specific heart beat as reflected on an EKG reading. *See infra* Part III-E for a more detailed explanation.

[3]Pursuant to 28 U.S.C. § 1407, civil actions filed in federal district courts with common issues of fact may be assigned to a designated transferee court for "coordinated or consolidated pretrial proceedings." 28 U.S.C. § 1407(a). The designations are made by the Judicial Panel on Multidistrict Litigation, and the case is assigned an MDL number, such as 1355 in the case of Propulsid.

II. Legal Standards

As noted above, the defendants challenge the experts' opinion as unreliable under Rule 702 of the Federal Rules of Evidence; the rule provides:

> If scientific, technical, or other specialized knowledge will assist the trier of fact to understand the evidence or to determine a fact in issue, a witness qualified as an expert by knowledge, skill, experience, training or education, may testify thereto in the form of an opinion or otherwise, if (1) the testimony is based upon sufficient facts or data, (2) the testimony is the product of reliable principles and methods, and (3) the witness has applied the principles and methods reliably to the facts of the case.

FED. R. EVID. 702.

The current version of Rule 702 was enacted in response to the Supreme Court's opinion in *Daubert v. Merrell Dow Pharmaceuticals*, 509 U.S. 579 (1993), which held that before an expert is allowed to testify the trial court must assess the reliability of the methodology used by the proposed expert and the relevance of the testimony to the facts at issue. According to the Advisory Committee Notes accompanying the rule, the amendment "affirms the trial court's role as gatekeeper and provides some general standards that the trial court must use to assess the reliability and helpfulness of proffered expert testimony." Advisory Committee Notes, FED. R. EVID. 702.

In *Daubert*, the Supreme Court identified a non-exclusive list of factors for a district court to consider in determining reliability: (1) whether the theory has been tested; (2) whether the theory has been subject to peer review and publication; (3) the known or potential rate of error; and (4) the general acceptance of the methodology in the scientific community. *Daubert*, 509 U.S. at 593-95. A district court

must focus on methodology, not conclusions. In *Kumho Tire v. Carmichael*, 526 U.S. 137 (1999), the Court cautioned that the district court must ensure "that an expert, whether basing testimony upon professional studies or personal experiences, employs in the courtroom the same level of intellectual rigor that characterizes the practice of an expert in the relevant field." *Id.* at 152. The person seeking to admit the expert testimony bears the burden of proving reliability by a preponderance of the evidence. *Moore v. Ashland Chemical, Inc.*, 151 F.3d 269, 276 (5th Cir. 1998) (en banc). After the proponent of the expert testimony has carried the burden of showing reliability, the party must also prove the expert opinions' relevance. That is, that the experts' opinions have "a valid ... connection to the pertinent inquiry." *Daubert*, 509 U.S. at 592. This Court heard the testimony of the experts and the arguments of the parties at a hearing set in advance of the trial date. After considering the testimony, the briefs of the parties, and the applicable law, the Court now rules on the motion.

III. Medical Background

Before analyzing the specific evidence presented in connection with the *Daubert* hearing, it is helpful to review the medical background surrounding cisapride (the generic name for Propulsid). This Court has had previous occasion to discuss this issue. *See In re Propulsid Products Liability Litigation*, 208 F.R.D. 133 (E.D. La. 2002). However, the Court finds it helpful to summarize its previous statements on the issue and update these statements to reflect new information presented in the context of these motions.

A. Pharmacology of Propulsid

Propulsid was developed to treat gastroesophageal reflux disease (GERD). GERD is the abnormal backflow (reflux) of stomach acids into the esophagus, the tube that leads from the throat to the stomach.

This backflow occurs because the valve between the lower end of the esophagus and the stomach (the lower esophageal sphincter) does not close tightly enough. The main symptom of GERD is frequent heartburn, a term used to describe gastrointestinal pain. If untreated, this condition can cause permanent damage to the esophagus, extreme pain, and even death. Some drugs treat this condition by neutralizing acid in the digestive tract or by decreasing the amount of acid produced by the stomach.

Propulsid is unique in that it is a prokinetic or motility agent. It treats GERD by increasing the rate at which the esophagus, stomach, and intestines move food during digestion. It also increases the rate at which the stomach empties into the intestines and strengthens the lower esophageal sphincter. Propulsid achieves this prokinetic effect by increasing the release of acetylcholine[4] in the body's enteric nervous system, specifically at the myenteric plexus.[5]

B. The Autonomic Nervous System

The enteric nervous system is a subset of the human nervous system, which is divided into the central nervous system and the peripheral nervous system. The peripheral nervous system breaks down into the somatic and the autonomic nervous systems. The autonomic nervous system is described as a "hard wire" system connecting the head with the heart and other organs and blood vessels in the body. The system has three major divisions: sympathetic, parasympathetic, and enteric. The sympathetic and parasympathetic divisions control cardiac muscle, and gladular tissues. The enteric division is a "self-contained system" that controls sensory and motor neurons in the gastrointestinal tract or gut and mediates

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[4]A biochemical substance that transmits nerve impulses from one nerve cell to another.

[5]A network of nerves and blood vessels around the esophagus, stomach, and intestines.

digestive reflexes.

The autonomic system includes checks and balances and involves two nerves affecting cardiac function: sympathetic nerves and vagal nerves. Vagal nerves are "inhibitory" in that they slow heart rate and slow conduction through the atrioventricular node and prolong ventricular refractoriness and the QT interval. Sympathetic nerve stimulation, on the other hand, speeds the heart rate, improves AV conduction, increases cardiac contraction, and increases blood pressure. The two nerves reciprocate each other.

The vagus nerves regulate the pacemaker by releasing and taking back acetylcholine. Sympathetic nerves do the same thing, but using the chemical norepinephrine, which is also a chemical produced by the cells. The release of the norepinephrine stimulates the heart rate and forces contraction of the heart. Acetylcholine, in contrast, slows the heart and decreases the heart rate.

Heart rate variability ("HRV") is the measurement of the variability of cardiac cycles (or "RR intervals"). HRV is important because the pacemaker of the heart is sensitive to vagal stimulation, and large standard deviations of heart rate are taken to indicate increased vagal effects on the sinus node. One of the effects of prolonged QT intervals is tachycardia, or an abnormally fast heart rate. When this occurs, blood pressure falls. Normally, sympathetic and vagal reflexes work to raise the pressure. However, when the autonomic nervous system fails, the pressure continues to fall. If it is not corrected, the heart ceases to adequately function, and death may occur. At this point, it is necessary to focus on the anatomy of the heart and the method of measuring the heart beat and any effect that Propulsid may have.

C. The Anatomy of the Heart

The human heart is a pear-shaped structure about the size of the possessor's fist. It lies obliquely within the chest cavity just left of center, with the apex pointing downward. The heart is constructed of a

special kind of muscle called myocardium and is enclosed in a double-layered, membranous sac known as the pericardium. A wall of muscle divides the heart into two cavities. The left cavity pumps blood throughout the body, while the right cavity pumps blood only through the lungs. Each cavity is in turn divided into two chambers, the upper ones are called atria, the lower ones, ventricles. Venous blood from the body, containing large amounts of carbon dioxide, returns to the right atrium. From there it enters the right ventricle, which contracts, pumping blood through the pulmonary artery to the lungs. Oxygenated blood returns from the lungs to the left atrium and enters the left ventricle, which contracts, forcing the blood into the aorta, from which it is distributed throughout the body.

D. The Electrical System of the Heart

In the normal heart, the heart beat (or heart contraction) originates in the natural pacemaker of the heart, the sinoatrial node (S.A. node) located high in the right atrium. The heart beat is caused by a special group of cells located in the S.A. node that have the ability to generate electrical activity by separating charged particles and leaking them into the extra-cellular space. The electrical impulses in the heart are created when the charged ions of sodium, potassium and other ions such as calcium pass via minute channels through the walls of the cardiac cells. This charge travels across the atria to another specialized group of cells called the atrioventricular node ("AVN"). Once there, the signal encounters a "delay" that allows both atria to contract which results in the filling of the larger ventricular cavities with blood. Under normal circumstances the signal then travels through the pathway in the septum (the wall between each ventricle) and then along each ventricles's bundle branches to the ventricles themselves which respond by contracting and pumping the blood out to the lungs and the rest of the body.

Although the pacemaker cells create the electrical impulse that causes the heart to beat, as

mentioned above, numerous nerves including the vagus nerve regulate the rate at which the pacemaker cells fire and control how strongly the heart contracts.

E. The Electrocardiogram

When the normal beating of the heart is disturbed, the heart can beat irregularly or erratically. This irregularity is known as an arrhythmia. Arrhythmias may be trivial and asymptomatic or severe and potentially life threatening.

The electrocardiogram (ECG or EKG) is a recording of the electrical waves produced by the above described electrical activity of the heart. The orderly progression of the electric impulses or waves associated with the heart beat are plotted on graph paper which allows for visualization of the heart's electrical activity along with a measurement of the heart rate. Each wave on the EKG is designated by a letter: P, Q, R, S, and T. The Q-wave is the beginning of the electrical discharge of the ventricles. The T-wave represents repolarization of the heart. The time lapse between the Q-wave and the T-wave is the QT interval. This interval represents the time it takes for the ventricles to discharge (or contract) and recharge (or recover).

Because the QT interval varies with the individual's heart rate, it must be corrected using one of several formulas available before a meaningful analysis may be made. The formula corrected measurement is referred to as QTc.

In perfectly healthy people, their QTc intervals vary throughout the day by as much as 50 to 75 milliseconds. Individuals with a prolonged QTc interval are at risk for developing a condition known as "torsade de pointes" (twisting of the points) which is a form of ventricular tachycardia (abnormally fast heart rate) and is characterized by a long QTc interval and a short-long-short sequence in the beat preceding its

outset.[6]

F. Propulsid's Effect on the QT Interval

It is generally agreed that Propulsid can temporarily induce a prolongation of the QT interval under certain circumstances. The post marketing reports from pharmacokinetic studies, the electrophysiological data, the clinical studies case reports and the literature provides evidence that Cisapride is associated or specifically can produce the prolongation of the QT interval. What is debated by the parties is whether Propulsid has a lasting or permanent effect on the QT interval after cessation of use.

Defendants suggest that there is no basis in science to support such a position. As explained above, the heart beat is caused in large part by the movement of potassium, sodium and calcium ions in and out of heart cells through what are known as ion channels which are units of protein on the surface of the heart cells. Propulsid can cause a temporary prolongation of the QT interval by chemically blocking the potassium ion channels. However, according to defendants' expert, these ion channels are very short lived and turn over constantly in the heart. Furthermore, because Propulsid has a half-life[7] of less than one day in the body, within minutes the drug washes out of the potassium ion channels. Defendants' experts contend that Propulsid has no lasting effect after it leaves the body.

The plaintiff contends that Propulsid can have long-term effects. Plaintiff's theory has developed over the course of the litigation; she now contends that Propulsid in addition to blocking the ion channels causes the pharmacological stimulation of the autonomic nervous system, specifically, the vagus nerve. She

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[6] A QTc interval of greater than 0.46 seconds is generally considered by the cardiology community to indicate a high possibility for future cardiac arrhythmias.

[7] The period over which the concentration of a specified chemical or drug takes to fall to half its original concentration in the specified fluid or blood.

argues that this stimulation can have long-lasting effects on the vagus nerve and that this prolongation can remain well after cisapride has left the body's system. Therefore, those who have such conditions, such as the plaintiff, must be monitored and treated for potential future cardiac problems.

Having considered the parties' contentions and the scientific explanation of the relevant issues, the Court now turns to the proposed experts' opinions regarding the long-term effects of cisapride and assesses the reliability of the methodology and the relevance of the proposed testimony on the facts at issue.

IV. The Experts' Testimony

A. Dr. William E. Shell

The plaintiff first offers the testimony of Dr. William E. Shell. Dr. Shell is board certified in cardiology and internal medicine. Since 1987, he has been the medical director of a testing laboratory that does extensive testing on QT intervals and heart rate variability, including study of autonomic nervous function. Dr. Shell's conclusion that cisapride is defective is based on the premise that the drug stimulates the HT4 receptors and causes the release of acetylcholine with adverse consequences on the autonomic nervous system. During his deposition, Dr. Shell gave the following explanation of how cisapride has a persistent effect on the autonomic nervous system:

> It alters the autonomic cells that it attaches to. So the way the agonist[8] works is it attaches to a receptor on the membrane of the cell, the so-called HT4 receptor, and it alters the cells so it's no longer the same.
>
> Q. How does it do that?
>
> A. How do I think it does that? *First of all, I don't know how it does that.* I

[8]"A substance which initiates a physiological response when combined with a receptor." CONCISE OXFORD DICTIONARY, 9th ed.

> have a theory of how it does that. Is that when these receptors work so that they are agonists, they cause release of the neurotransmitter and they prevent this re-uptake; that what happens is, for certain cells the reuptake cells fall below concentration necessary to make cells stay viable. In the process, aptosis (sic) occurs where the cell kills itself.[9]

The body's HT4 receptors are not limited to the gut area but are also present in the brain and heart. It is generally conceded that Propulsid can affect the HT4 receptors in the gut area; it is not generally accepted, however, that it can have any effect on the HT4 receptors in other areas of the body. An issue, therefore, is whether cisapride's effects extend beyond the gut and have long-lasting consequences. Dr. Shell postulates that it can. To support his theory regarding the sustained pervasive effects of cisapride, Dr. Shell relied on five areas: biologic plausibility, peer reviewed studies, the Janssen studies, the Shell-Morganroth studies, and the patient data of plaintiff Ernestine Brock. The Court will briefly review Dr. Shell's testimony and opinions regarding each of these five items, as well as the defendant's responses to Dr. Shell's theories.

1. Biologic Plausibility

The theory of biologic plausibility looks to whether similar drugs have had the same effect as the drug being studied. In this case, Dr. Shell attempted to identify drugs that are known to cause a prolonged QT interval.

He identified a group of anthracycline antibiotics that were used to treat cancer. He testified that treatment with these drugs causes an increase in the QT interval having a sustained effect well after the drugs are no longer in the system.

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[9]Deposition of William E. Shell, M.D., November 14, 2002 at 188-89, l. 23-12 (emphasis added).

Dr. Shell also identified amphetamines as a classic example of an agonist that has a damaging effect on the autonomic nervous system, leading to an sustained prolonged QT interval. Furthermore, he cites studies showing that veterans of the Gulf War suffered from prolonged QT intervals as a result of exposure to certain environmental toxins.

Based on these results, he extrapolates that drugs or toxins can permanently alter the QT interval by activating the autonomic receptors causing a destruction of such neurons leading to a permanent prolonged QT interval. Dr. Shell opines that "[i]f cisapride increased the QTc not only by blocking the ion-channels of the heart, but also by activating autonomic nervous system function, a mechanism would exist for creating a sustained effect of cisapride on the QTc interval."[10] The defendants dispute this theory, contending that a mere analogy is insufficient to support the experts' theories. They argue that Dr. Shell cannot point to any scientific literature approving of the comparisons between cisapride and amphetamines or environmental toxins.

2. Review of Peer Reviewed Literature

Dr. Shell's report cites several case studies which indicate that cisapride prolonged the QT interval and which discussed the effect of cisapride on the vagal nerve. Defendants point out that these case studies reveal that the QTc intervals actually returned to normal in the majority of the subjects. Moreover, the defendants note that Dr. Shell rejected the Fujii study. In the Fujii study, the vagal nerves of adult dogs were severed, and they were administered cisapride. The study showed that, even in the absence of vagal nerves, cisapride continued to have a motility effect. This, defendants argue, shows that cisapride does not

[10]Report of William E. Shell, M.D., October 14, 2002 at 22.

have any effect on the vagal nerves. Dr. Shell, however, responds that the article was not relevant to his opinion so he did not consider it.

3. Review of Janssen Studies

In addition to looking at other drugs that may cause a sustained prolonged QT interval, Dr. Shell also evaluated Janssen studies, which he interpreted as proving that cisapride causes a sustained prolonged QT interval. Dr. Shell's opinions focused most closely on the CIS-NED-32 study.[11] CIS-NED-32 was designed as an escalating dose study to examine the cardiovascular safety of cisapride after administration of various doses of the drug. During the study, 24 subjects would receive up to 5 single doses of cisapride at amounts up to 200 mg, with a 48-hour interval following consecutive days of administration.[12] The main parameter for determining cardiovascular safety would be variations of actual QT intervals and its corrected calculations.

The study was halted after nine days following administration of the 130 mg dose of cisapride; the termination of the study was based on the investigator's judgment of potential risk. The study showed that heart rate increased for all doses of cisapride during the time of administration and during wash out (48 hours). Single doses of cisapride of 40 mg to 130 mg showed an increased corrected QT interval. The study also noted that QT interval was measured using the traditional 12-lead ECG and the novel Holter technique with beat-to-beat analysis. The study noted that with this latter method, a small but statistically

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[11]Dr. Shell's reports submitted into evidence for the purpose of this motion also discussed the KET-BEL-46 and CIS-USA-98 studies. However, Dr. Shell admitted that he was relying on Dr. Eckberg's review of the studies. Accordingly, the Court will defer consideration of these studies until it reviews Dr. Eckberg's proffered theories.

[12]The normal prescribed single dose of cisapride was 10 mg.

significant increase in the QT interval was detected during administration of the 10 to 20 mg doses and during wash out. These changes were found to be of "no clinical importance." The study concluded "statistically significant relationships between changes in heart rate and corrected QT intervals on the one hand, and cisapride plasma levels at the other hand, although only 13-29% of the variance in corrected QT intervals could be explained by cisapride levels."[13] In other words, although a relationship exists between cisapride and QT intervals, the researchers could conclude only that part of the variance in QT intervals was due to cisapride.

Dr. Shell testified that he was involved in the design of the protocols for CIS-NED-32. In his opinion, the washout phase was designed to study the sustained effect theory. Although CIS-NED-32 was designed as an escalating dose study, Dr. Shell opined that the 40 milligram does was equivalent to giving 10 milligrams four times a day. Dr. Shell's review of the material concluded that CIS-NED-32 supports a dose-response relationship between the administration of cisapride and prolongation of the QTc; further, after the subjects' blood levels had returned to normal, the study showed a continued sustained effect on the QTc interval. Thus, he cites the CIS-NED-32 study in support of his theory that Propulsid can permanently alter the QT interval.

The defendants argue first that CIS-NED-32 was not designed to study the persistent effects of cisapride on the QT interval. Defendants also criticize Dr. Shell's reliance on the 40mg administration of cisapride because that amount is four times the recommended daily dose of cisapride. Their expert, Dr. Douglas Zipes, testified that Dr. Shell's assertion that one 40 mg dose of cisapride was equivalent to four

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[13]CIS-NED-32 at "Overall Conclusions."

10 mg doses of cisapride given in 10 mg increments throught the day was wholly without support in the scientific literature. According to Dr. Zipes, the single administration of a higher dosage of a drug will cause that drug to remain in the system much longer than administration of a normal dose.

The defendants also criticize Dr. Shell for failing to give any weight to a Janssen study authored by Cheron entitled Open Study by Continuous Electrocardiographic Registration of the Cardiac Tolerance of Cisapride in Babies. During the study, the effect on the vagal nerve was examined through an oculo-cardiac reflex ("OCR") test during which the researcher presses down on the eyes of the babies until he elicits a pain response. The researchers concluded that cisapride had no effect on the babies' vagal tone. Defendants assert that this study proves that cisapride had no effect while anyone was on cisapride much less after he or she had finished using the drug. Dr. Shell testified that he did not have the article as part of his original report, but that after having reviewed the study, he would have reached a different interpretation than the researchers in the study.

4. Shell-Morganroth I & II

Shell-Morganroth I is a study that was produced to specifically investigate the effects of cisapride on the QT interval. Several criticisms of the study emerged following its submission for peer review. Specifically, critics cited the method for measurement of the ECGs, and the failure to find patients that did not have a concomitant disease or were using a drug known to prolong the QTc interval. As a result, Dr. Shell re-designed the study and produced Shell-Morganroth II, using 9 patients. Dr. Shell concluded that all patients exposed to cisapride showed a sustained increase in the QT interval. Dr. Shell's study concludes that "the mechanism that can induce sustained prolongation of the QTc interval in patients exposed to cisapride is unknown at this time. Potential mechanisms include alteration of ion channels,

alteration of autonomic nervous function, central nervous system effects, and the effects of other drugs."[14] The study could conclude only that "cisapride induced autonomic dysfunction is a viable possibility to explain sustained QTc prolongation."[15]

Defendants criticize Shell-Morganroth II's make-up and conclusions. Defendants point out that the authors of the new study selected patients whose names were provided by the Plaintiffs' Steering Committee in this MDL. Defendants' summary of the evidence produced in Shell-Morganroth II showed that three of the patients with post-cisapride EKGs had multiple EKGs with no QTc prolongation. Furthermore, four of the nine suffered from conditions or used other medications known to increase the QTc interval. Finally, defendants contend that this study is not sufficient under Rule 702 because Dr. Shell is still unable to definitively answer how cisapride affects the autonomic nervous system.

5. Patient Data of Plaintiff Ernestine Brock

Regarding the plaintiff in this case, Dr. Shell testified that her QTc intervals were prolonged during and after her use of cisapride; specifically, he found heartbeats with QTc intervals as long as .605 seconds. He noted, however, that the "central weakness" in her case was the lack of an ECG before she began taking cisapride. Dr. Shell noted that Brock was hypertensive, but that the condition was controlled, meaning that the hypertension could not have caused her prolonged QTc interval. Dr. Shell observed that Brock's family history evidenced no instances of sudden death, and he concluded that there was no reason

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[14]Shell-Morganroth II, attached as Exhibit 50 to Declaration of Dr. William E. Shell in Response to Defendants' Motion to Exclude Expert Testimony.

[15]*Id.*

for her to be afflicted with a congenital long-standing QTc syndrome.

During direct examination of Dr. Shell, the Court asked why no tests were done to determine congenital prolongation. Dr. Shell conceded that he did not have an answer to that question and admitted that it was an important issue that should be done. On cross-examination, Dr. Shell testified that he had personally examined Ms. Brock, but failed to perform any such tests, despite the fact that he could have done so. Thus, defendants contend that Dr. Shell's testimony is not relevant to this case because he cannot establish a sufficient link between cisapride and this plaintiff's prolonged QTc interval.

B. Testimony of Dr. Dwain Eckberg

Plaintiff's other expert is Dr. Dwain Eckberg, professor of internal medicine and physiology at the Medical College of Virginia in Richmond, Virginia. He also has a clinical practice at the McGuire Veterans Hospital and currently serves on editorial boards for two scientific journals, *Environmental Medicine* and *Clinical Physiology*. He is also an editor for the *American Journal of Physiology*. Dr. Eckberg's areas of interest include studying autonomic mechanisms and the causes of sudden death.

Dr. Eckberg opined that cisapride is an autonomic drug that causes withdrawal of vagal restraint of the heart. However, when the Court asked Dr. Eckberg whether he had an opinion on whether Propulsid triggered some mechanism to increase the QTc interval, he gave the following answer:

> Well, I would have to say I'm not expert on cardiac ion channels, I would have to think that there is some persistent abnormality in cardiac ion channels. Similar to what is seen after drugs and after toxin exposure. So I do not necessarily say that it is due to the putative autonomic damage, I did not make that claim in anything that I have written, and I am not a channel person to understand such mechanisms. But I do know and I do accept the evidence that I've seen presented by Dr. Shell that there are substances and there are exposures to substances that can chronically prolong the QT interval.
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> And in an earlier, in one of my depositions I was, one of the documents that I read someone said, well, it can't prolong the QT interval and I said but it does so your theory

> that it cannot prolong the QT interval chronically has to be revised and you have to come up with an explanation. But I personally did not offer any sort of scientific explanation for why it does. I know only that it does prolong the QT interval chronically.[16]

Dr. Eckberg based his opinions on the theory of biologic plausibility, peer-reviewed literature, Janssen studies, and the plaintiff's medical history.

1. Biologic Plausibility

Dr. Eckberg compared the effects of metoclopramide to cisapride to determine that it was biologically plausible for cisapride to cause prolonged QT intervals. He noted that both were benzamide derivatives used to treat GERD and that both cause a release of acetylcholine and a lowering of blood pressure. Further, they both cause increased heart rates. Dr. Eckberg also compared cisapride to organophosphates that are known to prolong QT intervals. As noted above in discussing Dr. Shell's testimony, the defendants rebut this evidence because Dr. Eckberg is unable to support the assertion that metoclopramide and cisapride should be seen as related.

2. Review of Peer-Reviewed Literature

Dr. Eckberg's testified that the Fujii study on dogs showed that cisapride sets the baroreflex aside because both heart rate and blood pressure increased upon introduction of cisapride, a result that is not a normal occurrence. Defendants, as noted previously, argue that the study shows that cisapride does not have an effect on the vagal nerve.

Dr. Eckberg also relies on several instances of published case reports that he interprets as showing a prolonged QTc interval. Most of these case reports concerned only one subject, and the defense points

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[16]Transcript of *Daubert* Hearing, February 3, 2003 at 121-22.

out that in most of these instances, the subject's QTc intervals have returned to normal following cessation of use.[17]

3. Review of Janssen Studies

The main Janssen study relied on by Dr. Eckberg was the CIS-USA-97 study, which was designed to study the interaction between cisapride and fluoxetine (Prozac). Dr. Eckberg reviewed the results of CIS-USA-97 and concluded that cisapride has a prolonging effect on the QT interval at least seven days after taking the drug. He concluded that the study showed that about 5% of the subjects' ECGs showed QTc intervals greater than 450ms one week after discontinuing cisapride. He further observed that two of the subjects did not have prolonged QTc intervals before taking cisapride, but did have the condition after usage had been halted. Defendants contend that Dr. Eckberg does not consider the entire study and that he is only looking at the EKGs for patients who had not used Propulsid in one week, rather than the several years that the plaintiff, Brock, has been off Propulsid.

During his testimony, Dr. Eckberg was also particularly critical of the Cheron study involving the oculocardiac reflex tests, which involved pushing on infants' eyes to elicit a response. Dr. Eckberg queried whether such tests were proper because a researcher does not know how hard he presses from one baby to the next or from one time to the next. In his opinion, it was necessary to electronically monitor the electrocardiograms to determine the effects of cisapride. Defendants, as previously noted, contend that this article supports the notion that cisapride does not have an effect on the vagal nerve.

4. Review of Patient Data of Ernestine Brock

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[17]*See* Defendant's Exhibit 2, admitted into evidence on February 3, 2003.

Dr. Eckberg admitted that Brock's hypertension would contribute to an increased QTc interval, but argued that the increase would be mild. He then determined that her age would have a slight increase on the QTc interval, but her race would have the opposite effect on it. Dr. Eckberg admitted that no tests had been done to determine whether Brock's prolonged QTc interval pre-dated use of cisapride.

The Court having discussed the theories offered by Drs. Eckberg and Shell, will now undertake its role as gatekeeper to determine the reliability and relevance of these opinions.

V. Application of Rule 702 and *Daubert* to the Testimony of Drs. Shell and Eckberg

As noted above, the plaintiffs have the burden of proving by a preponderance of the evidence that the testimony of their proffered experts is both relevant and reliable. *See Moore*, 151 F.3d at 276. The issue, as it relates to this case, is whether the plaintiffs' experts have put forth reliable and relevant evidence that Propulsid caused Brock's prolonged QTc interval. Defendants contend that the plaintiff's experts fail both prongs of the test. They contend that Eckberg's and Shell's methodologies are not reliable because their opinions have not been tested, peer reviewed, published, or generally accepted in the medical community. Further, they argue that the experts' testimony as it specifically relates to the plaintiff is not relevant because no evidence exists showing that Brock's prolonged QT interval did not exist before Propulsid. Therefore, defendants argue, the plaintiff has failed to rule out other potential causes.

The plaintiff argues that *Daubert*'s familiar standards (i.e., publication, peer review, etc.) are not exclusive and are merely some of the factors upon which a district court may rely. Plaintiff relies on the written declarations of Drs. Shell and Eckberg and their testimony described above to carry her burden and show that the theory of prolonged QT interval has a sound scientific basis. Amicus Curiae, the Plaintiffs' Steering Committee ("PSC"), argues that Brock's experts should not be penalized for failing to

conduct their own studies because cisapride was removed from the market because of health and safety concerns. Thus, it would be probably impossible and certainly unethical for the experts to have attempted their own trials. The PSC contends that the experts have applied the available data to reach their conclusions. Further, it asserts that the defendants seek to have this Court evaluate the merits of the plaintiffs' position and substitute the Court's opinions for a matter more appropriate for jury determination.

In this case, the Court is mindful of the difficulties facing the plaintiff's experts in conducting their own tests and compiling data. Peer review has also been inhibited since publication has not occurred. The Court notes there is some possibility of future peer review. The PSC submitted to this Court in this MDL a motion, which the Court subsequently granted, to lift the confidential designation on several Janssen studies to permit Dr. Eckberg to pursue peer-reviewed publication of an article on the effects of cisapride on the autonomic nervous system. The Court is aware that the future may shed more light on this matter. Medical science may one day determine with sufficient reliability that a causal relationship exists between a sustained prolonged QT interval and Propulsid but it is not there yet and may never be. *See, e.g., Vargas v. Lee*, 317 F.3d 498, 501 (5th Cir. 2003). A trial court must function in the present assessing evidence that presently exists. At best, the experts in Brock's case presently have untested hypotheses. Both Shell and Eckberg admit that they do not know how or why Propulsid causes a sustained prolonged QT interval, although, in their opinion, it can. They rely on the theory of biologic plausibility to explain that it is possible for Propulsid to prolong the QT interval; however, they fail to show that Propulsid is so similar in chemical structure to those drugs as to produce the same result. Sound scientific method does not support an extrapolation from one substance to another without some showing of identity or at least close

similarity. As one noted scholar wrote: "Even minor changes in molecular structure can alter a substance's effect. The metabolic process stands as an unknown intervening variable between the original chemical structure and the adverse effect. Thus, structure-activity data presents a problem of internal validity." Joseph Sanders, *Scientific Validity, Admissibility, and Mass Torts After Daubert*, 78 MINN. L. REV. 1387, 1409 (1994). Further, the Supreme Court recognized in *General Electric Co. v. Joiner*, 522 U.S. 136 (1997), that although an expert may extrapolate his opinions from existing data, "nothing in either *Daubert* or the Federal Rules of Evidence requires a district court to admit opinion evidence that is connected to existing data only by the *ipse dixit* of the expert. A court may conclude that there is simply too great an analytical gap between the data and the opinion proffered." *Id*. at 146. Drs. Eckberg and Shell have left too great a gap in their theory of biologic plausibility to support their arguments. Such evidence is unreliable under *Daubert*.

Dr. Shell also relies on Shell-Morganroth II, but that study notes that the mechanism causing prolonged QT intervals is "unknown at this time."[18] At best, Shell can only opine that "cisapride induced autonomic dysfunction is a viable possibility to explain sustained QTc prolongation."[19] However, he offers no proof that such long-term damage has occurred in this case, or any other case. Furthermore, the very basis of his study is flawed. He uses nine subjects hand-picked by attorneys involved in this litigation. Several of the subjects have questionable medical histories making it difficult to determine that Propulsid was the cause of any QTc prolongation. The prolonged QTc interval itself is not evidence of a damaged

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[18]William E. Shell, M.D., et al., *Sustained Prolongation of the QTc Interval Following Use of Cisapride*, at 10.

[19]*Id.* at 10-11.

autonomic nervous system. To succeed, Dr. Shell must establish damage to the autonomic nervous system; he has not done so. His testimony, therefore, is mere theory at this point and is unreliable in a court of law.

As for Dr. Eckberg, he similarly fails to state how cisapride use can cause a prolonged QTc interval which can persist after the drug use is terminated. He testified that he knows that cisapride has such an effect, but does not know how that effect is achieved. In essence, he reasons that since Propulsid can cause prolonged QTc interval, this condition can persist apparently indefinitely. This testimony is similarly unreliable under *Daubert*. The expert's mere assertions that he knows Propulsid can cause prolonged QTc intervals and that such effects can be permanent simply cannot be reliable without some explanation of how or why it happens or proof that it has consistently happened.

Dr. Eckberg's testimony is also inconsistent with that of Dr. Shell. Eckberg testified before this Court at the *Daubert* hearing that there must be some "persistent abnormality in cardiac ion channels," although he cannot state that such an effect has occurred. Such a view, regarding Propulsid's long-term effects on ion channels, was previously discredited in expert testimony before this Court, and not even Dr. Shell relies anymore on that theory to support his views.

The Court finds the Fifth Circuit's opinion in *Black v. Food Lion, Inc.*, 171 F.3d 308 (5th Cir. 1999), instructive on the points just discussed. In *Black*, the plaintiff slipped on the floor of the defendant's supermarket and was injured. She continued to suffer from pain as a result of the injury, but all objective tests were negative; her treating physician thereafter diagnosed her as suffering from fibromyalgia

syndrome.[20] The district court permitted the plaintiff's expert to testify regarding fibromyalgia, and the defendant appealed contending that the evidence was inadmissible under *Daubert*. The Fifth Circuit reversed noting that "the underlying predicates of any cause-and-effect medical testimony are that medical science understands the physiological process by which a particular disease or syndrome develops and knows what factors cause the process to occur. Based on such predicate knowledge, it may then be possible to fasten legal liability for a person's disease or injury." *Id.* at 314. The court then concluded that no one knew the exact cause of fibromyalgia, and that expert testimony linking the fall to this condition was unreliable. *Id.* The court focused on the following testimony of the plaintiff's expert when asked to identify the cause of plaintiff's fibromyalgia: "'I didn't find the cause. I found an event that contributed to the development of the symptom. I did not find the cause.'" *Id.* at 313. The court concluded that this was "conjecture, not deduction from scientifically-validated information." *Id.*

In this case, at best, Drs. Shell and Eckberg have discovered an event, but not a cause. They fail to identify the exact mechanism by which a person's QT interval can become permanently prolonged well after that person has ceased taking Propulsid. Dr. Shell, in his testimony and reports, has admitted as much. Moreover, as demonstrated above, Drs. Shell and Eckberg have been unable to show that such a condition exists with regularity and that it is caused by Propulsid. They have theories, but they have no proof to support those theories. Furthermore, their theories have not been tested or subjected to peer review and publication. They have no known or potential rate of error and there is presently no general

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[20]The court defined fibromyalgia as "characterized by complaints of generalized pain, poor sleep, an inability to concentrate, and chronic fatigue. The condition is most common in women between the ages of 30 and 50 and is often associated with hormonal problems." *Black*, 171 F.3d at 309.

acceptance of their methods in the scientific community. Under the prevailing logic of *Daubert* and *Black*, their testimony is unreliable.

Finally, the experts' proposed testimony is not relevant to the plaintiff's, Brock's, case. As noted above, *Daubert* requires "a valid ... connection to the pertinent inquiry." *Daubert*, 509 U.S. at 592. This requires the plaintiff to show not only that Propulsid can cause a prolonged QT interval, but that it did cause a prolonged QT interval in her case. Here, no tests were ever done to determine whether she suffered from a congenital prolonged QTc interval, despite the opportunity to perform such tests. Further, no tests show her QTc intervals before taking Propulsid. Dr. Eckberg admits that Brock has a number of symptoms or characteristics placing her at risk for a prolonged QTc interval. The experts' bald assertion that cisapride caused Brock's prolonged QT interval lacks any reliability because the experts themselves cannot show that Brock did not have the condition before taking Propulsid. The experts have no baseline on which to rely. To properly show causation in this case, the experts must demonstrate that Brock did not suffer from a prolonged QT prior to taking Propulsid. They cannot do so. Furthermore, plaintiff's experts cannot explain why Mrs. Brock has none of the hallmarks of autonomic nervous system damage such as orthostatic hypotension, or light-headedness or fainting which is seen in people who have autonomic nervous system dysfunction. They also cannot rule out other explanations for the measurements that form the predicate of the QTc, the heart rate, or heart rate variability. They cannot even conclude that her QTc is abnormal for her because there are no pre-Propulsid measurements. Thus, their testimony is again unreliable and inadmissible since it fails to fit the facts of the case before this court.

For the reasons noted above, the opinions offered by Drs. Shell and Eckberg are unreliable and irrelevant under Rule 702 and *Daubert*. The defendants' motion to exclude their opinions is, therefore,

GRANTED. As the Supreme Court recognized in *Daubert*:

> [I]n practice, a gatekeeping role for the judge, no matter how flexible, inevitably on occasion will prevent the jury from learning of authentic innovations. That, nevertheless is the balance that is struck by the Rules of Evidence designed not for the exhaustive search for cosmic understanding but for the particularized resolution of legal disputes.

Daubert, 509 U.S. at 597. *See also Vargas v. Lee*, 317 F.3d 498, 501 (5th Cir. 2003) (holding that scientific understanding of the causes of fibromyalgia since the Fifth Circuit's holding in *Black* had not progressed to a sufficient degree to permit the admissibility of expert testimony).

VI. Defendants' Motion for Summary Judgment on the Issue of Medical Causation

To prevail on a claim for damages under the Louisiana Products Liability Act, the plaintiff must show that her damages were caused by an unreasonably dangerous defect in the product. *See* LA. REV. STAT. ann. § 9:2800.54(A). With the exclusion of the plaintiff's experts on causation, the plaintiff lacks an essential element of proof. Accordingly, summary judgment is appropriate, and the plaintiff's claim should be dismissed. *See Christopersen v. Allied-Signal Corp.*, 939 F.2d 1106, 1109-10 (5th Cir. 1991) (granting summary judgment where the plaintiff had failed to produce admissible evidence of causation); *Pennington v. Vistron Corp.*, 876 F.2d 414, 426 & n.14 (5th Cir. 1989) (same).

VII. Defendants' Motion for Partial Summary Judgment Dismissing Composition, Express Warranty, and Design Claims

This motion is unnecessary because the plaintiff's claims as a whole have failed because she cannot produce admissible evidence of causation. Accordingly, this motion is moot.

VIII. Conclusion

In conclusion, the plaintiff's proffered experts' testimony is inadmissible. Their theories are based

on unproven assumptions and improper scientific methodology. Further, they cannot show that Propulsid caused Brock's symptoms, as they have failed to exclude other possible symptoms or show that Brock's prolonged QTc interval did not pre-date the use of cisapride. Accordingly, this Court finds that their opinions fail to meet the requirements of reliability and relevance defined in Federal Rule of Evidence 702. The defendants' Motion to Exclude the Testimony of Drs. Shell and Eckberg is, therefore, GRANTED.

As the plaintiff has failed to produce admissible evidence of causation, she cannot prevail under the LPLA's theories of recovery. Accordingly, IT IS FURTHER ORDERED that the Defendants' Motion for Summary Judgment on the Issue of Medical Causation be GRANTED and the claims of Ernestine J. Brock be DISMISSED WITH PREJUDICE.

Since the plaintiff's claims have been dismissed for failure to prove causation, it becomes unnecessary for this Court to rule on the motion for partial summary judgment. This matter is DISMISSED AS MOOT.

IT IS FURTHER ORDERED that the status conference scheduled in this case for Monday, May 5, 2003 at 1:30 p.m. be CANCELED.

New Orleans, Louisiana this 29th day of April, 2003.

/s/ Eldon E. Fallon
UNITED STATES DISTRICT JUDGE