UNITED STATES DISTRICT COURT
NORTHERN DISTRICT OF OHIO
EASTERN DIVISION

IN RE: GADOLINIUM-BASED CONTRAST AGENTS PRODUCTS LIABILITY LITIGATION	)	**Case No. 1:08 GD 50000**
	)	**MDL No. 1909**
	)	
	)	**Judge Dan Aaron Polster**
	)	
	)	**MEMORANDUM OF OPINION AND ORDER**
	)	

THIS DOCUMENT APPLIES TO ALL CASES

Currently pending in this multi-district litigation ("MDL") are omnibus Generic *Daubert* motions filed by the Plaintiffs Steering Committee (**Doc #: 693**) and General Electric Healthcare, Inc., ("GEHC") (**Doc #s: 663-674**). The briefs are very comprehensive and, after reading them along with the expert definitions, the Court has determined that *Daubert* hearings are not necessary. Accordingly, the Court hereby **DENIES** GE Healthcare's Motion for an Evidentiary Hearing, etc. (**Doc #: 675**).

I. INTRODUCTION

Gadolinium-based contrast agents ("GBCA") are one type of contrast agent used in magnetic resonance scans ("MRI" or "MRA"). There are currently five different GBCAs approved by the FDA for use in MRI/MRA in the United States: (1) Omniscan, which is manufactured by a number of companies the Court will collectively refer to as General Electric Healthcare ("GEHC" or "Defendants"), (2) Magnevist, which is manufactured by a number of companies the Court will refer to collectively as Bayer Healthcare Pharmaceuticals, (3)

Optimark, which is manufactured by a number of companies the Court will refer to collectively as Mallinckrodt Inc., and (4) Prohance and Multihance, which are manufactured by Bracco Diagnostics.

The Plaintiffs in this MDL are individuals or estates of deceased individuals who developed a rare disease known as Nephrogenic Systemic Fibrosis ("NSF") following the administration of one or more GBCAs. NSF is a progressive fibrotic disease affecting tissues and organs with no known cure. Plaintiffs bring various common law and statutory product liability claims against the GBCA manufacturers.

The Court and counsel agreed early on that conducting bellwether trials would be an effective way to manage this MDL and advance it to a successful conclusion.[1] The parties agreed on a protocol for selecting cases for bellwether trials, and four cases were ultimately selected (*Bullock*, *Kono*, *Knase* and *Marino*). GEHC is the only named defendant in all four cases, and the parties consented to the undersigned MDL judge trying all of them. On May 3, 2010, the Court was advised by counsel that *Bullock*, which was scheduled for trial on May 24, 2010, has been settled. The *Kono* trial is scheduled to begin on September 20, 2010, and the *Knase* trial is scheduled to begin on December 6, 2010. A trial date has not yet been established for *Marino*.

The Court permitted the parties to each designate no more than ten generic experts for the bellwether trials. The parties agreed on a schedule for briefing *Daubert* motions with respect to those experts.

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[1]Under bellwether trial practice, certain cases within an MDL are selected to proceed to trial, and the bellwether trials are used to assist the parties in evaluating the other cases in the MDL. *Lexecon Inc. v. Milberg Weiss Bershad Hynes & Lerach*, 523 U.S. 26, 34-35 (1998).

II. LAW

Rule 402 of the Federal Rules of Evidence provides the evidentiary baseline:

> All relevant evidence is admissible, except as otherwise provided by the Constitution of the United States, by Act of Congress, by these rules, or by other rules prescribed by the Supreme Court pursuant to statutory authority. Evidence which is not relevant is not admissible.

Daubert v. Merrell Dow Pharm., Inc., 509 U.S. 579 (1993) (quoting FED. R. EVID. 402).

"Relevant evidence" is:

> evidence having any tendency to make the existence of any fact that is of consequence to the determination of the action more probable or less probable than it would be without the evidence.

Id. (quoting FED. R. EVID. 401). Rule 702 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 (2000 Amends.).

In *Daubert*, the Supreme Court set forth a non-exhaustive list for trial courts to consider in assessing the reliability of expert testimony, including: (1) whether the expert's theory can be or has been tested, (2) whether the expert's theory has been subject to peer review and publication, and (3) whether the expert's theory has been generally accepted in the relevant scientific, technical, or professional community. *Daubert*, 509 U.S. at 593-94. The 2000 Amendments to Rule 702's Advisory Committee Notes suggest additional factors for gauging expert reliability, including: (1) whether the expert is proposing to testify about matters growing naturally out of research he has conducted independent of the litigation, or whether he has

developed his opinions expressly for the litigation, (2) whether the expert has unjustifiably extrapolated from an accepted premise to an unfounded conclusion, and (3) whether the expert has adequately accounted for obvious alternative explanations. *Id.* (citations to cases omitted).

"The inquiry envisioned by Rule 702 . . . is a flexible one." *Daubert*, 509 U.S. at 594. No single factor is necessarily dispositive of the reliability of an expert's testimony. *See, e.g., Heller v. Shaw Indus., Inc.*, 167 F.3d 146, 155 (3rd Cir. 1999); *Daubert v. Merrell Dow Pharm., Inc.*, 43 F.3d 1311, 1317 n.5 (9th Cir. 1995) ("Daubert II"). The focus of the inquiry "must be solely on principles and methodology, not on the conclusions that they generate." *Daubert*, 509 U.S. at 594. "[T]he trial judge must have considerable leeway in deciding in a particular case how to go about determining whether particular expert testimony is reliable." *Kumho Tire Co. v. Carmichael*, 526 U.S. 137, 152 (1999).

According to the Advisory Committee Notes to Rule 702, caselaw after *Daubert* shows that the rejection of expert testimony is the exception rather than the rule. While trial judges are charged with the responsibility of acting as gatekeeper to exclude unreliable expert testimony, their role as gatekeeper "is not intended to serve as a replacement for the adversary system." *United States v. 14.38 Acres of Land Situated in Leflore County, Miss.*, 80 F.3d 1074, 1078 (5th Cir. 1996). "Vigorous cross-examination, presentation of contrary evidence, and careful instruction on the burden of proof are the traditional and appropriate means of attacking shaky but admissible evidence." *Daubert*, 509 U.S. at 595.

When a trial court rules that an expert's testimony is reliable, this does not necessarily mean that contradictory expert testimony is unreliable. Rule 702 is broad enough to permit testimony that is the product of competing principles or methods in the same field of expertise.

Id. (citing *Heller*, 167 F.3d at 160). "*Daubert* neither requires nor empowers trial courts to determine which of several competing scientific theories has the best provenance." *Ruiz-Troche v. Pepsi Cola*, 161 F.3d 77, 85 (1st Cir. 1998). Again, the focus must be solely on the methodology and principles used, not on the conclusions that they generate. *Daubert*, 509 U.S. at 595.

III. ANALYSIS

A. GEHC's Challenges to Plaintiffs' Experts and their Opinions

1. The "Free Gadolinium" Theory

Gadolinium is a lanthanide element (rare earth metal) which exhibits high paramagnetism, a form of magnetism occurring only in the presence of an externally applied magnetic field. It is this characteristic that led research scientists to explore its use as a contrast agent in magnetic resonance scans.

It is undisputed that gadolinium, in its free state, is highly toxic to humans. In order to develop a safe gadolinium-based contrast agent for use in humans, researchers found it necessary to chelate the gadolinium (i.e., bind it to a ligand) in order to render it inert during its passage through the body prior to elimination. Of particular concern was its use in renally impaired patients, whose ability to quickly excrete toxic substances is inherently compromised. Because renally-impaired persons might retain the GBCA for longer periods of time than non-renally impaired persons, the chelate's stability was considered crucial since retained GBCA might well dechelate, exposing the kidney patient to the toxic effects of gadolinium. Research shows that renally impaired persons do in fact retain GBCAs for a significantly longer period of time than non-renally impaired persons, renally impaired persons retain a significant portion of the

gadolinium that is injected into them, and dialysis is not very effective in ridding the body of the unrecovered gadolinium.

Nephrogenic systemic fibrosis, or NSF, was first described in the medical literature in 2000, with the first reported cases going back to 1997. NSF causes fibrosis of the skin, connective tissue and organs throughout the body. It is a painful, progressive and debilitating disease. While the precise pathogenesis of NSF is unknown, it has been reported only in patients who have severe kidney disease and, with the exception of a few reported cases with inconclusive medical histories, has been found exclusively in kidney patients who have had one or more exposures to GBCAs.

In June 2006, the FDA issued a Public Health Advisory notifying healthcare professionals and the public about the risk of NSF following the administration of GBCAs; in December 2006, the FDA issued an updated Public Health Advisory stating that there is a potential for NSF to occur in at-risk patients following administration of GBCAs; and in May 2007, the FDA asked GBCA license holders to issue a boxed warning about the risk of NSF in patients with renal failure. The issuance of the "blackbox warning," along with policies and procedures adopted by healthcare facilities and notice to healthcare providers, have all but led to the eradication of new NSF cases.

Plaintiffs have experts who will testify, based on some combination of their areas of expertise, experience, personal research and review of published case reports and research data, that GBCAs – here, Omniscan – cause NSF. More to the point, they will testify that Omniscan most likely causes NSF in renally impaired patients when, due to various processes (for example, transmetalation), the gadolinium becomes dechelated, dissociated, released or freed from the

ligand to which it is bound. This dechelation exposes tissue to labile, toxic gadolinium which rapidly bonds elsewhere in the body and begins the fibrotic process leading to NSF. This is, in short, the "free gadolinium" theory. It is, as acknowledged by GEHC's expert Ben B. Newton, Ph.D., the prevailing theory in the scientific community.

GEHC seeks to preclude all of Plaintiffs' experts from opining about the free gadolinium theory. First, GEHC argues that Plaintiffs' experts must be prohibited from opining about the free gadolinium theory of causation because it is just a theory and the precise pathogenesis of NSF is unknown. The Court disagrees.

It is unreasonable to require the subject of scientific testimony to be "known" to a certainty, since science is an evolving process, and there are no certainties in science. *Daubert*, 590 U.S. at 590. The *Daubert* Court recognized that there is a range in which experts might reasonably differ on issues of science, and that such conflicting evidence should be admitted to aid the jury in deciding those issues. *Kumho*, 526 U.S. at 153. The Sixth Circuit elaborated:

> 'Scientific knowledge' establishes the standard of evidentiary reliability, and to be considered appropriately scientific, the expert need not testify to what is 'known' to a certainty but must only state an inference or assertion derived by the scientific method. Testimony meets this threshold when an expert, whether basing testimony on professional studies or personal experience, employs in the courtroom the same level of intellectual rigor that characterizes the practice in the relevant field.

Jahn v. Equine Serv., PSC, 233 F.3d 382, 388 (6th Cir. 2000) (citations omitted); *see also U.S. v. Bonds*, 12 F.3d 540 (6th Cir. 1994) ("Absolute certainty of result or unanimity of scientific opinion is not required for admissibility so long as the conclusions drawn by the experts are based on generally accepted and reliable scientific principles.").

Furthermore, causation can be established even when the precise causal mechanism is unknown:

> Particularly in toxic tort cases, proving causation raises numerous complicated issues because the mechanisms that cause certain diseases and defects are not fully understood. Consequently, the proof of causation may differ from that offered in the traditional tort case in which the plaintiff details and explains the chain of events that produced the injury in question. In toxic tort cases in which the causal mechanism is unknown, establishing causation means providing scientific evidence from which an inference of cause and effect may be drawn.

Margaret Berger, *The Supreme Court's Trilogy on the Admissibility of Expert Testimony*, in REFERENCE MANUAL ON SCIENTIFIC EVIDENCE 32 (Federal Judicial Center, 2d ed. 2000).

Nothing in Rule 702, *Daubert* or the relevant case law requires experts to know the precise mechanical process underlying a cause when other evidence is sufficient to show causation. *See, e.g., Jahn*, 233 F.3d at 390 (reversing the district court ruling that plaintiff's expert testimony on the cause of a horse's death was inadmissible because specific knowledge of the precise physiological cause of the horse's death was unknown); *Silivanch v. Celebrity Cruises, Inc.*, 171 F.Supp.2d 241, 264 (S.D.N.Y. 2001) (on the subject of whether a passenger's Legionnaires' Disease, contracted from a whirlpool spa aboard a cruise ship line, caused his encephalopathy, the court observed, "Dr. Dickoff acknowledged that the etiology of this relationship is a matter of uncertainty. . . . However, debate concerning the precise biological mechanism at play does not undercut the general agreement in the scientific community concerning the causal connection between Legionnaires' Disease and encephalopathy.").

This is particularly true in product liability cases. *See, e.g., In Re Seroquel Prod. Liab. Liti.*, No. 6:06-mc-1769-Orl-22DAB, 2009 WL 3806435, at *8-9 (M.D. Fla. Jun. 23, 2009) (allowing expert testimony on causation where ample scientific evidence demonstrated a cause

and effect relationship between the drug and diabetes, and the expert offered plausible explanations of the physiological process that had been published and peer-reviewed in the scientific literature); *In re Baycol Prod. Liti.*, 532 F.Supp.2d 1029, 1066 (D. Minn. 2007) ("The fact that the exact mechanism of statin-induced myopathy is not yet known does not affect the admissibility of Dr. Smith's opinion. . . . Other courts have recognized that science is constantly evolving, and the fact that a theory is new or in the process of becoming generally accepted does not prevent its admission in court.") (citing *Ruiz-Troche*, 161 F.3d at 85); *In re Asbestos Liti.*, 911 A.2d 1176, 1204 (De. Super. 2006), (allowing plaintiffs' experts to rely upon the body of scientific data that had been developed regarding the link between exposure to unrefined chrysolite and an increased risk to develop mesothelioma, lung cancer and asbestosis, without identifying the exact biological or chemical cause); *In re Phenylpropanolamine Prod. Liab. Liti.*, 289 F.Supp.2d 1230, 1247 (W.D. Wash. 2003) (on the subject of whether phenylpropanolamine (PPA) caused the plaintiff's stroke, "The fact that the mechanism remains unclear does not call the reliability of the opinion into question: 'Not knowing the mechanism whereby a particular agent causes a particular effect is not always fatal to a plaintiff's claim. Causation can be proved even when we don't know precisely *how* the damages occurred, if there is sufficiently compelling proof that the agent *must* have caused the damage somehow.") (quoting *Daubert II*, 43 F.3d at 1314); *Kennedy v. Collagen Corp.*, 161 F.3d 1226, 1230 (9th Cir. 1998) (holding the same with regard to plaintiff's expert opining on whether Zyderm collagen injections caused the plaintiff's atypical systemic lupus erythematosus; *Hollander v. Sandoz Pharm. Corp.*, 289 F.3d 1193, 1211 (10th Cir. 2002) (" 'The first several victims of a new toxic tort should not be barred from having their day in court simply because the medical literature,

which will eventually show the connection between the victims' condition and the toxic substance, has not yet been completed.' ").

The cases cited by GEHC on this issue are factually distinguishable from the cases in this MDL because NSF is a singular disease. NSF rapidly emerged, and just as rapidly declined, with the administration of GBCAs to persons with severe renal impairment. Gadolinium is not a trace element normally found in the human body. Thus, the presence of gadolinium in the tissue of kidney patients who were administered chelated gadolinium during magnetic resonance studies, and subsequently developed NSF, permits the inference that there is a causal connection between GBCAs and NSF.

Published studies, and GEHC's own studies, show that the recovery of GBCAs from kidney patients takes significantly longer than non-kidney patients and is far from complete. Numerous techniques (e.g., radio-labeling in rats and mice, SEM/EDS, ICP-MS, SIMS and SXFRS in human NSF tissue samples) employed by a multitude of research scientists unrelated to this litigation have demonstrated the *in vitro* and *in vivo* dechelation of GBCAs. Many studies show that Omniscan is more prone to dechelation than other GBCAs. When dechelated, gadolinium is available to bond with other endogenous substances in blood and tissue. Gadolinium is found in the biopsied tissue of NSF patients.

The dominant theory is that dechelation occurs through transmetalation (simply, a chemical reaction involving the exchange of ligands between two metal centers), although there are other theories including that dechelated (or, free) gadolinium has a proliferative effect on human dermal fibrosis and gadolinium's propensities as a calcium blocker triggers the fibrotic process. In any event, given the wealth of evidence on causation – that is, the rapid emergence

and decline of NSF associated with the rise and fall of its use in renally impaired persons, the presence of gadolinium in the tissue of NSF patients, the known toxicity of gadolinium, and the majority view in the published and peer reviewed studies and articles that dechelated gadolinium causes NSF – the Court concludes that it is not necessary for Plaintiffs' experts to identify the precise mechanism by which dechelated gadolinium causes NSF in order to present the theory to a jury.

The free gadolinium theory passes the relevancy test because it has a tendency to make the existence of any fact that is of consequence to the determination of the action more probable or less probable than it would be without that evidence. FED. R. EVID. 401. The free gadolinium theory passes reliability muster under *Daubert* because it is based on research conducted by scientists and doctors performing animal studies, *in vitro* studies, *in vivo* studies, human clinical studies and retrospective case studies along with review of the relevant published scientific and medical studies; the theory has been subjected to publication and peer review; the theory has been generally accepted in the relevant scientific and medical community; the Plaintiffs' experts have adequately accounted for obvious alternative explanations; and the research of Plaintiffs' experts relates not only to their review of the literature but to matters growing naturally or necessarily out of research they have conducted independent of this litigation. *See Daubert*, 509 U.S. at 593-94; FED. R. EVID. 702 Advisory Committee's Notes (2000 Amends.)

Given the relevance and reliability of this theory, GEHC's challenge to that theory, which goes to weight of the evidence, is more properly made during cross-examination at trial rather than as a *Daubert* challenge to admissibility.

Next, GEHC argues that Plaintiffs' experts should be precluded from testifying about the free gadolinium theory because the analytical techniques used to assess the presence of retained gadolinium in published studies are not capable of distinguishing between free or chelated gadolinium in NSF tissue. GEHC further asks the Court to preclude Plaintiffs' experts from relying upon the work of Dr. Cramer, who has used Extended X-ray Absorption Fine Structure ("EXAFS") to locate dechelated gadolinium in NSF tissue, because his work has not been published and peer reviewed by other scientists. The Court agrees with GEHC that, because Dr. Cramer's work using EXAFS to locate dechelated gadolinium in NSF tissue has not been published and reviewed by his peers, it may not be used by Plaintiffs' experts to support their opinions that dechelated gadolinium causes NSF. Notwithstanding this ruling, Plaintiffs' experts may rely upon all the other evidence supporting the free gadolinium theory, just as GEHC may attempt to discredit that theory on cross-examination.

Finally, GEHC asks the Court to preclude Plaintiffs' experts from opining about the free gadolinium theory to the extent it is based on anecdotal reports of NSF patients who were exposed to GBCAs, and this type of extrapolation is inconsistent with *Daubert*. In support of this position, GEHC cites *Schudel v Gen. Elec. Co.*, 120 F.3d 991 (9th Cir. 1997); *Hollander v. Sandoz Pharms. Corp.*, 289 F.3d 1193 (10th Cir. 2002), and *Brumbaugh v. Sandoz Pharms. Corp.*, 77 F.Supp.2d 1153 (D. Mont. 1999).

As an initial matter, if an expert in this MDL cannot opine on a theory of causation based on a review of the medical literature only, then the Court would have to exclude many of the opinions of Dr. Ben Newton, GEHC's expert, since his published work appears to be based

solely upon the extrapolation of others' *in vivo* and *in vitro* studies. The Court will further discuss challenges to Dr. Newton's expert testimony, *infra*, at Section III (B)(1)(a).

In addition, the cases cited by GEHC in support of this position are all distinguishable from the facts in this MDL. In *Brumbaugh*, a plaintiff brought a products liability action against the manufacturer of Parlodel (a drug that suppresses postpartum lactation), alleging that the drug caused her to have seizures. There, the district court excluded expert testimony that Parlodel caused the plaintiff's seizures because it involved the temporal association between her prescription and her injury, as well as his review of case reports and adverse drug events. The expert hypothesized that plaintiff's seizures were caused by Parlodel-induced vasospasms, that drugs similar to Parlodel (a vasodilator) are vasoconstrictors and not vasodilators and some women cannot distinguish between the two – but he could not cite a study supporting his theory. Because his opinion was based on anecdotal reports and an untested theory as evidence of causation, the court prohibited his testimony. That case is clearly distinguishable from the cases in this MDL, where the free gadolinium theory is embraced by the majority in the medical and scientific community based on animal studies, *in vitro* studies, human clinical studies, retrospective case studies, etc. Additionally, unlike NSF, seizures have numerous understood causes that predate the marketing of Parlodel.

In *Hollander*, the plaintiff alleged that Parlodel caused her to suffer a stroke shortly after giving birth. There, three doctors testified that Parlodel caused plaintiff's brain hemorrhage based on case studies and a differential diagnosis analysis.[2] The doctors performed a differential

[2]Differential diagnosis refers to the process by which a physician rules in all scientifically plausible causes of the plaintiff's injury, then rules out the least plausible causes of injury until the most likely cause remains. *Hollander*, 289 F.3d at 1209 (citation omitted). The remaining cause is the expert's conclusion. *Id*. In conducting a differential diagnosis, physicians often use case

diagnosis, reviewing the plaintiff's medical history and records, excluding other causes of her stroke and then attributing the stroke to Parlodel. They also relied on case reports, both those reported to the FDA and those published in the professional literature. The court affirmed the district court's ruling rejecting this evidence noting that, in many decisions where a differential diagnosis had been deemed reliable, the party relying on the diagnosis has offered independently reliable evidence that the drug had harmful effects, such as scientific and clinical studies regarding the connection between the drug and the disorder, or scientific articles regarding the effects of the drug. The court took a similar view of the case reports of other women suffering various injuries after taking Parlodel because many of the case reports contained limited information regarding the medical histories of the patients and the nature of their injuries. Given the large number of women who took Parlodel and the variety of possible causes for many of the injuries, it was not unreasonable for the district court to characterize the reports as unreliable evidence of causation. Again, *Hollander* is distinguishable because brain hemorrhages have known causes that predate Parlodel, and the *Hollander* decision was based on an unsupported differential diagnosis opinion.

In *Schudel*, nine GEHC employees who cleaned up PCBs at a Kaiser facility alleged that they developed various neurological and respiratory problems from exposure to two cleaning solvents, trichloroethane (TCA) and perchloroethylene (Perc). There, the court determined that one expert's testimony failed to meet *Daubert's* relevance requirement because she testified that it was only a possibility that the plaintiff suffered organic brain damage from exposure to the

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reports (i.e., a doctor's account of a patient's reaction to a drug, accompanied by a description of the relevant surrounding circumstances). *Id.*

solvents. Furthermore, she relied on a "whole person aggravation" theory for her opinion without establishing a scientific basis for her theory. *Schudel* is distinguishable from the instant cases because none of the MDL Plaintiffs' experts are opining that GBCAs are a possible cause of NSF, and none has employed a "whole person aggravation" theory.

In summary, both Plaintiffs and GEHC cite the same standards, and similarly articulate the gatekeeper role the Court is to play in scrutinizing scientific experts. When it comes time to apply that standard, however, each side urges the Court to employ a very wide strike zone for its own experts, but a very narrow strike zone for the other side's experts.

This is a unique and challenging MDL. Millions of people have received MRIs with GBCAs manufactured by GEHC and others. Not only have they had no complications, but they have avoided the risks associated with iodine, the magnetic contrast agent used prior to gadolinium. A small subset of patients who have been administered GBCAs have renal failure, and in recent years, a very small percentage of these renally-impaired patients have developed a new disease, NSF.

One of the few things Plaintiffs and GEHC agree upon is that no one knows exactly how NSF develops or why only a tiny percentage of renally-impaired patients who have been administered GBCAs have developed NSF. Under these circumstances, the Court is reluctant to exclude from the jury's consideration any expert theory on NSF causation. While the free gadolinium theory advanced by Plaintiffs' experts is hardly established, neither is any other theory. Indeed, the only competing theory is that of GEHC's expert, Dr. Newton, who opines, based on his review of a few published *in vivo* and *in vitro* studies conducted by others, that chelated gadolinium may well trigger the fibrotic process leading to NSF. He employs this

theory to discredit Plaintiffs' theory that dechelated (or free) gadolinium triggers the fibrotic process leading to NSF. His theory, however, does not explain why the incidence of NSF in patients administered Omniscan far exceeds the number indicated by GEHC's market share. Nor does he advance any explanation why there are virtually no documented NSF cases attributed to renally-impaired patients who have been administered Bracco's Prohance, which has a different chemical configuration than Omniscan.

In any event, the parties are free to bring out through cross-examination the weaknesses of the other parties' experts. As such, the Court denies GEHC's motion to exclude the Plaintiffs' experts who advance the free gadolinium theory.[3]

2. The Use of Adverse Event Reports to Determine Comparative Risk

GEHC asks the court to exclude the testimony of four of Plaintiffs' generic experts (Drs. Fine, Plunkett, Blume and Semelka) opining that Omniscan causes a higher rate of NSF than other GBCAs based on the number of Adverse Event Reports ("AERs"). According to GEHC, their opinions are not based on reliable scientific methodology.

To provide some background on this subject, the FDA website provides, in pertinent part:

> The Adverse Event Reporting System (AERS) is a computerized information database designed to support the FDA's post-marketing safety surveillance program for all approved drug and therapeutic biologic products. The FDA uses AERS to monitor for new adverse events and medication errors that might occur with these marketed products.
>
> Reporting of adverse events from the point of care is voluntary in the United States. FDA receives some adverse event and medication error reports directly from health care professionals (such as physicians, pharmacists, nurses and others) and consumers (such as patients, family members, lawyers and others).

[3]For reasons explained *infra*, at Section III(b)(1)(a), the Court will also deny the Plaintiffs' motion to exclude in its entirety the testimony of Dr. Newton, who attacks the free gadolinium theory.

> Healthcare professionals and consumers may also report these events to the products' manufacturers. If a manufacturer receives an adverse event report, it is required to send the report to FDA as specified by regulations. . . .
>
> AERS is a useful tool for FDA, which uses it for activities such as looking for new safety concerns that might be related to a marketed product, evaluating a manufacturer's compliance with reporting regulations and responding to outside requests for information. The reports in AERS are evaluated by clinical reviewers in the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) to monitor the safety of products after they are approved by FDA. If a potential safety concern is identified in AERS, further evaluation might include epidemiological studies. Based on an evaluation of the potential safety concern, FDA may take regulatory action(s) to improve product safety and protect the public health, such as updating a product's labeling information, restricting the use of the drug, communicating new safety information to the public, or, in rare cases, removing a product from the market.
>
> AERS data do have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive all adverse event reports that occur with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, AERS cannot be used to calculate the incidence of an adverse event in the U.S. population.

See www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrug Effects/default.htm.

GEHC argues that experts' opining on comparative risk based on AERs should be excluded because (1) the FDA has made clear that AERs alone cannot be used to calculate estimates of drug risks and cannot be used to make comparisons of different medications; (2) federal courts uniformly exclude expert testimony about comparative risks of a medication where the opinion is based on AERs, (3) the regulations state that the existence of an AER does not necessarily reflect a conclusion that the report or information constitutes an admission that the drug caused or contributed to an adverse effect, and (4) Drs. Fine, Plunkett, Blume and

Semelka are not epidemiologists, and plaintiffs' own epidemiologist, Dr. Ix, rejects the use of AER data for this purpose.

Plaintiffs counter that their experts drew their conclusions regarding the relative risk of Omniscan from a combination of epidemiological studies, chemistry studies, *in vitro* studies, animal studies, their own experience and medically accepted knowledge, published, peer-reviewed articles and studies, along with AER data. Indeed, these are all the same data relied upon by the FDA's Office of Surveillance and Epidemiology ("OSE") when analyzing the relative risk of the various GBCAs.

The record shows that the FDA convened a meeting of its Cardiovascular and Renal Drugs and Drug Safety and Risk Management Advisory Committee in December 2009 to review data pertaining to the development of NSF in association with GBCAs. (See Doc #: 708-6, at 5.) The FDA sought the Committee's advice regarding measures to minimize this risk. (Id.) The FDA was particularly interested in differential risk considerations among the various GBCAs and any other considerations that should be addressed in labeling or other risk-reduction methods. (Id.) In preparation for that meeting, the FDA asked its Office of Surveillance and Epidemiology ("OSE") to review the evidence and reach a conclusion. The evidence reviewed by the OSE included AERs, sales data, physicochemical data and the literature.[4] Based on its review of <u>all</u> the evidence, which review included the limitations of each type of evidence, the OSE concluded:

> The different lines of evidence cited in this review all have limitations, some of which are substantial. These limitations are described in the review. However, based on the preponderance of the evidence in this review, it is OSE's judgment

[4]The section on the OSE's AER review is located at Doc #: No. 708 -1, at 6-15.

> that GBCAs are associated with varying risk of NSF. Of the five GBCAs considered, the highest risk is associated with Omniscan, Magnevist, and Optimark while the lowest risk is associated with ProHance and MultiHance.
>
> While this document represents OSE's current thinking on the subject, we note that the field of NSF research is rapidly evolving; as such, additional information may become available that will merit consideration at the upcoming Advisory Committee meeting.

(Doc #: 708-1, at 43.)

The Court has reviewed the cases cited by GEHC, which are distinguishable for the reasons cited by Plaintiffs in their opposition brief. (See Doc #: 708, at 13-15.) The Court has reviewed the opinions of the four experts and their reasons for opining that Omniscan has a higher risk of causing NSF than the other GBCAs on the market. AERs form only one of numerous bases for their opinions. The same bases and methodology have been used by the OSE in reviewing the relative risk of GBCAs, supporting the reliability of Plaintiffs' expert opinions. Indeed, GEHC's expert, Dr. Newton, recognizes that "Omniscan appears to be associated with a significant percentage of NSF cases" – although he questions the basis for it. (See Doc #: 736, at 34.)

The Court will not allow any expert to opine that Omniscan has a higher risk of causing NSF than other GBCAs based on AERs alone. And GEHC is free to cross-examine Plaintiffs' experts regarding the flaws in adverse event reporting.

3. The Use of GEHC's Internal Documents / Suzanne Parisian, M.D.

GEHC asks the Court to exclude part or all of the testimony of four of Plaintiffs' experts (specifically, Doctors Parisian, Blume, Plunkett and Semelka) to the extent they reference and depend upon GEHC's internal documents, and are narrative, speculative, conclusory or

rhetorical. Both parties cite *In re Fosamax Prod. Liab. Liti*., 645 F.Supp.2d 164 (S.D.N.Y. 2009) for guidance on this issue.

Fosamax was a product liability MDL in which plaintiffs alleged that they had developed osteonecrosis of the jaws ("ONJ") after taking Fosamax in IV and oral form. Plaintiffs alleged strict liability and negligence claims against Merck & Co., Inc., the manufacturer of Fosamax, predicated primarily on a failure-to-warn theory. The plaintiffs had the burden of proving that Fosamax was capable of causing ONJ and that Merck should have known of this risk and provided a warning. In *Fosamax*, the district court specifically reviewed and addressed Merck's challenges to the expert testimony of Dr. Suzanne Parisian. *See generally*, *Fosamax*, 645 F.Supp.2d at 189-192. The Court will use GEHC's challenge to Dr. Parisian's testimony as an example in addressing this issue (i.e., the use of GEHC's internal documents by Plaintiffs' experts).

By way of background, Suzanne Parisian, M.D., is a board-certified anatomic and clinical pathologist with a Masters Degree in Biology. She has been a general practitioner and President of Mountain Emergency Physicians. From 1991 to 1995, she served as a Commissioned Officer in the United States Public Health Service, achieving the rank of Lt. Commander. During this time, she was assigned to the Center for Devices and Radiological Health at the FDA where she served as a Medical Officer. As an FDA Medical Officer, she provided regulatory support to both FDA's Office of Compliance and Office of Device Evaluation from 1991 to 1993, where her responsibilities included health hazard and health risk assessment (she presided over 162 health risk assessments), Safety Alerts and physician and layperson communications, review of AERs and medical literature, and review of product labeling, promotions, advertising and

corporate records.[5] In 1993, Dr. Parisian was one of two Medical Officers in the Office of Device Evaluation, where she was primarily responsible for pre-marketing evaluation of new product applications and clinical trials that support safety and effectiveness leading to FDA approval, and where she conducted 100 health risk assessments. Regarding post-market surveillance, Dr. Parisian participated in 1993 with the FDA's Office of Compliance and General Counsel in the review of manufacturing records, product labeling, product complaints and AERs. She also trained new medical officers and scientific reviewers in application, clinical trial and labeling evaluation. In 1995, Dr. Parisian founded a consulting firm where she consults on topics regarding the FDA, pre-market clearance, design of clinical trials, product labeling, etc. In 1997, the FDA invited her to participate in a panel of experts convened to comment on changes proposed in requirements for medical device labeling. She has written a book entitled "FDA Inside and Out."

Turning back to *Fosamax*, Merck argued that Dr. Parisian was not qualified to offer the opinions in her report. The *Fosamax* court noted that Dr. Parisian had provided a report divided

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[5]In her report, Dr. Parisian provided an example of a drug safety issue that she helped identify and manage for the FDA. (*See generally* Doc #: 677-4, at ¶ 4.) The FDA had received AERs in its MedWatch databases of serious adverse events and deaths occurring in renal patients taking ACE Inhibitors ("ACEIs') for regulation of blood pressure. The renal patients shared a common precipitating event – blood exposure to certain types of hemodialyzer membranes during a dialysis session shortly after taking a dose of an ACEI. There had been relatively little safety information about the drugs, which had been approved in the 1980s, and none regarding hemodialysis safety. As the only FDA medical officer involved in the safety issue, she reviewed both drug and device AERs and the medical literature, performed a health risk assessment and made a clinical recommendation to the FDA to a reasonable degree of medical certainty. Notice had to go to the healthcare providers regarding the ACEI membrane association. FDA and the manufacturers needed help to identify the etiology of the reaction. Physicians needed recommendations as to emergency treatment. She worked with an FDA epidemiologist to design an epidemiologic study to quickly obtain data for the FDA and involved pharmaceutical and device industries. As a result, she helped draft current ACEI class drug warnings about the risks of membrane surface exposure and anaphylactoid reaction.

into four sections including the general role of the FDA and the duties and obligations of prescription drug manufacturers, the FDA's approval of Merck's New Drug Application for Fosamax, Merck's interactions with the FDA in reporting and investigating ONJ, and Merck's communication of ONJ risks to health care professionals and patients. The court noted that, at the beginning of each section, Dr. Parisian expressed a number of opinions as to the ways in which Merck's conduct failed to measure up to standards. The sections extensively summarized or quoted the record evidence that provided the basis for her opinions. (The organization of Dr. Parisian's expert report here is the same as in *Fosamax*.)

Merck argued that Dr. Parisian lacked the expertise to opine on FDA regulations for pharmaceutical drugs, on Merck's duty of care as a pharmaceutical company, and on the labeling or promotion of Fosamax. Merck pointed out that Dr. Parisian worked for the FDA less than five years and claimed that her experience was confined to devices, not drugs. Merck argued that Dr. Parisian was unqualified to speak about medical issues such as osteoporosis because she did not treat patients and had never performed research in that area. The PSC pointed out that Dr. Parisian gained expertise in various aspects of the regulatory process, including health risk assessment, product labeling and promotion, pre-marketing evaluation of product applications and clinical data, and post-marketing surveillance and compliance. Further, the FDA relied on Dr. Parisian to interpret the food and drug laws on medical devices, to train other employees, and to serve as the official agency representative at medical meetings and seminars. The PSC noted that Dr. Parisian's projects involved both devices and drugs.

The *Fosamax* court first determined that Dr. Parisian was qualified, based on her experience as a Medical Officer at the FDA, to offer testimony about regulatory requirements

relating to the development, testing, marketing and post-marketing surveillance of prescription drugs (or pharmacovigilance). The court noted that, in her report and at a *Daubert* hearing, Dr. Parisian demonstrated specialized knowledge about the standards applicable to drug manufacturers. The court further found that Dr. Parisian had drawn conclusions about Merck's conduct based on her review of pertinent portions of the regulatory filings and Merck's internal company documents, that she applied the methodology she had applied as an FDA Medical Officer, and noted that Merck's regulatory experts had followed the same methodology to prepare their reports. The court denied Merck's motion to the extent it sought to preclude Dr. Parisian from testifying about general FDA regulatory requirements and procedures and from offering an opinion as to Merck's compliance therewith. The court, however, granted Merck's motion to the extent it sought to preclude Dr. Parisian from offering a narrative history of Fosamax – noting that, to the extent such evidence was admissible, it should be presented to the jury directly. The court noted that Dr. Parisian's commentary on any documents and exhibits in evidence would be limited to explaining the regulatory context in which they were created, defining any complex or specialized terminology, or drawing inferences that would not be apparent without the benefit of experience or specialized knowledge. The court granted Merck's motion to the extent it sought to preclude Dr. Parisian from testifying as to the knowledge, motivations, intent, state of mind or purposes of Merck, its employees, and the FDA.

Fosamax is similar to this MDL, where the Plaintiffs must prove that Omniscan is capable of causing NSF and that GEHC should have known of this risk and provided timely and adequate warning. Relevant to these issues is whether GEHC conducted adequate testing and provided adequate information regarding the risks of GBCAs and Omniscan to the FDA during

the approval process; whether GEHC performed adequate surveillance of Omniscan post-approval; and whether GEHC provided adequate and timely information and warnings regarding the risks associated with Omniscan administration to renally impaired persons to the FDA, healthcare providers and the public, via labeling or otherwise.

With regard to labeling specifically, the Supreme Court in *Wyeth v. Levine*, 129 S.Ct. 1187 (2009), made clear:

> [T]hrough many amendments to the FDCA and to FDA regulations, it has remained a central premise of federal drug regulation that the manufacturer bears responsibility for the content of its label at all times. It is charged both with crafting an adequate label and with ensuring that its warnings remain adequate as long as the drug is on the market. *See, e.g.*, 21 CFR § 201.80(e) (requiring a manufacturer to revise its label "to include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug"); § 314.80(b) (placing responsibility for postmarketing surveillance on the manufacturer); 73 Fed.Reg. 49605 ("Manufacturers continue to have a responsibility under Federal law . . . to maintain their labeling and update the labeling with new safety information").
>
> Indeed, prior to 2007, the FDA lacked the authority to order manufacturers to revise their labels. *See* 121 Stat. 924-926. When Congress granted the FDA this authority, it reaffirmed the manufacturer's obligations and referred specifically to the CBE regulation, which both reflects the manufacturer's ultimate responsibility for its label and provides a mechanism for adding safety information to the label prior to FDA approval. *See id.*, at 925-926 (stating that a manufacturer retains the responsibility "to maintain its label in accordance with existing requirements, including subpart B of part 201 and sections 314.70 and 601.12 of title 21, Code of Federal Regulations (or any successor regulations)" (emphasis added)).

Id. at 1197-1198. With this, the *Wyeth* Court concluded that, when the risk of developing gangrene from IV-push injection of Phenergan became apparent, "Wyeth had a duty to provide a warning that adequately described that risk, and the CBE regulation permitted it to provide such a warning before receiving the FDA's approval." *Id*. at 1198.

This Court finds, as did the *Fosamax* court, that Dr. Parisian is a regulatory expert who is qualified, based on her experience as a Medical Officer at the FDA and related experience thereafter, to offer testimony about regulatory requirements relating to the development, testing, marketing and post-marketing surveillance of prescription drugs. At trial, Dr. Parisian may offer an opinion as to GEHC's compliance therewith based only on the documents and exhibits in evidence (which necessarily includes GEHC internal documents and regulatory filings). As in *Fosamax*, Dr. Parisian may not provide a narrative history of Omniscan, which must be presented through direct evidence. Nor may she testify as to the knowledge, motivations, intent or purposes of GEHC, its employees, and the FDA.

Based on the analysis of this particular issue with regard to Dr. Parisian alone, the Court concludes that Plaintiffs' experts may offer opinion testimony based on GEHC internal documents, studies and regulatory filings to the extent it is relevant to the issues in this case and the experts are qualified to offer opinions on those issues.

The Court will next address GEHC's challenges to the individual experts.

4. GEHC's Challenge to Individual Experts

a. Laura M. Plunkett, Ph.D., DABT

Laura M. Plunkett, Ph.D., DABT, received a Ph.D. in pharmacology from the University of Georgia, College of Pharmacy, in 1984. She served as a Pharmacology Research Associate Training Fellow at the National Institute of General Medical Sciences until 1986. Thereafter, Dr. Plunkett joined the faculty at the College of Medicine, University of Arkansas for Medical Sciences, as an Assistant Professor of Pharmacology and Toxicology. In 1989, Dr. Plunkett began work as a consultant at Environ Corporation, where she served clients in the areas of

pharmacology, toxicology, risk assessment and regulatory strategy, and focused specifically on issues involving products or processes regulated by the FDA. In 1993, Dr. Plunkett became board-certified as a Diplomate of the American Board of Toxicology. She left Environ in 1997 and continued her consulting career as owner of Plunkett & Associates from 1997 to 2001, then as President of Integrative Biostrategies LLC from 2001 to the present. In her drug development consulting work, she has assisted clients with regulatory issues and strategies for their products, including designing preclinical and clinical studies for efficacy and safety. Many of her consulting projects have involved a human risk assessment component. She has authored or co-authored approximately thirty scientific publications and three book chapters. In addition, Squibb retained Dr. Plunkett as a pharmaceutical consultant in the early 1990s to provide a risk assessment on the relative safety and stability of GBCAs.

Dr. Plunkett opines that Omniscan causes NSF, Omniscan is the least stable GBCA which poses the greatest risk to patients to whom it is administered, and Omniscan should have been contraindicated in patients with significant renal impairment as early as 1996. She based her opinions on all types of data available during the development and post-marketing of Omniscan including *in vitro* assessments of stability, *in vivo* data on biodistribution in animals, pharmacokinetic studies in patients with renal impairment, and internal GEHC studies. It is noteworthy that, with regard to previously discussed experts, GEHC challenges their qualification to opine on NSF causation and instability because they are not toxicologists and pharmacologists.

The Court finds that Dr. Plunkett's background in pharmacology with expertise in pharmacokinetics, toxicology, risk assessment generally and her prior work on GBCA risk

assessment specifically, more than adequately qualifies her to opine on NSF causation, the stability of Omniscan, and the free gadolinium theory. She is qualified to interpret the results of any of GEHC's toxicology, pharmacology or pharmacokinetic studies and to opine on the significance of the results. The Court finds that Dr. Plunkett has amply established the methodology underlying her opinions. While the Court will not allow Dr. Plunkett to opine broadly that Omniscan should have been contraindicated in patients with significant renal impairment as early as 1996, the Court finds that Dr. Plunkett may opine, based on the facts adduced at trial (including GEHC internal studies, documents and regulatory filings), on the accuracy and adequacy of the toxicology, pharmacology and pharmacokinetics data appearing on the Omniscan label at the time the scan(s) in question were administered. *See also In Gerber et al. v. Bayer Corp. et al.*, Case No. CGC-07-468577 (Super. Ct. CA) (tentatively qualifying Dr. Plunkett to testify on Magnevist labeling).

b. Cheryl Blume, Ph.D.

Cheryl Blume received her Ph.D. in Pharmacology and Toxicology from the West Virginia University Medical Center where she was the recipient of a pre-doctoral fellowship from the National Institute of Health. She is the president of Pharmaceutical Development Group, Inc., a consulting firm specializing in pharmaceutical development and registration activities. Over a twenty-year period, she has held executive positions in pharmaceutical companies, including Executive Vice President of Scientific Affairs for Mylan Laboratories, Inc. and Executive Vice President and Chief Operations Officer for Somerset Pharmaceuticals, Inc. She has designed, executed and interpreted preclinical and clinical studies associated with pharmaceutical product development and has secured pre-market approval for over 100

prescription drugs. She has directed all phases of interaction with the FDA relating to the prosecution of New Drug Applications. She has directed the collection and evaluation of AERs, prepared amplified product labeling and disseminated updated product information to healthcare providers and consumers.

Based on Dr. Blume's education in pharmacology and toxicology and her background in drug development and safety surveillance, Plaintiffs asked Dr. Blume to evaluate the scientific and regulatory actions undertaken by GEHC in the design, development, marketing and post-marketing surveillance of Omniscan. Dr. Blume approached the assignment from the perspective of a pharmaceutical industry employee. She independently researched (1) safety issues with contrast agents generally and concerning NSF, (2) the scientific literature concerning non-clinical and clinical studies relating to GBCAs, (3) the regulatory communications and interactions concerning GBCAs, (4) the FDA's database regarding pharmacovigilance, labeling and related interactions with GEHC. Dr. Blume reviewed voluminous materials reflecting GEHC's internal studies, communications, and marketing materials relating to Omniscan. Dr. Blume explains that this is the same methodology she employed over the past 30 years performing drug development and pharmacovigilance assignments. *See also Wright v. Am. Home Prod. Corp.*, 557 F.Supp.2d 1032, 1037-38 (W.D. Mo. 2008) (holding that Dr. Blume was qualified to testify about the risks and benefits of a diet drug as it related to pharmaceutical industry practice and whether Wyeth followed or failed to follow those standards prior to marketing and distribution of the drug).

As with Dr. Plunkett, the Court finds that Dr. Blume's background in pharmacology, toxicology and risk assessment qualify her to opine on NSF causation, the stability of Omniscan,

and the free gadolinium theory. Dr. Blume is also qualified to interpret the results of any of GEHC's toxicology, pharmacology or pharmacokinetic studies and to opine on the significance of the results. The Court finds that Dr. Blume may testify, based on the facts adduced at trial (including GEHC internal studies and documents), on the accuracy and adequacy of the toxicology, pharmacology and pharmacokinetics data appearing on the Omniscan label at the time a given plaintiff was administered Omniscan.

GEHC does not challenge Dr. Blume's qualification to testify as a regulatory expert on FDA regulations and standards. GEHC does argue, however, that Dr. Blume's opinion that four adverse event reports constitute a safety signal is inadmissible. The Court disagrees.

In the *Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment* (Mar. 2005), the FDA generally describes the role of pharmacovigilance in risk management as follows:

> Risk assessment during product development should be conducted in a thorough and rigorous manner; however, it is impossible to identify all safety concerns during clinical trials. Once a product is marketed, there is generally a large increase in the number of patients exposed, including those with co-morbid conditions and those being treated with concomitant medical products. Therefore, postmarketing safety data collection and risk assessment based on observational data are critical for evaluating and characterizing a product's risk profile and for making informed decisions on risk minimization.
>
> This guidance document focuses on pharmacovigilance activities in the post-approval period. This guidance uses the term *pharmacovigilance* to mean all scientific and data gathering activities relating to the detection, assessment, and understanding of adverse events. This includes the use of pharmacoepidemiologic studies. These activities are undertaken with the goal of identifying adverse events and understanding, to the extent possible, their nature, frequency, and potential risk factors.
>
> Pharmacovigilance principally involves the identification and evaluation of safety signals. In this guidance document, *safety signal* refers to a concern about an excess of adverse events compared to what would be expected to be associated

> with a product's use. Signals can arise from postmarketing data and other sources, such as preclinical data and events associated with other products in the same pharmacologic class. It is possible that even a single well-documented case report can be viewed as a signal, particularly if the report describes a positive rechallenge or if the event is extremely rare in the absence of drug use. Signals generally indicate the need for further investigation, which may or may not lead to the conclusion that the product caused the event. After a signal is identified, it should be further assessed to determine whether it represents a potential safety risk and whether other action should be taken.

Id. at 3-4 (underlining added).

One federal court addressing Dr. Blume's ability to testify on adverse event reports as a safety signal has recognized the above-quoted standard and declined to exclude her testimony, stating that such challenges to her methodologies are better left to cross-examination. *See In re Viagra Prod. Liab. Liti.*, 658 F.Supp.2d 950, 961-62 (D. Minn. 2009). Even Hugo Flaten, M.D., GEHC's Vice President of Global Pharmacovigilance, acknowledges that one or more adverse event reports may constitute a safety signal. (Doc #: 751-5, at 3-4.) The Court notes that the referenced adverse event reports form only some of numerous data upon which Dr. Blume relies to form her opinions about GEHC's compliance with FDA standards.

GEHC argues that the Court should not permit Dr. Blume to opine about foreign regulatory events and foreign law. The Court finds that Dr. Blume is not qualified to testify as an expert on foreign regulatory law. That said, direct evidence of foreign regulatory events that bear upon GEHC's knowledge of Omniscan's safety risks and its post-marketing surveillance efforts may be admissible and relied upon by Dr. Blume in forming her opinions regarding GEHC's compliance with FDA standards.

c. Derek M. Fine, M.D.

Derek M. Fine, M.D. is an Associate Professor of Medicine of Nephrology at Johns Hopkins University School of Medicine. Dr. Fine is on the faculty in the Division of Nephrology where he has served continuously since 1999 as an instructor, Assistant Chief of Service and Assistant Professor of Medicine. He is a board-certified clinician, lecturer, peer-reviewed author and investigator of various research projects, including a retrospective review of 33 NSF cases at Johns Hopkins between the years 2003 and 2008. His clinical practice, research and publications have focused on NSF, the treatment and prevention of the disease, its pathogenesis, the role of GBCAs in NSF, and its incidence. Based on his background and expertise, he co-authored and implemented policies and procedures for the safe administration of GBCAs in renal patients at Johns Hopkins in January 2007. With regard to GBCAs administered to persons with acute renal failure, the policy specifically requires radiologists to determine that gadolinium is essential for a diagnosis and there is no available alternative test available; the radiologist must consult a nephrologist; the patient must sign a consent form that states that NSF is a risk of GBCA use that can cause permanent disability and death; a contrast agent other than Omniscan (specifically, MultiHance) is preferred and may have a lower risk of NSF. The aim of the policy was to reduce the incidence of NSF, it did in fact reduce NSF incidence, and Fine published an article observing, among other things, "Besides the previously reported epidemiologic considerations of NSF associations, the success of such a policy in the reduction of NSF due to GBCA exposure strengthens the belief that there is a causal relationship between GBCA and NSF." *Nephrogenic Systemic Fibrosis: Incidence, Associations, and Effect of Risk Factor Assessment – Report of 33 Cases*, Perez-Rodriguez, J., Lai, S., Ehst, B., Fine, D.

Bluemke, D., 250 RADIOLOGY 367 (Feb. 2, 2009); *see also Nephrogenic Systemic Fibrosis: What the Hospitalist Needs to Know*, Fine, D., Perazella, M., 5 JOURNAL OF HOSPITAL MEDICINE (Jan. 1, 2010). In summary, Dr. Fine is a clinician who has treated patients with NSF and routinely orders diagnostic studies, he is an academic who has researched, lectured and published peer-reviewed articles on GBCAs and their causal relationship to NSF, and he co-authored a policy at a renowned hospital designed to restrict GBCA use in renally impaired patients with the goal of reducing NSF incidence.

Dr. Fine offers numerous opinions including:

•NSF is caused by GBCAs in patients with renal failure;

•renal failure allows gadolinium to accumulate in the body due to poor clearance;

•dialysis is not sufficiently effective to remove all GBCAs from an exposed patient;

•the most plausible explanation for development of NSF is the accumulation of free gadolinium, through transmetalation, in affected tissues;

•Omniscan, due to its non-ionic linear structure, is most likely to cause NSF due to its inherent instability compared with other GBCAs;

•the macrocyclic GBCAs are least likely to cause NSF;

•accurate and complete information regarding toxicity of Omniscan was not appropriately shared with the scientific and medical community;

•had nephrologists known about the inherent toxicity of these agents, they would have sought safer alternatives for at-risk patients;

•with the identification of GBCAs as a cause of NSF and the institution of protocols to avoid NSF, there has been a rapid decrease in NSF occurrence.

Dr. Fine also offers an explanation for why there are five reported cases where there is no evidence of GBCA administration.

GEHC concedes that Dr. Fine is qualified to offer (1) general nephrology opinions, and (2) opinions about his own interpretation of GEHC's renal studies. It objects, however, to Dr. Fine's opinions that:

> •Omniscan is unstable, and releases "free" gadolinium when administered to renally impaired patients, causing NSF, and
>
> •GEHC should have provided different warnings to the medical community about the adverse effects associated with Omniscan in the renally impaired patient population, which would have changed doctors' treatment decisions.

Ex. F, at 1-2.

GEHC argues that Dr. Fine should not be able to opine about Omniscan's stability or the mechanism by which he believes Omniscan causes NSF because he has no training or experience with animal studies, radiology, chelate chemistry, toxicology, the toxicity of gadolinium chelates, or mass spectrometry. GEHC argues that Dr. Fine should not be able to opine about the regulation of pharmaceutical products, labeling requirements or product warnings because he has no expertise with respect to the FDA or its regulations. Even if Dr. Fine had the required expertise, GEHC argues that his opinions are not the product of sound methodology on NSF causation because he did nothing more than review and regurgitate select literature about which he has no underlying knowledge or experience. He did even less work to reach his opinions on warnings, even though the labeling of prescription drugs like Omniscan is regulated by the FDA – and he did not read the regulatory file, GEHC/FDA communications or, prior to 2006, the label or package insert for Omniscan.

Dr. Fine is a nephrologist who has conducted his own research on NSF, reflected in peer-reviewed articles, and had to review the relevant literature regarding GBCA stability and risks in renal patients in order to draft and implement policies and procedures at Johns Hopkins Hospital

regarding those risks. Dr. Fine concluded, based on his knowledge, experience, research, and review of the literature that NSF is a preventable disease, and his policies led to a significant reduction in NSF cases at Johns Hopkins. The Court finds that Dr. Fine does not have to have to be a toxicologist, chemist, radiologist and/or have personally conducted animal studies to be able read, understand, interpret and rely upon the published literature of those experts on the science related to his field of expertise in order to offer an opinion on the cause of NSF, the instability of Omniscan, or the free gadolinium theory. *See, e.g., Loeffel Steel Prod., Inc. v. Delta Brands, Inc.*, 387 F.Supp.2d 794 (N.D. Ill. 2005); *see also Jahn*, 233 F.3d at 388 ("Experts are permitted a wide latitude in their opinions, including those not based on firsthand knowledge, so long as the expert's opinion has a reliable basis in the knowledge and experience of the discipline.") (quoting *Daubert*, 509 U.S. at 592). Indeed, it is vital for physicians like Dr. Fine to keep up with the literature on subjects that bear on their field of expertise in order to ensure they are properly and safely caring for their patients.

The Court agrees with GEHC that Dr. Fine is not a regulatory expert who has the expertise to opine on FDA regulations and the regulatory process, or whether GEHC complied with those regulations or process. Nonetheless, the question becomes whether Dr. Fine, based on his background as a nephrologist and his review of GEHC renal studies, internal documents and the published literature at the time, may offer opinions about the adequacy of GEHC's warnings regarding the risks associated with Omniscan administration to renally impaired patients.

This situation is similar to *In re Diet Drugs*, No. MDL 1203, 2000 WL 876900 (E.D.Pa. Jun. 20, 2000). At issue in that case was whether the defendant pharmaceutical company

adequately warned physicians and patients about the risks associated with their diet drugs. There as here, the pharmaceutical company did not challenge the qualifications of the doctors to opine on their respective disciplines. While the court did not permit the doctors to testify as to regulatory requirements for labels or warnings, the court did allow the experts to offer opinions concerning medical facts and science regarding the risks of the drugs in question, and to compare that knowledge with what was provided in the drug label and warning.

> In other words, Drs. Rubin and Avorn are qualified to render an opinion as to the labels' completeness, accuracy, and – it follows from that – the extent to which any inaccuracies or omissions could either deprive a reader or mislead a reader of what the risks and benefits of the diet drugs in issue are or were at the time the labeling was published.

2000 WL 876900, at *10.

Here, GEHC agrees that Dr. Fine is a nephrologist who is qualified to interpret, and offer opinions about, GEHC's renal studies. The Court thus finds that Dr. Fine may offer opinions on whether Omniscan's labeling information or Dear Doctor letters contained adequate information, or inaccuracies or omissions that could deprive or mislead physicians like himself who treat renally impaired patients about the risks associated with Omniscan administration.

d. Derrick J. Todd, M.D., Ph.D.

Derrick J. Todd, M.D., Ph.D. received his undergraduate degree in molecular biophysics and biochemistry from Yale University in 1995. He received both his M.D. from the University of Massachusetts Medical School, and his Ph.D. in biomedical sciences immunology from University of Massachusetts Graduate School of Biomedical Sciences, in 2003. He completed his residency in internal medicine in 2005. He is board-certified in both internal medicine (since 2006) and rheumatology (since 2008). He is presently an instructor in rheumatology at the

Brigham and Women's Hospital. Since 2003, Dr. Todd participated in NSF research under the mentorship of Dr. Jonathan Kay of Massachusetts General Hospital. The purpose of the study was to establish the prevalence of NSF and associated risk factors in hemodialysis patients.

Dr. Todd's study revealed that exposure to GBCAs in hemodialysis patients was associated with an increased risk of developing skin changes characteristic of NSF compared with non-exposed patients, and concluded that exposure to GBCAs was a significant risk factor for the development of NSF. He published his study methodology, data and findings in 2007 in an article entitled *Cutaneous Changes of Nephrogenic Systemic Fibrosis: Predictor of Early Mortality and Association with Gadolinium Exposure*, 56:10 ARTHRITIS & RHEUMATOLOGY 3433-3441 (Oct. 2007). He has written at least two other articles based on his review of published reports and data regarding the association between GBCAs and NSF in renally impaired individuals. In one of the articles, he cites growing evidence that GBCAs are a trigger in the development of NSF, and proposes that a more appropriate name for NSF is GASF (short for gadolinium-associated systemic fibrosis). *See Nephrogenic Systemic Fibrosis: An Epidemic of Gadolinium Toxicity*, 10 CURRENT RHEUMATOLOGY REPORTS 195-204 (2008).

Dr. Todd opines on the epidemiology, clinical manifestations, etiology, and diagnosis of NSF. GEHC does not directly challenge Dr. Todd's qualifications as an expert witness in rheumatology capable of diagnosing NSF, but criticizes his opinions because Dr. Todd completed his medical training "only seven months ago" and he has not participated in the care, diagnosis or treatment of any patient with NSF; his only contact with NSF patients occurred while he was in training; and he is not an expert in radiology, gadolinium chemistry, nephrology or dermatopathology.

The Court has reviewed Dr. Todd's published study. *See generally Cutaneous Changes*, at 3433-3441. In order to conduct the study, Dr. Todd examined approximately 216 hemodialysis patients at 6 outpatient centers in the Boston metropolitan area. The study participants were examined for three skin changes characteristic of NSF (i.e., hyperpigmentation, hardening and tethering of the skin). Clinical evidence of NSF was defined as a patient having any 2 or all 3 skin findings on the extremities bilaterally. Patients were considered examination-negative if they had none or only 1 of the skin findings. There had to be agreement on NSF diagnosis between three clinicians who performed independent examinations. Of the 216 study participants, Dr. Todd diagnosed at least 30 hemodialysis patients with NSF. Skin biopsies were performed on 5 of the 30 clinically diagnosed NSF patients to confirm the researchers' methodology when diagnosing NSF. The research scientists intentionally limited their analysis for NSF to noninvasive skin examinations:

> so as to maximize the number of patients who would participate and to avoid the less than trivial infectious complications of a full-thickness (often lower extremity) skin biopsy, especially given that the patients in this study universally had renal failure and a high prevalence of skin fibrosis and diabetes mellitus, which are known risk factors for surgical wound infection and poor wound healing. By not requiring a skin biopsy, we were able to achieve a 94% participation rate and to minimize selection bias. Had consent to skin biopsy been required for study entry, those patients who were concerned that they had skin changes might have participated preferentially, thereby overestimating the prevalence of NSF. The paucity of available skin biopsy specimens highlights that NSF likely is underrecognized by many practicing physicians.

Id. at 3440.

GEHC apparently challenges Dr. Todd's NSF diagnoses on the basis that he diagnosed at least 25 of the 30 NSF patients without the benefit of actual skin biopsies. Plaintiffs argue that while a skin biopsy may confirm NSF in patients with ambiguous clinical presentations, it may

not be necessary or possible to perform in others. For instance, as noted above, where patients have unambiguous clinical presentations, performing a biopsy would subject them to unwarranted health risks. The Court finds that, for reasons explained by Plaintiffs at Doc #: 750, at 9-25, a biopsy is not the only means of diagnosing NSF. The Court concludes that Dr. Todd has sufficiently explained his reason for not performing biopsies on 25 of 30 NSF study participants, his study has a discernible rate of error, and GEHC is free to cross examine Dr. Todd on the method he used to diagnose NSF in his study.

GEHC also challenges Dr. Todd's opinions on the mechanism by which GBCAs cause NSF. It argues that, because his formal training is limited to internal medicine and rheumatology, he is not qualified to base his opinions on the work of experts in related fields such as radiology, nephrology, dermatopathology, gadolinium chemistry, toxicology or mass spectometry. The Court concludes that Dr. Todd does not need to be, at one and the same time, an expert in radiology, nephrology, dermatopathology, gadolinium chemistry, toxicology or mass spectometry to be able to read, understand, interpret and rely upon the published literature of those experts on the science related to his field of expertise and the areas of his personal research. Indeed, in the alleged absence of information on the risk of NSF to renal patients with GBCA exposure, Dr. Todd and others chose to conduct a study to determine the prevalence of a then-emerging disease entity in renal patients called nephrogenic fibrosing dermopathy (NFD), now called NSF, and associated risk factors. His continued review of the literature has resulted in his opinion that any preliminary model that attempts to explain the pathogenesis of GASF must include GBCA exposure and renal dysfunction and that, until proven otherwise, each case

of NSF is the direct result of an exposure to GBCAs. Again, GEHC is free to challenge his opinions and methodology on cross examination.

e. Jerrold L. Abraham, M.D.

Jerrold L. Abraham, M.D. is a board-certified pathologist, specializing in environmental and occupational pathology at the State University of New York, Syracuse. Dr. Abraham has published numerous articles predating his work as Plaintiffs' generic expert in this MDL, reflecting his research identifying gadolinium in the tissues of NSF/NFD patients, finding that gadolinium is not deposited in the skin of patients with normal renal function after exposure to GBCAs, and the likely causative mechanism of NSF.

GEHC asks the Court to limit Dr. Abraham's expertise to matters of pathology, construing the scope of a pathologist's work narrowly, as defined in Taber's *Cyclopedic Medical Dictionary* 1606 (20th ed. 2005) (i.e., as one who is trained to examine tissues, cells and specimens of body fluids for evidence of disease). GEHC asks the Court to further limit Dr. Abraham's testimony to apparently exclude skin pathology, since he is not a dermatopathologist.

Plaintiffs argue that the definition of a pathologist should be construed more broadly, as defined in *Black's Law Dictionary* (9th ed.) (i.e., one trained in the scientific study of disease, its causes, development and consequences), *Dorland's Medical Dictionary* (29th ed.) (i.e., one who studies the structural and functional changes in tissues and organs of the body which cause or are caused by disease), and WordNet Dictionary at Princeton University (i.e., one who studies the causes and nature and effects of diseases).

The Court has confirmed both parties' definitions of pathology and has also reviewed other definitions of pathology, including the *Medline Plus Medical Dictionary* and *Merriam*

Webster's Collegiate Dictionary (10th Ed.) definition (i.e., the study of the essential nature of diseases and especially of the structural and functional changes produced by them), and the *Oxford English Dictionary* definition (i.e., the study of disease; the branch of science that deals with the causes and nature of diseases and abnormal anatomical and physiological conditions). In reviewing this question, the Court has also reviewed several noted medical school websites which define pathology as the study and/or basic understanding of human disease, and describe the study of pathology as encompassing numerous disciplines, including microbiology, chemistry, hematology, cytology and toxicology.[6] The Court finds that Taber's *Cyclopedic Medical Dictionary* definition of pathology, as espoused by GEHC, is significantly narrower than every other definition of pathology the Court can find, that it does not account for what appears to be a rather broad field of study and expertise, and it is certainly too narrow to describe the work of research pathologists such as Dr. Abraham.

Given Dr. Abraham's 30-year background in pathology and his extensive and non-litigation related research on NSF and its etiology all of which has been published and peer-reviewed, the Court denies GEHC's request to preclude Dr. Abraham from testifying regarding the cause of NSF. Although the exact cause of NSF is unknown, Dr. Abraham's work on this issue qualifies him to offer an opinion on the pathogenesis of the disease. Moreover, Dr. Abraham does not have to be a dermatopathologist to diagnose or study skin disorders, and the record shows that Dr. Abraham's research on skin disorders and their etiology has been widely published and peer-reviewed in the leading pathology and dermatopathology journals.

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[6]See, e.g., University of Maryland Medical Center Overview of Pathology, http://www.umm.edu/pathology-info/overview.htm; Harvard Medical School Pathology, http://pathology.hms.hardvard.edu/faculty-research.htm; Stanford School of Medicine Department of Pathology, http://pathology.stanford.edu.

f. Joachim H. Ix, M.D., M.A.S.

Defendants seek to exclude the testimony of Joachim H. Ix, M.D., M.A.S., whom Plaintiffs intend to call as an expert on the issue of general causation. Dr. Ix is Assistant Professor of Medicine in the Division of Nephrology, Department of Medicine and Division of Preventive Medicine, Department of Family and Preventive Medicine at the University of California at San Diego. Dr. Ix completed his M.D. in 2000, a combined fellowship in clinical and research nephrology in 2006 and a Master's Degree in Advanced Studies in Epidemiology and Biostatistics in 2007.

Based on a meta-analysis of five studies selected from an original group of thirty-seven, Dr. Ix has concluded that GBCAs are causally linked with NSF among patients with moderate to severe kidney disease. Defendants argue that Dr. Ix's opinion, generated solely for litigation, is unreliable because Dr. Ix: (1) has never researched or published a study on GBCAs or NSF; (2) did not use protocols he normally uses in his own independent research; and (3) did not apply reliable methods and principles.

Because Dr. Ix's opinions were developed solely for litigation, his testimony should be examined with greater scrutiny than if his opinions had been developed independent of this litigation. *See Johnson v. Manitowoc Boom Trucks, Inc.*, 484 F.3d 426, 435 (6th Cir. 2007). Even applying greater scrutiny, the Court finds that Dr. Ix's testimony is admissible.

While Dr. Ix has not published any studies on GBCAs or NSF, as a nephrologist who devotes approximately 75% of his time to epidemiologic research, Dr. Ix possesses the necessary expertise to conduct a meta-analysis of studies involving NSF, a kidney disease with systemic effects. Similarly, because of his background, Dr. Ix is capable of applying the Bradford Hill

criteria both parties acknowledge are widely used in assessing whether exposure causes disease. That Dr. Ix has not published any studies using the Bradford Hill criteria is of no consequence. The criteria – (1) strength; (2) consistency; (3) specificity; (4) temporality; (5) biological gradient; (6) plausibility; (7) coherent; (8) experimental evidence; and (9) analogy (A. Bradford Hill. *The Environment and Disease: Association or Causation*. 58 PROCEEDINGS OF THE ROYAL SOCIETY OF MEDICINE 295-300) – can reliably be applied by someone with the epidemiological expertise of Dr. Ix. Moreover, as Plaintiffs assert, several peer-reviewed meta-studies have been published by authors applying the Bradford Hill criteria for the first time.

Furthermore, whether Dr. Ix followed procedures he uses in his own independent research is irrelevant. The critical issue is whether Dr. Ix's testimony is reliable, based upon factors such as whether sufficient facts or data were considered, whether the testimony is the product of reliable principles and methods, and whether these principles and methods have been reliably applied to the facts of this case. *See* FED. R. EVID. 702; *In re: Scrap Metal Antitrust Liti.*, 527 F.3d 517, 528-29 (6th Cir. 2008). That is, even if Dr. Ix utilized different procedures than he normally employs, these procedures may still be reliable under Rule 702.

The previously-used procedures GEHC takes issue with are: (1) the failure to consult with experts about which studies to include; (2) the failure to independently verify which studies to select for the meta-analysis; (3) using retrospective and non-randomized studies; (4) relying on studies with wide confidence intervals; and (5) using a "more likely than not" standard for causation that would not pass scientific scrutiny.

First, Dr. Ix need not consult with other experts as to which studies to include in his meta-analysis because he has the expertise to make this determination on his own. Dr. Ix

consulted with experts in his previous meta-studies because he had not completed his nephrology fellowship and sought the assistance of others more experienced in the field. However, Dr. Ix has now been an assistant professor of nephrology for four years and is capable of independently selecting which studies to include.

Similarly, Dr. Ix does not need to utilize another expert to separately verify which studies to select for meta-analysis. Dr. Ix did not ask another expert to verify which studies to use so that his own expert opinion would not be influenced by another expert. While independent verification might ensure that the most appropriate studies were selected, the introduction of the influence of another researcher could just as easily undermine the credibility of Dr. Ix's testimony. Thus, as long as Dr. Ix utilized a thorough process for selecting his studies, as he did here, all reliability requirements have been satisfied.

Additionally, Dr. Ix should not be precluded from testifying because he used retrospective, non-randomized studies for his meta-analysis. Though controlled, double-blind studies are widely regarded as more reliable, for obvious ethical reasons the association between GBCA exposure and NSF cannot be tested in this manner.

Finally, the Court will not strike Dr. Ix's testimony because it is based upon studies with wide confidence intervals or because his opinions are based on a "more likely than not" standard. During cross-examination, Defendants are free to question Dr. Ix about the wide confidence intervals to pinpoint weaknesses in Dr. Ix's assessment. However, the Court is not persuaded that the wide confidence intervals render the methodology of the meta-study unreliable, particularly because a published peer-reviewed meta-analysis of GBCAs and NSF, cited frequently by both parties, featured a wider pooled confidence interval than Dr. Ix's analysis.

See R. Agarwal, *et al. Gadolinium-Based Contrast Agents and Nephrogenic Systemic Fibrosis: A Systematic Review and Meta-Analysis*. 24(3) NEPHROL. DIAL. TRANSPLANT. 856-63. (March 2009). Defendants also characterize Dr. Ix's statement that his opinions are based on a "more likely than not" standard for litigation as proof of failure to adhere to requisite scientific rigor. Defendants challenge the strength of the conclusion reached by Dr. Ix, i.e. how likely it is that GBCAs cause NSF, and not necessarily the specific methodology used by Dr. Ix. While Defendants are free to cross-examine Dr. Ix about this conclusion, without determining that Dr. Ix's methods were unreliable, the Court will not prevent Dr. Ix from offering his opinon on the likelihood of GBCAs causing NSF. Given how recently NSF was identified as a disease, the causation opinion of any expert is still just a theory.

Defendants contend that Dr. Ix's testimony should also be excluded because the methodology he utilized for his generic expert report, along with varying from his normal practice, was unreliable. Specifically, Defendants assert that: (1) Dr. Ix could not identify a source he relied upon to conduct his meta-analysis; (2) Dr. Ix imputed data into the study; (3) Dr. Ix failed to consider studies not reporting an association between GBCAs and NSF; and (4) Dr. Ix ignored confounding factors.

Though he did not identify a text he relied upon to carry out his meta-study, Dr. Ix's background in epidemiology, which includes two peer-reviewed meta-analysis publications, provides him the necessary expertise to conduct such an analysis.

Next, there is no dispute that Dr. Ix imputed data into his meta-analysis. However, as Defendants acknowledge, there are valid scientific reasons to impute data into a study. Here, Dr. Ix had a valid basis for imputing data. As explained by Plaintiffs, Dr. Ix's imputed data is an

acceptable technique for avoiding the calculation of an infinite odds ratio that does not accurately measure association.[7] Moreover, Dr. Ix chose the most conservative of the widely accepted approaches for imputing data.[8] Therefore, Dr. Ix's decision to impute data does not call into question the reliability of his meta-analysis.

The failure to consider studies not reporting an association between GBCAs and NSF also does not render Dr. Ix's meta-analysis unreliable. The purpose of Dr. Ix's meta-analysis was to study the strength of the association between an exposure (receiving GBCA) and an outcome (development of NSF). In order to properly do this, Dr. Ix necessarily needed to examine studies where the exposed group developed NSF.

Finally, the Court rejects Defendants' argument that Dr. Ix failed to consider confounding factors. Plaintiffs argued and Defendants did not dispute that, applying the Bradford Hill criteria, Dr. Ix calculated a pooled odds ratio of 11.46 for the five studies examined, which is higher than the 10 to 1 odds ratio of smoking and lung cancer that the *Reference Manual on Scientific Evidence* deemed to be "so high that it is extremely difficult to imagine any bias or confounding factor that may account for it." *Id*. at 376. Thus, from Dr. Ix's perspective, the odds ratio was so high that a confounding factor was improbable. Additionally,

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[7]As explained by Plaintiffs, the infinite odds ratio results from the presence of a zero in the denominator of an odds ratio calculation. In a cohort study featuring four scenarios (exposure with disease development, exposure without disease development, non-exposure with disease development and non-exposure without disease development), the denominator in an odds-ratio consists of exposure without disease development multiplied by non-exposure with disease development. Therefore, if there are zero cases of exposure without disease development or zero cases of non-exposure with disease development, the denominator value will be zero and the odds ratio will be infinite, regardless of the value of the numerator.

[8]This conservative approach was to add one only to the scenario with zero cases, as opposed to adding one-half or one to each scenario.

in his deposition, Dr. Ix acknowledged that the cofactors that have been suggested are difficult to confirm and therefore he did not try to specifically quantify them. (Doc #: 772-20, at 27.) This acknowledgement of cofactors is essentially equivalent to the Agarwal article's representation that "[t]here may have been unmeasured variables in the studies confounding the relationship between GBCAs and NSF," cited by Defendants as a representative model for properly considering confounding factors. (See Doc #: 772, at 4-5.)

g. Richard Semelka, M.D.

Defendants have moved to exclude certain portions of the testimony of Richard Semelka, M.D. Dr. Semelka is a dermatologist who has been a faculty member in the Department of Radiology at the University of North Carolina at Chapel Hill Medical Center since 1992. He is also the Department of Radiology's Director of Magnetic Resonance Services, Vice Chair of Clinical Research and Vice Chair of Quality and Safety.

Dr. Semelka's expert report details his experience with Omniscan and GBCAs as a long-time radiologist at an academic medical center. It includes a discussion of research he conducted on GBCAs and his attempts on several occasions to convince the Department of Radiology to switch from using Omniscan. The report also contains Dr. Semelka's opinions, based on a review of medical and scientific literature and GEHC's internal documents, that: (1) GEHC "failed to timely and adequately warn radiologists" of safety concerns with Omniscan; (2) Omnsican has the "strong potential" to cause NSF in patients with renal failure; (3) "free gadolinium toxicity poses an increased risk to do harm in other vulnerable subpopulations"; and (4) "Omniscan should be contraindicated in persons with renal impairment, and perhaps other populations such as pregnant women and children." (Doc #: 677-6, at 16, 21.)

Defendants urge that the Court prevent Dr. Semelka from testifying about the mechanistic cause of NSF because, as a radiologist, he does not have the necessary qualifications. Furthermore, Defendants argue that Dr. Semelka's opinions have been manufactured for litigation and contradict opinions he has expressed in peer-reviewed journals.

The Court denies Defendants' motion to strike Dr. Semelka on both grounds. Dr. Semelka has the background necessary to opine on the mechanistic cause of NSF. He has authored numerous peer-reviewed studies on NSF and his expert report details his significant experience with GBCAs and Omniscan in his practice.

Moreover, Dr. Semelka's opinions do not contradict those in his peer-reviewed publications and are not solely a byproduct of this litigation. Defendants' arguments are based on out-of-context statements from Dr. Semelka's previous publications and his deposition. For example, GEHC notes that a published article co-authored by Dr. Semelka states "[t]he exact mechanism for the development of NSF remains uncertain." D.R. Martin, et al. *Nephrogenic Systemic Fibrosis Versus Contrast-Induced Nephropathy: Risks and Benefits of Contrast-Enhanced MR and CT in Renally Impaired Patients*. 30 J. MAGN. RESON. IMAG. 1350, 1351 (2009). GEHC argues that this contradicts Dr. Semelka's opinion that free gadolinium is the cause of NSF. However, the two are not mutually exclusive. Dr. Semelka can still conclude that he believes free gadolinium causes NSF even if the exact mechanism of causation is still uncertain. Furthermore, immediately following the sentence highlighted by Defendants, begins a lengthy discussion of the free gadolinium theory and the research supporting that theory of causation. The article does not cite evidence of any other mechanism for NSF. Thus, despite the sentence in question, the implication from this article is that free gadolinium causes NSF.

Additionally, about the only thing concerning NSF upon which all parties agree is that the exact mechanism for NSF causation is uncertain. A corollary of GEHC's argument would therefore be that nobody could opine about what causes NSF, and that GEHC should be granted summary judgment in this MDL. This is not going to happen.

Defendants' support for the proposition that Dr. Semelka's opinions are unreliable because they have been developed for litigation are similarly flawed. GEHC asserts that Dr. Semelka's testimony that "one has to be very cautious not to say too many inflammatory words, because that can cause an article to be rejected" is proof of a conflict between Dr. Semelka's published opinions and his litigation opinions. Defendants argue that this is a concession by Dr. Semelka that his litigation opinions would be rejected by reviewers and therefore are not reliable under the standards of Federal Rule of Evidence 702. Yet, it is evident that Dr. Semelka was emphasizing that there is a tendency to "err, if anything, on the side of caution . . ." in making conclusions in published articles and was characterizing the realities of the peer-reviewed publication process. (See Doc #: 679-2, at 64.) He is not admitting that the opinions expressed in this litigation are any different from those expressed in his peer-reviewed publications.

B. Plaintiffs' Challenges to GEHC's Experts and their Opinions

1. Bryan Benjamin Newton, Ph.D.

a. Free Gadolinium

As discussed *supra*, the Court will permit Plaintiffs' experts to opine on the free gadolinium theory of NSF causation. The Court will also permit defense expert Dr. Benjamin Newton to opine on flaws with the free gadolinium theory of causation. Dr. Newton, who is a GEHC employee, has an undergraduate degree in pharmacology and a Ph.D. in General

Medicine which involved studying a "range of techniques, cell biology techniques, electrophysiology techniques, and also innate immunity, as well as *in vivo* pharmacology and physiology." GEHC tasked Dr. Newton with studying the relationship between Omniscan and NSF in September 2007, *after* the first lawsuits alleging that Omniscan caused NSF were filed in March 2007. (See Doc #: 722, at 28.) Thus, notwithstanding GEHC's protests to the contrary, the conclusions reached by Dr. Newton, who had no prior experience researching gadolinium or NSF, arise out of litigation faced by GEHC. Consequently, Dr. Newton's opinions should be examined with greater scrutiny than if his opinions had been developed independently of litigation. *See Johnson v. Manitowoc Boom Trucks, Inc.*, 484 F.3d 426, 435 (6th Cir. 2007).

Even applying greater scrutiny, Dr. Newton's opinions on the free gadolinium theory meet *Daubert*'s reliability test and are therefore permissible. Significantly, Dr. Newton is the author of *Mechanism of NSF: New Evidence Challenging the Prevailing Theory*, which was published last year in the Journal of Magnetic Resonance Imaging, a peer-reviewed journal. In this article, Dr. Newton assesses weaknesses in the dechelated/free gadolinium theory of NSF by reviewing research on the effect of GBCAs (or chelated gadolinium) on fibrocytes, monocytes and macrophages. Dr. Newton references research concluding that chelated gadolinium, such as Omniscan, is not as inert as once believed. He also discusses studies demonstrating that, *in vitro*, chelated gadolinium can stimulate proliferation of fibroblasts, which are cells present in the early stages of NSF. Additionally, Dr. Newton cites literature finding that chelated gadolinium stimulates monocytes and macrophages, cells also present in NSF tissue, to release cytokines and growth factors. Cytokines and growth factors regulate tissue fibrosis, a process characteristic of NSF.

While Dr. Newton had no background in NSF or gadolinium prior to the commencement of litigation, research on fibrosis has been a significant part of Dr. Newton's work as a translational scientist and provides him with the expertise necessary to publish the aforementioned article and opine on certain scientific issues involved in this MDL. Moreover, the majority of the opinions expressed in Dr. Newton's journal article and expert report, though not a result of independent research, are based on reliable, published scientific evidence.

Dr. Newton's testimony, grounded in his expertise in cellular biology and translation science, must be limited to assessing flaws in the free gadolinium theory. In disputing this theory, the Court will permit Dr. Newton to testify about his alternative hypothesis of NSF causation, which he has based on the research done on chelated gadolinium and monocytes, macrophages and fibroblasts. The alternative hypothesis suggests that chelated gadolinium, which is retained in patients with renal insufficiency, is internalized by monocytes and macrophages. The monocytes and macrophages then release cytokines and growth factors which stimulate fibroblasts to initiate fibrosis. Ben B. Newton & Sergio A. Jimenez, *Mechanism of NSF: New Evidence Challenging the Prevailing Theory*, 30 J.MAGNETIC RESONANCE IMAGING. 1277, 1280-81 (2009). The implication of Dr. Newton's hypothesis is that the chelated gadolinium in Omniscan and other GBCAs causes NSF and therefore that the chemical composition of Omniscan makes it no more likely to cause NSF than any other GBCA.

While Dr. Newton's alternative hypothesis has not been independently tested, the free gadolinium theory advanced by Plaintiffs is also unproven, though more commonly accepted. As there is no definitively proven mechanism for NSF causation, the Court, in exercising its gatekeeper function, will allow both sides to present their respective theories to the jury.

The Court, however, will not permit Dr. Newton to testify that NSF has occurred in the absence of GBCA exposure. The Court agrees with Plaintiffs that the two studies cited by Dr. Newton in support of this proposition - Wahba IM, Simpson EL, White K. *Gadolinium Is Not The Only Trigger For Nephrogenic Systemic Fibrosis: Insights From Two Cases And Review Of The Recent Literature*. 7 AM. J OF TRANS. 1-8 (2007) and Collidge TA, Thomson PC, Mark PB, *et al*. *Gadolinium-Enhanced MR Imaging And Nephrogenic Systemic Fibrosis: Retrospective Study of a Renal Replacement Therapy Cohort*. 245 RADIOLOGY 168-175 (2007) – are fundamentally flawed. The Collidge study did not examine whether the one NSF patient who had not received a GBCA while undergoing an MRI had undergone any non-MRI procedures in which a GBCA was used. The Wahba study, which concluded that two patients developed NSF without exposure to a GBCA, did not confirm its findings by testing these patients' tissue for the presence of gadolinium.

b. Forseeability, Animal Predictive Studies and *In Vitro*/*In Vivo* Chemical Stability

Along with challenging the free gadolinium theory, Dr. Newton may also provide limited expert testimony on whether it was foreseeable that GBCA exposure would lead to the injuries encountered by renally compromised NSF patients. His degree in pharmacology and background as a translational scientist and cellular biologist, which is the basis for his foreseeability opinions, provide him with the necessary expertise to offer a reliable opinion.

However, Dr. Newton's lack of significant training or experience in dermatology, pathology or histology makes his testimony challenging the similarity of rat lesions to the symptoms of NSF unreliable. It is clear from Dr. Newton's deposition that he lacks the requisite level of comfort with basic dermatohistology or dermatologic clinical manifestations, such as

dermal induration, to render a reliable expert opinion on this topic. Additionally, Dr. Newton may not testify about the relationship between *in vitro* and *in vivo* chemical stability of Omniscan. Dr. Newton's background does not include the focused study of chemistry necessary to be considered an expert on the stability of chemical compounds.

2. Alan D.Watson, Ph.D., M.B.A.

The Court will not permit defense expert Dr. Alan Watson to testify on matters outside the field of bioinorganic chemistry. Dr. Watson holds a B.Sc. degree in Chemistry, a Ph.D. in Coordination and Bioinorganic Chemistry and an M.B.A. Since receiving his M.B.A. in 1988, his responsibilities appear to have been more on the business side than on the science side.

Dr. Watson's expert report contains the following substantive subject headings: (1) The Need for GBCAs; (2) GBCA Design and Stability; (3) Thermodynamic and Kinetic Stability Factors; (4) Macrocyclic Chelate Complexes as GBCAs; (5) Toxicity Studies of GBCAs; (6) The Issue of Gadolinium Retention; (7) Skin Lesions During Preclinical Testing; (8) The Early History of Salutar; (9) Salutar and Nycomed Publications; (10) Nycomed's Own Internal Documents; (11) Foreseeability; and (12) Commonality of All the Current Commercially Available GBCAs.

Given that Dr. Watson's responsibilities have been primarily on the business side at least since 1999 and perhaps since 1988, he is not qualified to provide expert testimony on most of the subjects discussed in his expert report. Because of his background, Dr. Watson is qualified to speak generally about bioinorganic chemistry, the study of how inorganic elements function in living organisms. The topics which may correspond to his knowledge of bioinorganic chemistry are: The Need for GBCAs, GBCA Design and Stability, Thermodynamic and Kinetic Stability

Factors, Macrocyclic Chelate Complexes as GBCAs and The Issue of Gadolinium Retention. Dr. Watson does not have the requisite expertise to opine on the other issues within his report. In particular, Dr. Watson may not provide an opinion on the FDA's review of Omniscan, his assessment of Omniscan or GBCA toxicology or toxicology studies, any preclinical or clinical studies of Omniscan (including those done by Salutar and Nycomed), analysis of relevant publications on GBCAs, or foreseeability of gadolinium poisoning.

3. Anthony A. Gaspari, M.D.

The Court will not permit defense expert Dr. Anthony Gaspari's generic testimony on NSF diagnosis or his medical analysis of four adverse event reports. Dr. Gaspari is the Chairman of the Department of Dermatology at the University of Maryland School of Medicine. His areas of specialty are dermatology, allergic skin diseases and immunology.

Dr. Gaspari's generic expert report discusses the history of NSF, how it is diagnosed, the differential diagnosis, complicating factors in diagnosing NSF, and an analysis of four Adverse Event Reports received by GEHC. The testimony concerning NSF diagnosis shall not be permitted because it is irrelevant and does not assist the trier of fact. To the extent that GEHC disputes that any of the plaintiffs in the four bellwether trials has NSF, it will need to offer a case-specific expert, who has examined the plaintiff and reached a conclusion on that plaintiff's NSF diagnosis. If there is no challenge to a given plaintiff's NSF diagnosis, generic expert testimony about various NSF diagnostic issues is not relevant. A generic expert testifying at length about how NSF is diagnosed and how other conditions, such as diabetes, complicates NSF diagnosis is not relevant unless the particular plaintiff has diabetes and a case-specific expert

testifies that the plaintiff does not have NSF. In that case, the generic expert's testimony would be superfluous.[9]

Moreover, Dr. Gaspari may not draw conclusions from the four Adverse Event Reports received by GEHC that GEHC was unaware of Omniscan's potential risks. In his generic expert report, Dr. Gaspari examines four Adverse Event Reports received by GEHC between April 2002 and July 2005 and concludes that the data did not support a diagnosis of NSF in any of these cases and therefore that they did not offer "a compelling, consistent clinical history to alert GE Healthcare to the presence of any association between Omniscan and NFD/NSF." (Doc #: 736-5, at 18.) As observed by Plaintiffs, Dr. Gaspari only examined four Adverse Event Reports and was not provided any preclinical or animal studies conducted by GEHC, any medical literature, or any other relevant data GEHC had at its disposal. Adverse Event Reports examined in a vacuum have significant limitations and are therefore only useful when assessed in the context of other available date. *See* Adverse Event Reports Discussion, Sec. III (B), *supra*. Accordingly, Dr. Gaspari's conclusions are based on incomplete information and therefore do not satisfy the Federal Rule of Civil Evidence 702 requirement that expert testimony be based on sufficient facts or data.

4. Sushrut S. Waikar, M.D.

Dr. Waikar, a nephrologist, is an Associate Physician in the Renal Division of Brigham and Women's Hospital and Assistant Professor of Medicine at Harvard Medical School. Currently, approximately 75% of Dr. Waikar's time is spent conducting clinical research.

[9]A case specific expert (such as Dr. Gaspari) who opines that a particular plaintiff does not have NSF could, of course, give the basis for his conclusion, which could include an explanation of the difficulty in diagnosing NSF and how other conditions that plaintiff suffers from has complicated the diagnosis.

Plaintiffs seek to prevent Dr. Waikar from testifying about: (1) NSF causation because he lacks epidemiological training; (2) the lack of an association between GBCA exposure and toxicity due to conflicts with established epidemiological evidence; (3) causation due to misapplication of the Rothman Disease Causation Model and because his causation opinions rely upon the erroneous belief that NSF has occurred in the absence of GBCA exposure; and (4) GEHC's ability to anticipate NSF or to understand the connection between NSF and GBCAs based upon clinical evidence, including adverse event reports.

Dr. Waikar's extensive experience conducting clinical research as a nephrologist provides the necessary knowledge to offer his opinions on NSF causation. The Court will permit Dr. Waikar to testify on the lack of an association between GBCA exposure and toxicity and also to apply the Rothman Disease Causation Model.

However, the Court will limit Dr. Waikar's testimony on two subjects. First, Dr. Waikar may not testify about reports of NSF without GBCA exposure. Dr. Waikar's conclusions on this issue stem from the Collidge and Wahba studies which, as discussed *supra*, are fundamentally flawed. Second, for the reasons discussed above with regard to Dr. Gaspari, Dr. Waikar may not testify and draw conclusions solely from GEHC Adverse Event reports because his opinions are based on incomplete information.

5. J. Paul Waymack, M.D., Sc.D.

The Court will not permit the testimony of defense expert Dr. J. Paul Waymack, a pharmaceutical consultant with an M.D. who was a full-time medical officer at the FDA from 1993-1995 and a part-time officer from 1995-1996. Based on his expert report, the purpose of

Dr. Waymack's testimony appears to be (1) to explain the FDA drug approval and labeling process and (2) to opine that Omniscan complied with all FDA requirements.

The Court will not permit Dr. Waymack to offer his expert opinion on either of these topics because, as evidenced by both his expert report and deposition testimony, Dr. Waymack intends to offer opinions that are contrary to the Supreme Court's recent opinion in *Wyeth v. Levine*, 129 S.Ct. 1187 (2009). In his expert report, Dr. Waymack writes that the "FDA possesses a significant advantage over the sponsor in evaluating safety data" within a particular class of drugs. (Doc #: 693-2 at ¶ 60.) Dr. Waymack also notes that "the FDA has ultimate authority over pharmaceutical development and marketing, including the labeling of such products." (Id. at ¶ 76.) In rejecting a manufacturer's argument that it could not have modified a warning label that had already been approved by the FDA, the Supreme Court in *Wyeth* observed that "through many amendments to the FDCA and to FDA regulations, it has remained a central premise of drug regulation that the manufacturer bears responsibility for the content of its label at all times." *Wyeth*, 129 S.Ct at 1197-98. Moreover, "[f]ailure-to-warn actions, in particular, lend force to the FDCA's premise that manufacturers, not the FDA, bear primary responsibility for their drug labeling at all times." *Id*. at 1202. The Supreme Court also pointed out that "[t]he FDA has limited resources to monitor the 11,000 drugs on the market, and the manufacturers have superior access to information about their drugs, especially in the postmarketing phase as new risks emerge." *Id*.

Technically, Dr. Waymack's observations in his report that the FDA possesses an advantage in evaluating safety data for particular classes of drugs and has ultimate authority over labeling may not wholly contradict *Wyeth*. However, Dr. Waymack's opinions are misleading

because they attempt to minimize the manufacturer's role in the labeling process and therefore should not be presented to the trier of fact.

The opinions expressed by Dr. Waymack in his deposition demonstrate a more blatant disregard of the Supreme Court's pronouncements in *Wyeth*. During the deposition, Plaintiffs' counsel read to Dr. Waymack excerpts from *Wyeth*, without informing Dr. Waymack the excerpts had been taken from a Supreme Court opinion. When asked about the Supreme Court's statement that drug regulation is premised on the manufacturer being responsible for labeling, Dr. Waymack noted that "obviously, it's inaccurate" and "it's grossly a misstatement of facts." (Doc #: 737-9, at 55.) Upon being questioned about the *Wyeth* holding that a manufacturer does not need FDA preapproval to update a label, he concluded that "this was written by someone who is not very familiar obviously with FDA regulations" and that he disagreed with this holding. *Id*. at 212:11-214:6. Dr. Waymack offered this testimony even though he recognized the principle he disagreed with "could have been written by a Supreme Court justice." *Id*.

Given that Dr. Waymack's probable testimony is at best misleading and at worst directly contrary to the Supreme Court's holdings in *Wyeth*, the Court, pursuant to Rule 702, precludes Dr. Waymack from testifying. While the Court was unable to find, nor did either party cite a Sixth Circuit case on this issue, common sense dictates that the Court prohibit a witness from offering opinions in direct conflict with Supreme Court holdings or observations made by the Supreme Court that serve as a foundation for reaching a conclusion (i.e. that the FDA's limited resources mean the manufacturer has superior access to information about its own product). The expression of opinions contrary to law, while perhaps only a part of the witness' probable

testimony, are sufficient to characterize the witness as unreliable and therefore subject to exclusion.

Moreover, the Court will not permit Dr. Waymack to testify that the FDA would have prevented any attempt by GEHC to unilaterally change Omniscan labeling. (See Doc #: 722, at 55 (". . . the facts here unequivocally demonstrate that the FDA would have prevented any attempt by GEHC unilaterally to change the Omniscan labeling through a CBE supplement").) GEHC must introduce such testimony through its own witnesses or FDA employees with specific knowledge of the FDA's regulation of the Omniscan label.

IT IS SO ORDERED.

/s/ Dan A. Polster May 4, 2010
Dan Aaron Polster
United States District Judge