UNITED STATES DISTRICT COURT
DISTRICT OF MASSACHUSETTS

IN RE: ZOFRAN (ONDANSETRON) PRODUCTS LIABILITY LITIGATION	)	**MDL No. 1:15-md-2657-FDS**
This Document Relates To:	)	
All Actions	)	

MEMORANDUM AND ORDER ON
MOTIONS TO EXCLUDE REGULATORY EXPERTS

SAYLOR, J.

This is a multi-district litigation ("MDL") proceeding arising out of product-liability claims that the use of the drug Zofran (ondansetron) by pregnant women caused birth defects in their children.

Plaintiffs have moved to exclude certain portions of the testimony of the regulatory expert of GlaxoSmithKline LLC ("GSK"), Dr. Dena Hixon. GSK has moved to exclude the testimony of plaintiffs' regulatory expert, Dr. Brian Harvey. For the reasons set forth below, plaintiffs' motion will be denied and GSK's motion will be granted in part and denied in part.

I. Standard of Review

Federal Rule of Evidence 702 provides as follows:

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

of the case.

Fed. R. Evid. 702. The adoption of Rule 702 in its present form codified the standard of admissibility for expert testimony that was set forth in *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 509 U.S. 579 (1993). *United States v. Diaz*, 300 F.3d 66, 73 (1st Cir. 2002).

Under Rule 702, district courts considering the admissibility of expert testimony must "act as gatekeepers, ensuring that an expert's proffered testimony 'both rests on a reliable foundation and is relevant to the task at hand.'" *Samaan v. St. Joseph Hosp.*, 670 F.3d 21, 31 (1st Cir. 2012) (quoting *Daubert*, 509 U.S. at 597). That gatekeeping function requires that the court consider three sets of issues: (1) whether the proposed expert is qualified by "knowledge, skill, experience, training or education"; (2) whether the subject matter of the proposed testimony properly concerns "scientific, technical, or other specialized knowledge"; and (3) "whether the testimony [will be] helpful to the trier of fact, *i.e.*, whether it rests on a reliable foundation and is relevant to the facts of the case." *Bogosian v. Mercedes-Benz of N. Am., Inc.*, 104 F.3d 472, 476 (1st Cir. 1997) (quoting Fed. R. Evid. 702) (internal quotation marks omitted). "These two requirements—a reliable foundation and an adequate fit—are separate and distinct." *Samaan*, 670 F.3d at 31.

The requirement that an expert's testimony must be based on reliable methods is often the "central focus of a *Daubert* inquiry." *Ruiz-Troche v. Pepsi Cola of P.R. Bottling Co.*, 161 F.3d 77, 81 (1st Cir. 1998). In *Daubert*, the Supreme Court enumerated a non-exhaustive list of factors that a court may consider in undertaking its reliability analysis: (1) whether the scientific theory or technique can be (and has been) tested; (2) whether it has been subjected to peer review and publication; (3) whether it has a known rate of error; (4) whether there are standards controlling its application or operation; and (5) whether it is generally accepted in the relevant

scientific community. *Daubert*, 509 U.S. at 593-94; *see also Samaan*, 670 F.3d at 31-32.

Less centrally, but importantly, Rule 702 requires the court to examine whether those methods have been reliably applied. In other words, the court must "ensure that there is an adequate fit between the expert's methods and his conclusions." *Samaan*, 670 F.3d at 32 (citing *Daubert*, 509 U.S. at 591). "This prong of the *Daubert* inquiry addresses the problem that arises when an expert's methods, though impeccable, yield results that bear a dubious relationship to the questions on which he proposes to opine." *Id.* (citing *Daubert*, 509 U.S. at 591-92).

In evaluating whether expert testimony will be helpful to the trier of fact, the court must determine whether it is relevant, "not only in the sense that all evidence must be relevant, but also in the incremental sense that the expert's proposed opinion, if admitted, likely would assist the trier of fact to understand or determine a fact in issue." *Ruiz-Troche*, 161 F.3d at 81 (citations omitted); *see also Cipollone v. Yale Indus. Prods., Inc.*, 202 F.3d 376, 380 (1st Cir. 2000) ("The ultimate purpose of the *Daubert* inquiry is to determine whether the testimony of the expert would be helpful to the jury in resolving a fact in issue.").

The focus of the inquiry is on the principles and methodology employed by the expert, not the ultimate conclusions. *Daubert*, 509 U.S. at 595. The court may not subvert the role of the factfinder in assessing credibility or in weighing conflicting expert opinions. Rather, "[v]igorous 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." *Id.* at 596; *see also Ruiz-Troche*, 161 F.3d at 85 (admitting testimony notwithstanding a lack of peer-reviewed publications because the opinion rested upon good grounds generally and should be tested by the "adversary process").

Expert testimony that is admissible under Rule 702 may nonetheless be excluded under

Rule 403 "if its probative value is substantially outweighed by the danger of one or more of the following: unfair prejudice, confusion of the issues, misleading the jury, undue delay, wasting time, or needlessly presenting cumulative evidence." Fed. R. Evid. 403; *see also Daubert*, 509 U.S. at 595. Thus, expert testimony that is relevant and that passes muster from a scientific or technical standpoint may nonetheless be excluded if it is likely to be misinterpreted or misused by the jury.

II. Analysis

A. Plaintiffs' Motion to Exclude Testimony of Dr. Hixon

Plaintiffs seek to exclude certain portions of the testimony of GSK's regulatory expert, Dr. Dena Hixon. They contend that her opinions on two topics—determination of teratogenicity (or pregnancy labeling) and pharmacovigilance—should be excluded on the grounds that she is not qualified to render the opinions and that the opinions are based on unsound methodology.

Dr. Hixon is a medical doctor and a former board-certified obstetrician/gynecologist with thirteen years of clinical experience. She also worked at the Food and Drug Administration ("FDA") for thirteen years, first as a medical officer within the Center for Drug Evaluation and Research ("CDER"), and then as an advisor on safety issues in the Office of Generic Drugs. For three of those years, she was the primary reviewer of human clinical studies submitted as part of Investigational New Drug ("IND") applications and New Drug Applications ("NDAs"). She also served on the FDA's Pregnancy Labeling Task Force. That task force assessed pregnancy-related drug-labeling categories, developed the Pregnancy and Lactation Labeling Rule ("PLLR"), and developed FDA guidance documents concerning risk assessment of drugs used in pregnancy. She now works as a regulatory consultant, advising on drug development and regulation for both new and generic drugs, from early development through product approval and

post-market surveillance.

Dr. Hixon produced an expert report in this case on September 21, 2018. Among other things, the report concluded—in what plaintiffs refer to as a "determination of teratogenicity," or "pregnancy labeling," opinion—that the FDA "appropriately assigned ondansetron Pregnancy Category B in the labeling, based on the data available to GSK and FDA and the applicable regulations." (Hixon Report at 4). It further concluded—in what plaintiffs refer to as a "pharmacovigilance" opinion—that GSK "appropriately monitored the drug's safety in pregnancy and complied with the regulations in collection, analyzing[,] and reporting pregnancy-related safety information," and that GSK "performed several thorough internal assessments of pregnancy exposure and outcome data." (*Id.*).

Plaintiffs contend that both of those opinions should be excluded on the grounds that they exceed her regulatory experience and lack reliable scientific foundation.

1. <u>Determination of Teratogenicity (or Pregnancy Labeling) Opinions</u>

Plaintiffs first object to Dr. Hixon's opinion that Zofran was properly labeled as a pregnancy Category B Drug. Specifically, they contend that (1) her methodology is flawed because one of the Japanese animal studies (Study 424) was never submitted to the FDA and she does not have the expertise to opine on whether the FDA would have found evidence of teratogenicity if that study had been taken into consideration; and (2) her opinions are unreliable because she is not qualified to opine on whether reproductive toxicology animal studies provide evidence of teratogenicity.

It is undisputed that GSK has never provided a complete version of Study 424 to the FDA. According to plaintiffs, the factfinder will have to rely on expert-witness testimony to assess whether the data from all of the animal studies at issue, when considered in totality,

demonstrated sufficient fetal risk such that GSK should have requested a Pregnancy Category C warning. They further contend that Dr. Hixon cannot offer an opinion that the disclosure of Study 424, or any of the other disputed Japanese animal studies, would not have changed the pregnancy category for Zofran without also opining that the study does not show evidence of teratogenicity. Because, they contend, she is not qualified to offer such an opinion, and did not consult with a toxicologist, her opinions as to those topics are unreliable and should be excluded.

Plaintiffs identify four such "determination of teratogenicity," or "pregnancy labeling," opinions—that is, "[o]pinions regarding whether the Japanese animal studies provided evidence of teratogenicity and whether their disclosure to FDA would have changed the pregnancy categorization of Zofran"—that they seek to exclude:

> (1) "FDA appropriately assigned ondansetron Pregnancy Category B in the labeling, based on the data available to GSK and FDA and the applicable regulations." (Hixon Report at 4).
>
> (2) "Because data from the studies did not lead to different conclusions regarding safety than the studies that had already been provided to FDA in previous IND and NDA submissions . . . , GSK appropriately determined that the data in these studies did not constitute 'new' information relevant to safety." (*Id.* at 36).
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> (3) "The evidence must provide a reasonable basis to believe that there is a causal association between the risk and the drug. At no time did such evidence exist, including in reproductive toxicity studies, scientific literature, or GSK's safety database." (*Id.* at 36, 72).
>
> (4) "GSK's scientists uniformly concluded that none of the reproductive toxicology studies showed evidence of teratogenicity in animals, and FDA's experts agreed." (*Id.* at 72).

Under the circumstances, the opinions will not be excluded. Dr. Hixon does not claim to determine independently whether the data from reproductive toxicity studies show that Zofran is teratogenic. Instead, she is relying upon the conclusions of GSK's scientists that those studies did not show that Zofran is teratogenic. Starting with that assumption, Dr. Hixon applied what

she says are the relevant regulatory standards, which she appears qualified to provide based on her background and training.

For that reason, the Court will construe Dr. Hixon's opinions (2) and (4) as regulatory opinions conditioned on a specific assumption: the assumption that GSK's experts correctly interpreted the toxicity studies. Of course, if that assumption is incorrect, that would likely undermine her conclusions, if not vitiate them completely.[1] Furthermore, any opinion she expresses must be carefully couched to make clear that she is not testifying (and cannot testify) as to whether the toxicity studies were correctly interpreted.

As to opinions (1) and (3), GSK contends that they do not turn on a toxicological determination of "non-teratogenicity," but are instead based on Dr. Hixon's regulatory analysis of the study reports, FDA standards, and other materials. She appears qualified to deliver those opinions based on her thirteen years of clinical experience as a practicing OB/GYN and her thirteen years of experience at the FDA, including her work on the Pregnancy Labeling Task Force and her role as a team leader in the Office of New Drugs. At the FDA, she directly participated in redeveloping the regulations setting forth the pregnancy categories; worked on guidances concerning pregnancy-related risk assessment; and reviewed NDAs, including the evaluations of pharmacologist/toxicologist reviewers.[2] (Hixon Report at 1). In short, Dr. Hixon is qualified to testify about the accuracy and completeness of Zofran's drug labeling, based on her experience with the types of data included in pregnancy labeling and her familiarity with

[1] Plaintiffs further contend that FDA reviewers consider the totality of the evidence, but GSK's experts only analyzed each study in isolation. If that is true, it may also undermine Dr. Hixon's conclusions.

[2] The fact that Dr. Hixon did not serve as a primary reviewer of reproductive toxicity study data does not, by itself, disqualify her from providing the regulatory opinions in question. An expert's testimony is not excludable simply because she has not personally engaged in the specific task on which she is testifying. *See In re Depakote*, 2015 WL 4775868, at *7 (S.D. Ill. Feb. 13, 2015); *In re Celexa and Lexapro Prods. Liab. Litig.*, 2013 WL 791784, at *4 (E.D. Mo. Mar. 4, 2013).

how the FDA treats such data.

The Court further concludes that Dr. Hixon's methodology is not so unreliable as to require exclusion. Courts have previously permitted qualified FDA regulatory experts to testify about the adequacy of product labeling and compliance with regulatory requirements where, as here, the testimony is based on an analysis of the regulatory record in light of applicable standards and practices. *See In re Depakote*, 2015 WL 4775868, at *6; *In re Celexa*, 2013 WL 791784, at *6. Here, Dr. Hixon provides a reasoned discussion grounded in regulatory standards and record evidence to support her opinions. Specifically, she analyzed multiple factual sources, including assessments by GSK scientists, regulatory provisions and guidance documents, and the FDA's and GSK's analyses of Zofran's safety in pregnancy. While she cannot independently interpret the data from reproductive toxicity studies (for example, calculating the background rate), she can opine that based on her regulatory experience and knowledge, the FDA would not find reasonable evidence of causality without taking certain steps (for example, it would not find causality in a certain number of ventricular septal defects ("VSDs") without comparing it to the background rate).

Again, the Court will construe Dr. Hixon's opinions (1) and (3) as predicated on the assumption that GSK's scientists correctly interpreted the data from toxicity studies. The fact that she did not serve as a primary reviewer of that data goes to the weight of her testimony, but it is not a basis for excluding it. Furthermore, and again, any opinion she expresses must be carefully couched to make clear that she is not testifying as to whether the toxicity studies were correctly interpreted.

Accordingly, Dr. Hixon's opinions concerning determination of teratogenicity, or pregnancy labeling, will not be excluded.

2. Pharmacovigilance Opinions

Plaintiffs further contend that Dr. Hixon's opinion that GSK conducted appropriate pharmacovigilance is not based on a reliable methodology. Specifically, they contend that she did not conduct an independent analysis of the "raw data"—that is, the adverse event reports—or consider the testimony of the four GSK safety scientists or physicians who were responsible for routine pharmacovigilance.[3] Instead, they contend, what she did was to simply reiterate and agree with GSK's conclusions of what that data revealed.

Among other things, plaintiffs rely on cases where regulatory experts *did* analyze raw internal pharmacovigilance data and adverse event data, and argue that such analyses are routinely performed. *See In re Tylenol (Acetaminophen) Mktg., Sales Practices, & Prods. Liab. Litig.*, 2016 WL 4039271 at *7 (E.D. Pa. July 28, 2016); *In re Celexa & Lexapro*, 2013 WL 791784, at *5-7. According to plaintiffs, such an analysis would have been feasible for Dr. Hixon to complete here, where the excerpt of the Zofran safety database that GSK produced included only 1,471 cases of Zofran use during pregnancy.[4]

Plaintiffs specifically identify three such "pharmacovigilance opinions"—that is, "[o]pinions regarding whether Zofran safety data was appropriately monitored, collected, analyzed, and reported to FDA"—that they contend should be excluded:

> (1) "GSK appropriately monitored the drug's safety in pregnancy and complied with the regulations in collection, analyzing[,] and reporting pregnancy-related safety information. GSK . . . performed several thorough internal assessments of pregnancy exposure and outcome data." (Hixon Report at 4).
>
> (2) "GSK conducted appropriate routine pharmacovigilance and made required

[3] The parties have devoted a portion of their briefing on this motion to the discussion of what appears to be a factual dispute as to the accuracy, or completeness, of one specific adverse event report involving Wolff-Parkinson-White syndrome. The Court will not attempt to resolve that dispute here.

[4] According to plaintiffs, their own expert, Dr. Harvey did in fact analyze the FDA database for potential Zofran pregnancy-related cases, as did Novartis when it took over pharmacovigilance from GSK.

disclosures to FDA regarding pregnancy-related exposures and safety issues concerning ondansetron." (*Id.* at 47).

(3) "The 19-year cumulative data from GSK's safety database, including the data provided in these [periodic safety] reports to FDA, did not provide a safety signal related to the use of ondansetron during pregnancy, and there was no need for a labeling change or other action in response to the available data." (*Id.* at 50-51).

GSK contends that Dr. Hixon did what the FDA would have done itself when it received a safety report from a sponsor: review the information reported and compare it to information in the agency's own safety database. The agency would not, it says, redo the sponsor's analysis of the total set of raw data. Nor would such a method be workable, where (as here) there are more than twenty years of raw data underlying the safety reporting and analysis at issue. Finally, it contends that Dr. Hixon did, in fact, consider the deposition testimony of GSK safety team members.

Under the circumstances, the Court finds that Dr. Hixon's failure to conduct an independent review of the adverse event reports is not fatal to the admissibility of her pharmacovigilance opinions. She provided a detailed pharmacovigilance analysis grounded in the regulatory standards and record evidence, which was not so scientifically unsound as to require exclusion. Again, to the extent that her analysis may have been less rigorous or exhaustive than that of Dr. Harvey or other experts in the field, those factors go to the weight to be given her testimony, not its admissibility.

Accordingly, Dr. Hixon's pharmacovigilance opinions—that is, her opinions concerning whether Zofran safety data was appropriately monitored, collected, analyzed, and reported to FDA—will not be excluded.

B. GSK's Motion to Exclude Testimony of Dr. Harvey

GSK seeks to preclude the testimony of plaintiffs' regulatory expert, Dr. Brian E.

Harvey. While GSK seeks to exclude his testimony in its entirety, it specifically objects to six opinions offered by Dr. Harvey on the grounds that those opinions are speculative, unsupported, intrusive on the factfinder's role, and unreliable.

Dr. Harvey is a medical doctor and has a Ph.D. in biochemistry. His medical training included post-doctoral research in cancer biology, a three-year residency in internal medicine, and a fellowship in gastroenterology and hepatology. He then practiced as a physician for the next 15 years, including throughout his time at the FDA, treating adult patients with cardiac and other conditions.

Dr. Harvey worked at the FDA for eleven years, from 1995 to 2007, with a detail from 2000 to 2001 focusing on health policy as an American Political Association Congressional Fellow. At the FDA, he began as a medical officer at the Center for Devices and Radiological Health ("CDRH"), working in the Gastroenterology and Renal Devices branch, as well as the Cardiovascular Devices Division and In Vitro Diagnostic Devices Division/Office. He received progressive promotions at the FDA and ultimately served as Director of the Division of Gastroenterology Products in CDER. As Division Director from 2005 to 2007, he had direct responsibility for Zofran, which fell within his division.

Dr. Harvey left the FDA in 2007 to serve as Vice President of U.S. Regulatory Policy at Sanofi-Aventis. In that role, he worked with all therapeutic areas in providing guidance on interactions with the FDA. In 2012, he became Vice President of U.S. Regulatory Strategy at Pfizer, working with the FDA for all Pfizer business units.

Since 2015, Dr. Harvey has been an independent regulatory consultant, working with biopharmaceutical companies, consulting groups, and law firms, including consulting with pharmaceutical companies on advertising and promotion, reviewing and analyzing toxicology

data, and making recommendations about pregnancy registries and drug labeling.

Dr. Harvey produced an expert report in this case on September 26, 2018. In the summary of that report, he attests that he reached the following five opinions:

(1) "Prior to FDA approval of ondansetron (Zofran), GSK conducted reproductive toxicology animal studies in Japan that demonstrated an association between Zofran and birth defects, including cardiovascular, cleft and skeletal malformations, when rats and rabbits were exposed to the drug in utero during the first trimester. GSK deviated from agency guidance and industry practices by not submitting these Japanese animal study results to FDA, nor accurately reporting the full results of these animal studies. GSK failed to provide FDA and healthcare providers, with complete information relating to the risks of teratogenicity, specifically cardiovascular and craniofacial malformations during the first trimester." (Harvey Report at 6). "Based on my agency experience, had GSK done so, FDA would have taken into consideration all seven reproductive toxicology animal studies including the findings of evidence of developmental teratogenicity." (*Id.* at 56). "Therefore FDA would not have approved a Pregnancy Category of B for Zofran at the time of initial approval." (*Id.*).

(2) "GSK's internal documents demonstrated it was aware Zofran crossed the placental barrier and had knowledge of animal studies with results showing teratogenicity before the drug was first approved by FDA. Despite this unreported evidence of animal teratogenicity, GSK initiated a program of off-label marketing targeting Obstetrician/Gynecologists (OB/GYNs) to use Zofran for an unapproved indication of the treatment of pregnancy-related nausea and vomiting. GSK's off-label marketing efforts created a false sense of safety relating to the use of Zofran during pregnancy and failed to fully inform healthcare providers and patients of the teratogenic risks associated with Zofran. GSK's off-label marketing of Zofran for use in pregnancy deviated from FDA guidance and regulations." (*Id.* at 6).

(3) "GSK deviated from industry practices and guidelines by failing to establish a pregnancy registry for Zofran, despite the fact that GSK was promoting Zofran to OB/GYNs for use in pregnancy-related nausea and vomiting as well as data obtained by GSK that demonstrated that Zofran was being prescribed to women during their first trimester. Internal documents show that individuals within GSK contemplated a pregnancy registry for the purpose of tracking the known risks of cardiovascular and skeleton malformations, but GSK management chose not to establish a registry for Zofran even though GSK maintained pregnancy registries for several of their other drugs." (*Id.*).

(4) "GSK failed to implement adequate pharmacovigilance practices and failed to provide FDA with all adverse pregnancy outcomes that they had. Since GSK

did not include all pregnancy-related adverse birth outcomes within its global safety base, GSK's ability to properly detect safety signals and complete risk assessments was compromised. By failing to accurately monitor, assess and report adverse events to FDA, GSK altered the mix of evidence available to the agency and deprived FDA of the ability to evaluate Zofran's pregnancy related risks based on a complete record. As the former Division Director with responsibility for regulating Zofran, the omitted information was material to me and based on my experience would have been material to a reasonable FDA official performing the same regulatory functions." (*Id.* at 6-7).

(5) "GSK was aware that it had the ability to communicate with the agency and update risk disclosures (i.e., contraindications, warnings, precautions, adverse events) in Zofran's labeling through the CBE process after Zofran had been approved by FDA, since GSK had utilized this regulatory pathway with other drug labels. Despite the publication of a number of studies suggesting a link between birth defects and the use of Zofran during pregnancy, GSK chose not to update medical practitioners and the public with complete risk disclosures. GSK's failure to timely update risk disclosures postmarketing, based upon information that the company knew or should have known, was a deviation from industry practices and agency requirements." (*Id.* at 7).

GSK objects to all five of Dr. Harvey's opinions. It has also identified a sixth category of opinions, which it calls "causation-related statements or opinions," which it also seeks to exclude. That category includes statements such as:

- "Zofran blocks the cardiac hERG (human Ether-à-go-go-Related Gene) channel; this mechanism is known to cause cardiovascular and orofacial birth defects when ingested during pregnancy" (*Id.* at 40); and

- Zofran is "associated with" "known teratogenic risks." (*Id.* at 54, 60, 97-98).

1. Opinions on Zofran Reproductive Toxicity Studies

GSK contends that Dr. Harvey's opinions as to Zofran reproductive toxicity studies are speculative, without basis, and inconsistent with the FDA's statements and actions. First, it asserts that he has no regulatory authority for his opinion that GSK was required to submit all of the Japanese animal studies to the FDA, but instead relies on his view of what the agency's expectations would have been. (*See* Harvey Dep. at 153, 159). According to GSK, the FDA has

stated that full study reports should be submitted only if they provide new information and are not duplicative of what the agency "already has." *See* 50 Fed. Reg. 7452, 7478 (Feb. 22, 1985). Second, it asserts that Dr. Harvey's opinion that the FDA would have assigned Zofran a different label if GSK had submitted the Japanese animal studies is speculative and unreliable.

In response, plaintiffs first point to Dr. Harvey's reliance on 21 C.F.R. § 314.50, which (he concludes) required GSK to submit the full study reports for the Japanese animal studies in its initial NDA for Zofran. Dr. Harvey further testified as to why the Japanese animal studies were not duplicative of the studies that were submitted to the FDA: because they were conducted at different doses, and because the Japanese studies presented with cardiac findings of septal defects. (Harvey Dep. at 155-57). GSK replies that 21 C.F.R. § 314.50 only requires the inclusion of "appropriate" reproductive toxicity study data in an NDA filing, not the submission of all data.

Plaintiffs also point to Dr. Harvey's reliance on a 2011 FDA guidance document for industry, which describes assessment of human risk based on nonclinical data generated in animal studies. According to Dr. Harvey, that document shows that the Japanese animal studies were particularly important for evaluating human risk because they suggested a dose-related response. (Harvey Report at 32). He also testified that, based on the document and his own experience, it was the FDA's expectation and industry practice that all animal studies would be submitted to the FDA to make the totality of evidence available for its review. (Harvey Dep. at 151-152, 156-57; *see* Harvey Report at 34). GSK replies that the document directly contravenes Dr. Harvey's alleged "absolute numbers" approach towards VSDs, because that document concerns the assessment of human risk after a "positive signal" has been identified in a reproductive toxicity study, and further defines a "positive signal" not as the absolute number of

defects seen, but rather as "a biologically meaningful difference in dosed animals compared to concurrent or historic controls." (Harvey Report at 31; GSK Ex. 6 (2011 Guidance) at 6-7).[5]

Under the circumstances, Dr. Harvey has provided sufficient support for his opinion that GSK was required to submit the full Japanese animal studies to the agency. Whether the studies would have been "appropriate" FDA submissions, or whether they provided any "new" information, are questions for the factfinder, not a basis to exclude the opinion altogether. Similarly, the extent to which any inconsistencies between Dr. Harvey's methodology and that prescribed by the 2011 guidance document undermine his credibility or his conclusions is also a question for the factfinder.

Second, GSK contends that Dr. Harvey's opinion that the FDA would have changed Zofran's pregnancy category, based on two studies showing three VSDs within historical ranges, is speculative and inconsistent with the FDA's statements and actions. Dr. Harvey opined that based on his FDA experience, three VSDs observed at the highest dose is evidence of an adverse effect that would have raised a red flag for the FDA, triggering further evaluation, if those results had been timely submitted to the agency. (Harvey Dep. at 116-18). According to GSK, he erroneously relies on "absolute numbers" of defects, while plaintiffs assert that he relies on the totality of the evidence, an approach they say is supported by his FDA experience and review of the regulatory standards.

Essentially, this issue boils down to a disagreement as to how the FDA would have interpreted the data from the two Japanese animal studies—that is, whether they would have

[5] GSK further argues that plaintiffs are trying to "backfill on the issue," because Dr. Harvey only refers to the 2011 guidance document as part of his report's general discussion of the regulatory framework, and did not specifically refer to it as a basis for his opinion about the submission of the Japanese animal studies, either in his report or in his deposition.

found three VSDs significant. Their significance appears to turn on whether the regulators would have compared three VSDs to historical controls, thereby finding no evidence of teratogenicity, or, instead, whether they would have looked at the three VSDs in conjunction with the other studies, and after considering issues of dose-dependency and the severity of VSDs. Whatever the merits of that issue, Dr. Harvey's opinion is not unduly unsupported or speculative, and will not be excluded on that basis.

Accordingly, GSK's motion will be denied as to Dr. Harvey's opinion on Zofran reproductive toxicity studies.

2. Opinions on GSK's Sales and Marketing Practices

Dr. Harvey opined that "[d]espite [possessing] unreported evidence of animal teratogenicity, GSK initiated a program of off-label marketing targeting Obstetrician/Gynecologists (OB/GYNs) to use Zofran for an unapproved indication of the treatment of pregnancy-related nausea and vomiting." (Harvey Report at 6). He further opined that "GSK's off-label marketing efforts created a false sense of safety relating to the use of Zofran during pregnancy and failed to fully inform healthcare providers and patients of the teratogenic risks associated with Zofran." (*Id.*). Finally, he opined that "GSK's off-label marketing of Zofran for use in pregnancy deviated from FDA guidance and regulations." (*Id.*).

GSK has moved to exclude Dr. Harvey's opinions on this topic, contending that he has no direct evidence of explicit off-label promotion of Zofran, and therefore his opinions are improper and speculative.

While Dr. Harvey is qualified to provide other regulatory opinions in this case, his opinion on this issue will be excluded. First, he interprets several company documents to provide "evidence of GSK's intent for Zofran" to be marketed for off-label use. (Harvey Report

at 78). But such "[i]nferences about the intent or motive of parties or others lie outside the bounds of expert testimony." *See In re Solodyn (Minocycline Hydrochloride) Antitrust Litig.*, 2018 WL 734655, at *2 (D. Mass. Feb. 6, 2018) (quoting *In re Rezulin Prods. Liab. Litig.*, 309 F. Supp. 2d 531, 547 (S.D.N.Y. 2004)). Moreover, his opinion on this issue is little more than a narrative summary of GSK's internal documents, many of which could be presented directly to a factfinder. He draws on little, if any, of his regulatory expertise in developing that narrative. In effect, Dr. Harvey "does no more than counsel for plaintiff[s] will do in argument, i.e., propound a particular interpretation of [defendant]'s conduct." *In re Rezulin*, 309 F. Supp. 2d at 551 (quoting *LinkCo, Inc. v. Fujitsu Ltd.*, 2002 WL 1585551, at *2 (S.D.N.Y. July 16, 2002)); *see also In re Trasylol Prods. Liab. Litig.*, 709 F. Supp. 2d 1323, 1337-38 (S.D. Fla. 2010). GSK's motion will therefore be granted as to that opinion.

3. Opinion on the Establishment of a Zofran Pregnancy Registry

Dr. Harvey opined that "GSK deviated from industry practices and guidelines by failing to establish a pregnancy registry for Zofran." (Harvey Report at 6). He further opined that "[i]nternal documents show that individuals within GSK contemplated a pregnancy registry . . . , but GSK management chose not to establish a registry for Zofran even though GSK maintained pregnancy registries for several of their other drugs." (*Id.*).

GSK contends that Dr. Harvey has no basis for offering that opinion. It specifically points to his alleged admissions that that there is no regulatory requirement for a pregnancy registry, and that GSK funded a Zofran study very similar to a pregnancy registry—the Einarson observational study.

Dr. Harvey acknowledges that there is no explicit FDA regulation requiring a pregnancy registry. (Harvey Dep. at 196). However, his opinion was based not on a particular regulation,

but rather on his experience and FDA guidance documents. He specifically relied on his experience with pregnancy registries while working at the FDA and then at Pfizer. (Harvey Dep. at 44-45, 52-54). He also stated that he relied on industry practices and guidelines, including a March 2005 guidance document for industry that discussed pregnancy registries among other methods of "good pharmacovigilance practices," and a 2002 FDA guidance document recommending that a sponsor seriously consider a pregnancy registry when it is likely that a medical product will be used during pregnancy. (Harvey Report at 26, 37).

GSK's response to those points is essentially that because there is no FDA regulation or guidance document that expressly *requires* a pregnancy registry, that Dr. Harvey should be precluded from opining that the company *should have* established one. However, his opinion is that "GSK *deviated from industry practices and guidelines*" in its failure to establish a registry, not that one was required by law. (*Id.* at 6). Dr. Harvey appears to be qualified to render such an opinion based on his experience at the FDA and in industry.

As to the second point, GSK contends that Dr. Harvey's admission that GSK funded the Einarson observational study, while ignoring the FDA's treatment of that study in its denial of the Reichman petition, further undermines his opinion that GSK deviated from industry standards. Whatever the significance of that funding, and the FDA's denial of the Reichman petition despite knowing of that study, they are not an appropriate basis for excluding Dr. Harvey's pregnancy-registry opinion altogether.

While the Court will permit Dr. Harvey to testify about GSK's alleged deviation from industry practices and guidelines concerning establishing a pregnancy registry, he will be precluded from opining as to GSK's intent on the subject. For example, he will be precluded from testifying that GSK "contemplated . . . but . . . chose not to establish a registry for Zofran.

(*See* Harvey Report at 6). While Dr. Harvey purports to base that opinion on GSK internal documents, that is not sufficient to allow him to opine on the motive, intent, or knowledge of individual employees of a company, much less of the company itself. That aspect of his pregnancy-registry opinion is outside his expertise and therefore will be excluded. *See In re Solodyn*, 2018 WL 734655, at *2. Otherwise, however, his opinion as to the pregnancy registry will be permitted.

4. Pharmacovigilance Opinions

Dr. Harvey opined that "GSK failed to implement adequate pharmacovigilance practices and failed to provide FDA with all adverse pregnancy outcomes that they had." (Harvey Report at 6). He specifically opined that GSK "did not include all pregnancy-related adverse birth outcomes within its global safety base," and therefore "fail[ed] to accurately monitor, assess and report adverse events to FDA," which "altered the mix of evidence available to the agency and deprived FDA of the ability to evaluate Zofran's pregnancy related risks based on a complete record." (*Id.*). He further opined that "[a]s the former Division Director with responsibility for regulating Zofran, the omitted information was material to me and based on my experience would have been material to a reasonable FDA official performing the same regulatory functions." (*Id.* at 6-7).

The Court will not endeavor to outline every dispute between the parties about specific adverse event reports, as such a granular analysis is not necessary to resolve the issues presented. For example, one such dispute concerns 11 adverse event reports involving cardiac murmurs in children exposed to both Zofran and another drug, Paxil. As Dr. Harvey acknowledged at his deposition, those cases were, in fact, reported to the FDA. (Harvey Dep. at 240-241; Harvey Report at 89). However, he opined that they were not *appropriately* reported, because they were

reported with Paxil as the "suspect drug," not Zofran, notwithstanding FDA reporting forms, instructions, and expectations that, he says, allow and encourage manufactures to report more than one suspect medication where needed. (Harvey Dep. at 240-41; Harvey Report at 19-23, 89-90). GSK contends that Dr. Harvey's regulatory support for that opinion is not grounded in any specific regulation.

The parties similarly dispute the adequacy of regulatory support for Dr. Harvey's opinion that GSK improperly failed to provide several adverse event reports from the Einarson study to the FDA, apparently because GSK concluded that the events were not caused by Zofran. (Harvey Report at 90-91). That dispute similarly seems to turn on whether Dr. Harvey can opine that those adverse events should have been reported to the FDA differently, based on his experience with the adverse event reporting regulations, the agency's general practice, and the agency's expectations.

Dr. Harvey also opined that GSK should have reconciled adverse event reports from the FDA's database with GSK's own safety database—in other words, independently analyzed FDA's adverse event database—as Novartis apparently did when it took over pharmacovigilance responsibility for Zofran. (Harvey Report at 91 (citing ZFN00815292-93)). Again, GSK contends that this opinion is not based on a specific FDA regulation, and plaintiffs respond that it is based on his experience with the standard of behavior of a reasonable pharmaceutical company, and also the general expectations of the agency. (Harvey Dep. at 246-48; Harvey Report at 91-92).

GSK's objections to the lack of specific regulatory support for Dr. Harvey's pharmacovigilance opinions are not an appropriate basis on which to exclude his testimony. Again, those objections go to the weight of his testimony, rather than its admissibility. The

motion to exclude Dr. Harvey's pharmacovigilance opinions will therefore be denied.

5. Labeling Opinions

Dr. Harvey opined that "GSK was aware that it had the ability to communicate with the agency and update risk disclosures . . . in Zofran's labeling through the CBE process . . . [but] chose not to update medical practitioners and the public with complete risk disclosures." (Harvey Report at 7). He further opined that "GSK's failure to timely update risk disclosures postmarketing, based upon information that the company knew or should have known, was a deviation from industry practices and agency requirements." (*Id.* at 7). He went on to suggest a number of detailed labeling provisions, and prefaced them with his opinion that "[a]cceptable drug labeling . . . would have included labeling providing the following information . . . ," or that "GSK should have included information describing the following concerns . . . ." (*Id.* at 98-100).

GSK contends that Dr. Harvey has no data to support his proposed labeling changes, despite acknowledging that the agency requires drug labeling to be supported by data. It characterizes his labeling opinion as essentially "that FDA would have reversed its position on the Reichmann Citizen Petition and on the pregnancy labeling proposed by Novartis based on the Japanese animal studies and the cardiac murmur cases." (GSK's Mem. in Supp. at 29).[6] Among other things, it asserts that his labeling opinion is "undercut" by the following statements and real-life actions by the FDA:

> (1) the fact that it defines a "positive signal" in a reproductive toxicology study by comparison to concurrent or historical control data; (2) its decision to assign Zofran ODT Pregnancy Category B after seeing a VSD in Study 100422; (3) its assignment of Pregnancy Category B to Viagra after seeing five VSDs exceeding

[6] GSK further "boils down" Dr. Harvey's labeling opinion, based on concessions he apparently made at his deposition, to be essentially "that FDA would have changed its positions on the Citizen Petition and Novartis labeling proposals—both grounded in analysis of years of human data—based on two VSDs in rats falling within historical control ranges." (GSK's Mem. in Supp. at 31).

> historical controls; and (4) its repeated statements that human data is more clinically relevant than, and can supersede, animal data.

(GSK's Reply at 32).

Plaintiffs respond that each of GSK's arguments concerns a factual issue subject to disagreement by reasonable, qualified experts. Dr. Harvey employed a reliable methodology, they assert, because he reviewed the relevant safety data, including the Japanese animal studies and Dr. Bengt Danielsson's report, as well as the relevant regulatory standards, including 44 Fed. Reg. 37,434, 37,441 (June 26, 1979), which require reasonable evidence of an association between birth defects and Zofran. According to plaintiffs, he then reliably evaluated that data using his expert knowledge, experience, and training from his decades of pharmaceutical work, and ultimately came to the opinion that GSK had reasonable evidence of Zofran's association with certain birth defects and had the ability to update its labeling accordingly.

Under the circumstances, this dispute essentially amounts to a factual disagreement between experts as to the regulatory significance of the Japanese animal studies and other evidence allegedly showing an association between Zofran and birth defects. Where both experts have a sufficient basis for reaching their opinions under Rule 702, the opinions should not be excluded. The motion to exclude Dr. Harvey's labeling opinions will therefore be denied.

6. <u>Causation-Related Statements or Opinions</u>

Finally, Dr. Harvey opined that "Zofran blocks the cardiac hERG (human Ether-à-go-go-Related Gene) channel; this mechanism is known to cause cardiovascular and orofacial birth defects when ingested during pregnancy." (Harvey Report at 40). He further opined that Zofran is "associated with" "known teratogenic risks." (*Id.* at 54, 60, 97-98).

GSK contends that Dr. Harvey should be precluded from providing causation-related opinions: because (1) he is not an expert in the relevant fields; (2) he is not being proffered as a

general causation expert; (3) he did not review the reproductive toxicology data or epidemiologic data on Zofran and birth defects himself, instead relying on Dr. Danielsson's summary of that data; and (4) he did not apply the Bradford Hill criteria, or any other scientific methodology to assess whether Zofran can cause birth defects.[7] According to GSK, permitting him to testify in a conclusory fashion about a critical scientific question at issue in this case—essentially, whether there is a causal relationship between Zofran and certain birth defects—without having the qualifications to do so, without holding himself out as a scientific expert, and without applying the accepted methodology, would be highly prejudicial.

Dr. Harvey is not being offered as a causation expert in this case, nor does he hold himself out as such. In addition, while plaintiffs ask the Court to deny GSK's motion to exclude Dr. Harvey in its entirety, they have not specifically addressed GSK's arguments for excluding his causation-related statements and opinions. The Court will therefore assume plaintiffs have conceded this issue.

Accordingly, GSK's motion to exclude will be granted as to that ground. Dr. Harvey will be precluded from giving causation-related testimony, including opinions or statements to the effect of 'Zofran blocks the hERG channel, a known mechanism of action for causing birth defects,' and 'Zofran is associated with known teratogenic risks.'

III. Conclusion

For the foregoing reasons, plaintiffs' motion to exclude the testimony of GSK's regulatory expert Dr. Hixon on determination of teratogenicity and pharmacovigilance analysis is

[7] "Developed by Sir Bradford Hill in the 1960s, the criteria are nine factors which researchers often consider when judging whether an observed association is truly causal." *In re Neurontin Mktg., Sales Practices, & Prod. Liab. Litig.*, 612 F. Supp. 2d 116, 132-33 (D. Mass. 2009) (citing A. Bradford Hill, *The Environment and Disease: Association or Causation?*, 58 PROC. ROYAL SOC'Y MED. 295 (1965)).

DENIED. GSK's motion to exclude the testimony of plaintiffs' regulatory expert Dr. Harvey is GRANTED as to (1) his opinions on GSK's sales and marketing practices; (2) his opinions on GSK's knowledge or intent concerning establishing a pregnancy-registry for Zofran; and (3) his opinions on causation, and is otherwise DENIED.

So Ordered.

_F. Dennis Saylor_____
F. Dennis Saylor, IV
Dated: November 1, 2019 United States District Judge