No. 21-1517

IN THE

United States Court Of Appeals

FOR THE FIRST CIRCUIT

IN RE: ZOFRAN (ONDANSETRON) PRODUCTS LIABILITY LITIGATION

HEATHER PERHAM, et al.,

Plaintiffs - Appellants,

— v. —

GLAXOSMITHKLINE LLC,

Defendant - Appellee,

SUN PHARMACEUTICAL INDUSTRIES LTD.; SANDOZ, INC.; PROVIDENCE HEALTH SYSTEM; NOVARTIS PHARMACEUTICALS CORP.; MCKESSON CORPORATION; DOES 1 THROUGH 100, INCLUSIVE, TEVA PHARMACEUTICAL USA; GLAXOSMITHKLINE HOLDINGS (AMERICAS) INC.,

Defendants.

ON APPEAL FROM THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF MASSACHUSETTS

REPLY BRIEF FOR PLAINTIFFS-APPELLANTS

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Plaintiffs-Appellants' failure-to-warn claim against Defendant-Appellee GlaxoSmithKline LLC ("GSK") is straightforward: GSK's anti-nausea drug, Zofran, should have been designated as a Pregnancy Category C drug (animal studies reveal some evidence of teratogenicity) under then-existing FDA regulations, rather than as a Pregnancy Category B drug (no evidence of birth defects in animal studies). Had Zofran been properly labeled as a Pregnancy Category C drug, Plaintiffs allege, their doctors would not have prescribed, and/or Plaintiffs would not have taken, Zofran to treat pregnancy-related nausea and vomiting during the first trimester of pregnancy, and their children would not have been born with cardiac or orofacial defects as a result of their use of Zofran.

Plaintiffs-Appellants' argument on appeal against preemption is equally straightforward. The Supreme Court's recent decision in *Merck Sharp & Dohme Corp. v. Albrecht*, 139 S. Ct. 1668 (2019), explains that "a drug manufacturer will not ordinarily be able to show that there is an actual conflict between state and federal law such that it was impossible to comply with both." *Id.* at 1679. As the Court articulated:

> showing that federal law prohibited the drug manufacturer from adding a warning that would satisfy state law requires the drug manufacturer to show that it fully informed the FDA of the justifications for the warning required by state law and that the FDA, in turn, informed the

> drug manufacturer that the FDA would not approve changing the drug's label to include that warning.

Id. at 1678. GSK has not met that test here and the district court erred in concluding otherwise.

There is no dispute that, prior to 2019, GSK had not fully informed FDA about the justifications for placing Zofran in Pregnancy Category C, because it had withheld from the agency the results of certain pre-clinical animal reproduction studies conducted in Japan that contained evidence that Zofran caused birth defects. And, since that date, FDA has taken no formal agency action that makes clear that FDA would not permit a change to the Zofran label to inform doctors and patients of the evidence of birth defects in the Japanese animal studies. For these reasons, the decision below must be reversed.[1]

GSK's brief is a masterwork of misdirection and obfuscation. It discusses numerous irrelevant matters, and repeatedly disparages plaintiffs and their counsel, but never squarely addresses the legal issue before this Court. Indeed, somewhat

[1] Contrary to the alarmist assertions of Appellee and its amicus, reversal of the district court's grant of summary judgment on grounds of preemption does not, of course, mean that Plaintiffs will necessarily prevail on their failure-to-warn claims. Plaintiffs still must establish, by a preponderance of the evidence, that Zofran can cause birth defects when used early in pregnancy, that it did cause birth defects in their pregnancies, and that they would not have used Zofran to treat their pregnancy-related nausea had they been properly informed of the risks. The only issue before this Court is whether Plaintiffs should be allowed the opportunity to make this showing at trial.

shockingly, GSK's brief never once acknowledges the test for impossibility preemption announced (twice) by the Supreme Court in *Albrecht*, quoted above. *See* 139 S. Ct. at 1672, 1678.[2]

Contrary to GSK's contentions, FDA's actions on Novartis's 2020 prior approval supplement (PAS) application do not have preemptive effect. Novartis did not ask to change the sections of the label concerning animal data and FDA never said that such a change would not be permitted. In fact, FDA permitted Novartis to include data in the label from human epidemiological studies that show an association between Zofran and birth defects, even though FDA did not believe that those studies conclusively established causation. Analogously, there is no reason to believe that FDA would have prohibited Novartis from adding data about the evidence of birth defects in the Japanese animal studies, while acknowledging the studies' limitations.

Likewise, contrary to GSK's contention, there is no valid argument that FDA's actions on the 2015 Reichmann citizen petition or Novartis's 2016 PAS had preemptive effect. As the district court recognized, Addendum at 33, FDA had not

[2] Appellee's *amicus*, the Pharmaceutical Research and Manufacturers of America (PhRMA), likewise never once references the *Albrecht* legal standard in its brief.

been "fully informed" about the Japanese animal studies at the time of those administrative actions. They thus cannot have preemptive effect under *Albrecht*.[3]

Finally, contrary to GSK's contention, it is not entitled to preemption on the alternate grounds that the withheld Japanese animal studies do not constitute "newly acquired information" sufficient to support a CBE label change. They unquestionably do, as they "indicate[] new or greater risks" than the studies submitted to FDA in connection with Zofran's approval. *In re Celexa & Lexapro Mktg. & Sales Pracs. Litig.*, 779 F.3d 34, 41 (1st Cir. 2015).

ARGUMENT

I. Contrary to GSK's Arguments, FDA's Actions on Novartis's 2020 PAS Do Not Have Preemptive Effect.

GSK's primary argument on appeal, like that of the district court, is that FDA's so-called "rejection" of Novartis's 2020 PAS application is "clear evidence" that FDA would not have approved a label change to reflect that pre-clinical animal studies showed evidence of teratogenicity. But that is simply not the case. Novartis did not ask FDA to change the animal data sections of the labeling and none of FDA's actions regarding the label preclude Novartis (or formerly GSK) from making the label change Plaintiffs claim was required by state law.

[3] Whether or not GSK's disclosures complied with FDA regulatory requirements, as GSK contends, is irrelevant to the question whether GSK could have relied on those studies to support a "Changes Being Effected" ("CBE") labeling change to Pregnancy Category C.

A. GSK Ignores the Legal Standard for Impossibility Preemption Announced in *Albrecht.*

GSK never once acknowledges, let alone quotes, the test for impossibility preemption announced in *Albrecht*:

> showing that federal law prohibited the drug manufacturer from adding a warning that would satisfy state law requires the drug manufacturer to show that . . . *the FDA*, in turn, *informed the drug manufacturer that the FDA would not approve changing the drug's label to include that warning*.

139 S. Ct. at 1678 (emphasis added). GSK simply rejects this clear statement from the Supreme Court as to the legal standard for preemption: "*Albrecht* does not require express disapproval of the verbatim warning urged by plaintiffs in litigation." GSK Br. 50 (citing a pre-*Albrecht* decision).

In GSK's view, the correct legal standard is found in a single line of *dicta* in *Wyeth v. Levine*, 555 U.S. 555 (2009): "absent clear evidence that the FDA *would not have approved* a change to Phenergan's label, we will not conclude that it was impossible for Wyeth to comply with both federal and state requirements." *Id.* at 571 (emphasis added). But GSK simply ignores the fact that *Albrecht* was the opportunity for the Supreme Court to "elaborate *Wyeth*'s requirements," and that the Supreme Court did so by announcing that the test, quoted above, applied "[i]n a case like *Wyeth*." 139 S. Ct. at 1677-78.

Moreover, it makes sense that a determination like impossibility preemption would require an express statement by FDA that it would not permit a particular

label change. As the Supreme Court has repeatedly held, impossibility preemption only arises when federal and state law "irreconcilably conflict"; "[t]he existence of a hypothetical or potential conflict is insufficient to warrant . . . pre-emption." *Rice v. Norman Williams Co.*, 458 U.S. 654, 659 (1982). The drug manufacturer, not the FDA, "bears responsibility for the content of its label at all times," *Wyeth*, 555 U.S. at 570–71, and FDA's CBE regulation allows the manufacturer to immediately implement a label change to add or strengthen a warning without prior agency approval, *see* 21 C.F.R. § 314.70(c)(6)(iii). Therefore, only the clearest statement from FDA prohibiting the change required by state law should be understood to have preemptive effect.

Likewise, requiring an explicit statement from FDA meshes neatly with the additional *Albrecht* requirement that only formal agency actions with the force of law can have preemptive effect: "Federal law permits the FDA to communicate its disapproval of a warning by means of notice-and-comment rulemaking setting forth labeling standards, by formally rejecting a warning label that would have been adequate under state law, or with other agency action carrying the force of law." 139 S. Ct. at 1679 (citations omitted). Whatever FDA silence may imply (especially on

an issue the agency was not asked to consider), it is not a "formal[] rejecti[on of] a warning label that would have been adequate under state law." *Id.*[4]

Moreover, contrary to GSK's argument, GSK Br. 45, it is not Plaintiffs' position, but GSK's, that would require a court "'to probe the mental processes' of administrative officers." *Braniff Airways, Inc. v. Civil Aeronautics Bd.*, 379 F.2d 453, 460 (D.C. Cir. 1967). It is GSK that seeks to tease an implicit disapproval out

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[4] GSK asserts that "*Albrecht* does not require 'formal agency action,'" claiming that only Justice Thomas's concurring opinion expressed this view. GSK's Br. 56. It is hard to imagine how GSK could take this position in the face of the just-quoted language from the *Albrecht* majority, which says that FDA can "communicate its disapproval" by "rulemaking," "by formally rejecting a warning label," or by "other agency action carrying the force of law." *Id.* Each is unquestionably "formal agency action." FDA silence on a label change that the sponsor has not requested is not.

The cases cited by GSK, *see* GSK Br. 50–52, do not lead to a different conclusion. The *Cerveny v. Aventis, Inc.*, 783 F. App'x 804 (10th Cir. 2019), *In re Fosamax (Alendronate Sodium) Products Liability Litigation*, 2022 WL 855853 (D.N.J. Mar. 23, 2021), and *In re Incretin-Based Therapies Products Liability Litigation*, 524 F. Supp. 3d 1007 (S.D. Cal. 2021), *aff'd*, No. 21-55342, 2022 WL 898595 (9th Cir. Mar. 28, 2022), cases simply stand for the proposition that the FDA may communicate its disapproval through means other than rejection of a label change proposed by the manufacturer. *Silverstein v. Boehringer Ingelheim Pharmaceuticals, Inc.*, 2020 WL 6110909 (S.D. Fla. 2020), improperly relies on pre-*Albrecht* precedent to conclude that the "clear evidence" standard "can be satisfied even if the labeling change has not been presented to, and rejected by, the FDA." *Id.* at *9 (citing *Seufert v. Merck Sharp & Dohme Corp.*, 187 F. Supp. 3d 1163, 1170 (S.D. Cal. 2016)). Finally, *Dolin v. GlaxoSmithKline LLC*, 951 F.3d 882 (7th Cir. 2020), which expressly acknowledged that the "informed the drug manufacturer" language in *Albrecht* appeared to narrow the standard for impossibility preemption, nevertheless found that "the FDA unambiguously rejected a Paxil-specific warning in 2007 when it formally mandated that all SSRIs carry a uniform, class-wide warning label." *Id.* at 891.

of FDA silence. *Albrecht*'s express disapproval requirement, by contrast, provides clarity about precisely what labeling changes the agency has prohibited, without any need to interrogate the agency.

Because GSK's entire argument on appeal is premised on a legal standard that is inconsistent with the Supreme Court's holding in *Albrecht*, it must be rejected.[5]

B. FDA's Actions on Novartis's 2020 PAS Do Not Prohibit a CBE Label Change to Include the Results of the Japanese Animal Studies.

The actions FDA actually took on Novartis's 2020 PAS do not amount to agency disapproval of the label change Plaintiffs contend was required by state law: the inclusion of information about the birth defects that occurred in the Japanese animal studies. GSK points to four specific actions taken by FDA in that proceeding; none precludes that labeling change. By contrast, at least one change expressly approved by FDA—the inclusion of data from human epidemiological studies that

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[5] Both GSK and its *amicus*, the Pharmaceutical Research and Manufacturers of America ("PhRMA"), make much of the provision that empowers the FDA to initiate a label change when it "becomes aware of . . . new safety information" that "should be included in the labeling," 21 U.S.C. § 355(o)(4)(A), suggesting that the FDA's failure to take action, in light of this provision, should have preemptive effect, *see* GSK Br. 53–54; PhRMA *Amicus* Br. 9–15. But that position, which is in direct conflict with the holding in *Wyeth*, *see* 555 U.S. at 579 ("[M]anufacturers, not the FDA, bear primary responsibility for their drug labeling at all times."), was endorsed in *Albrecht* by only three Justices, *see* 139 S. Ct. at 1684 (Alito, J., concurring in the judgment with Roberts, C.J., and Kavanaugh, J.). And the majority, along with Justice Thomas's concurrence, required express FDA disapproval for preemption. *See supra* n.4.

found correlations between Zofran use and birth defects—strongly suggests that FDA would permit such a change.[6]

[redacted]

[6] Of course, whether the FDA would permit the change is not the relevant preemption test; because the FDA did not prohibit such a change, impossibility preemption does not apply.

[redacted]

Third, GSK's claims, "FDA affirmed language stating that animal data revealed 'no significant effects of ondansetron [*i.e.*, Zofran] on the maternal animals or the development of the offspring." GSK Br. 42. Of course, what GSK really means is that FDA made no change to the pre-existing animal data section of the label that Novartis had not asked to change. There are at least thirty sections of the Zofran label for which Novartis sought no changes and FDA made none. It is hard to see how FDA silence in this situation can amount to the agency *informing* the drug sponsor that it would not permit a label change. *See Wyeth*, 555 U.S. at 578–79 ("The FDA has limited resources to monitor the 11,000 drugs on the market, and manufacturers have superior access to information about their drugs, especially in the postmarketing phase as new risks emerge." (footnote call number omitted)); *Albrecht*, 139 S. Ct. at 1679 ("[T]he CBE regulation permits changes, so a drug manufacturer will not ordinarily be able to show that there is an actual conflict between state and federal law such that it was impossible to comply with both.").

Finally, GSK hangs its hat on FDA's *sua sponte* addition of the word "oral" to one sentence in the animal data section for the injectable form of Zofran. GSK

Br. 48. GSK describes this as a "devastating fact" that "prov[es] conclusively that FDA considered the animal data." *Id.* GSK should look more closely. As Plaintiffs explained in their opening brief, it is clear, in context, that this change was an attempt to conform the labeling for injectable Zofran to that for other formulations of the drug. Appellants' Br. 56 n.19. And a sloppy attempt at that. The change ordered by FDA now redundantly identifies the route of administration: "In an *oral* pre- and post-natal development study pregnant rats received *oral* doses of ondansetron . . . ." PUB_011031 (emphasis added). That FDA sought (imperfectly) to achieve consistency across Zofran labels hardly constitutes proof that the agency intended to prohibit the inclusion of data from the Japanese animal studies.

By contrast, one change in the Zofran labeling FDA approved strongly supports Plaintiffs' position. FDA approved Novartis adding language describing human epidemiological studies that had found positive associations between ondansetron use during pregnancy and birth defects, even though FDA did not regard these studies as conclusive due to methodological limitations. Appellants' Br. 22–23 (quoting PUB_011030–31). This strongly suggests that FDA would also have permitted Novartis to add, with appropriate caveats, information about the positive correlation between Zofran use and birth defects in the Japanese animal studies.

Nothing FDA actually said or did regarding Novartis's 2020 PAS informed Novartis that FDA would not approve the addition of information about the Japanese studies and thus Novartis remained (and remains) free to add such information to the label through a CBE supplement. Therefore, Plaintiffs' claims are not preempted by FDA's actions on Novartis's 2020 PAS.

II. Contrary to GSK's Arguments, FDA's Actions on the 2015 Reichmann Citizen Petition and the 2016 Novartis PAS Do Not Have Preemptive Effect.

GSK next argues that FDA's actions on the 2015 Reichmann Citizen Petition and Novartis's 2016 PAS have preemptive effect. GSK Br. 57–63. GSK concedes that FDA lacked full information about the Japanese animal studies at that time, *id.* at 58, but argues that this shouldn't matter, because—GSK contends—it had complied with all FDA disclosure requirements, *id.* at 58–59.

GSK's argument improperly conflates the requirements of FDA regulatory compliance with the requirements for impossibility preemption. *Albrecht* does not say that a manufacturer can establish preemption by showing that it complied with regulatory disclosure requirements. Rather, it says that "the drug manufacturer [must] show that it fully informed the FDA of the justifications for the warning required by state law," 139 S. Ct. at 1678, regardless of whether disclosure was

required. And there is no question that GSK had not disclosed the results of the Japanese animal studies to FDA.[7]

Indeed, there is even a serious question whether GSK complied with FDA regulatory requirements. As GSK acknowledges, GSK Br. 59, 21 C.F.R. § 312.33(b)(6) required GSK to disclose a "list of the preclinical studies (including animal studies) completed or in progress during the past year and a summary of the major preclinical findings." GSK did list the Japanese animal studies in its annual report, but told FDA that "[t]hese studies [were] either repetitive or provide no new significant safety information." PUB_003872–73. If, as Plaintiffs and their experts contend, these studies revealed evidence of Zofran's teratogenicity, it is hard to see how this submission can be said to provide a proper "summary of the major preclinical findings."[8]

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[7] GSK accuses Plaintiffs of asking this Court "to be the first to adopt a novel 'fully informed' requirement that disregards FDA disclosure requirements," GSK Br. 62, without acknowledging that it was *Albrecht*, not Plaintiffs, that articulated this requirement for impossibility preemption.

[8] Moreover, as discussed below, *see infra* pp. 23–25, when FDA specifically asked GSK in 2014 for "full details of animal reproduction studies" of Zofran, PUB_003105, GSK responded by simply describing the same U.K. animal studies that had been submitted to FDA in 1989, without any reference to the Japanese animal studies, PUB_003139. GSK asserts, without any evidence, that "FDA's comment referred to *the U.K. animal studies* that were summarized in the existing labeling," GSK Br. 61, but fails to explain why FDA would only want it to resubmit study data that the agency already had. To the contrary, FDA's request highlights the agency's interest in the results of animal reproduction studies that had not been previously submitted. *Cf. In re Taxotere (Docetaxel) Prods. Liab. Litig.*, 508

As explained in Plaintiffs-Appellants' Opening Brief, because FDA had not been fully informed of the justifications for a Pregnancy Category C warning at the time it took action on the Reichman petition and Novartis's 2016 PAS, those administrative actions cannot have preemptive effect under *Albrecht*. Appellants' Br. 49–52.

III. Contrary to GSK's Arguments, the Japanese Animal Studies are "Newly Acquired Information" that Would Have Supported a CBE Change from Pregnancy Category B to Pregnancy Category C.

GSK makes one final argument in support of affirmance: that "the CBE regulation would not have 'allowed [GSK] to use the CBE procedure to alter the FDA label in the manner that plaintiffs allege is necessary.'" GSK Br. 63 (quoting *In re Celexa*, 779 F.3d at 43). GSK contends that the Japanese animal studies do not constitute "newly acquired information" that provides "reasonable evidence of a causal association" between Zofran and birth defects. *Id.* at 63–73. GSK's argument is both factually and legally incorrect.

To be clear, this is GSK's argument, not the District Court's argument. The District Court assumed, without deciding, that the Japanese animal studies "constituted 'newly acquired information' as defined by the CBE regulations, and therefore GSK could have attempted to amend the Zofran label unilaterally at one or

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F. Supp. 3d 71, 84 (E.D. La. 2020) (finding it significant that FDA asked Sanofi to analyze whether Taxotere use resulted in permanent alopecia).

more points during the period that it owned the rights to the drug." Addendum 54. That assumption was correct.

To begin with, it is important to note that the standard for such "newly acquired information" is not onerous. FDA regulations define the term as:

> data, analyses, or other information not previously submitted to the Agency, which may include (but is not limited to) data derived from new clinical studies, reports of adverse events, or new analyses of previously submitted data (e.g., meta-analyses) if the studies, events, or analyses reveal risks of a different type or greater severity or frequency than previously included in submissions to FDA.

21 C.F.R. § 314.3(b). "The rule accounts for the fact that risk information accumulates over time and that the same data may take on a different meaning in light of subsequent developments," *Wyeth*, 555 U.S. at 569, and "covers virtually all situations in which new information indicates new or greater risks, " *In re Celexa*, 779 F.3d at 41.

Likewise, for a CBE label change, the drug manufacturer need only have "reasonable evidence of a causal association" between the drug and a "clinically significant hazard" such as a birth defect; "a causal relationship need not have been definitely established." 21 C.F.R. § 201.57(c)(6)(i); *see also* § 314.70(c)(6)(iii). According to FDA, such "reasonable evidence" of a causal association is a lower evidentiary standard than the "preponderance of the evidence" standard Plaintiffs must meet to prove causation at trial. Supplemental Applications Proposing Labeling Changes for Approved Drugs, Biologics, and Medical Devices, 73 Fed.

Reg. 49603, 49604 (Aug. 22, 2008) (describing "a 'preponderance' of evidence that a product actually causes a particular kind of adverse event" as "a higher evidentiary standard").

Moreover, the only expert testimony in the record on this issue supports Plaintiffs. Plaintiffs' expert teratologist, Dr. Bengt Danielsson, and their regulatory expert, Dr. Brian Harvey, are unopposed on the scientific and regulatory significance of the Japanese animal studies. GSK has no expert to contradict Drs. Danielsson and Harvey.[9]

Turning to the substance, there is considerable evidence that the withheld Japanese animal studies constitute "newly acquired information." First, Dr. Danielsson offers testimony that the rats tested in the Japanese studies were exposed to higher levels of ondansetron than the rats in the U.K. studies. JA_003590 ("Compared to the studies evaluated by FDA [*i.e.*, the U.K. studies], the doses in the Japanese oral and iv studies resulted in higher exposure margins in relation to the exposure in human pregnancy.").[10] This fact, in and of itself, should be sufficient to establish that the Japanese studies are "newly acquired information."

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[9] The district court struck as untimely the declaration of GSK's reproductive toxicologist, Dr. Patrick Wier. PUB_007268–97. GSK's regulatory expert, Dr. Dena Hixon, offered no opinion on the regulatory significance of the Japanese studies vis-à-vis the U.K. studies. PUB_000921–997.

[10] Dr. Danielsson explains that the exposure levels in the main U.K. teratology study "resulted in low system exposures compared to human exposures in early

As Dr. Danielsson explains, the international standards for teratology testing were updated in 1993, shortly after GSK's animal studies. The new standards issued by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) call for "both significantly higher total exposure per day (AUC) and higher maximal exposure (Cmax) [in animal teratology studies] than human therapeutic exposures/concentrations, in order to detect teratogenic potential in humans." PUB_000623. "Only at higher exposures than in humans (both regarding Cmax and AUC) is it possible to fully characterize the drug's human teratogenic potential." PUB_000653.

Because rats have a significantly higher metabolism rate, ondansetron's bioavailability is much lower in rats (4%) than in humans (62%). JA_003590. Therefore, their exposure to ondansetron is much lower at equivalent dosage levels in milligrams per kilogram. *Id.* (even at 125 times higher dose, by mg/kg, rats had lower systemic exposure (AUC) compared to human taking one 8 mg tablet per day during pregnancy). Generally speaking, therefore, the Glaxo animal studies were inadequately dosed to assess Zofran's teratogenicity. PUB_000647 ("The low exposures of ondansetron in the Glaxo animal studies did not meet regulatory expectations and industry standards today, especially for a drug which can be

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pregnancy . . . most likely due to increased susceptibility to CNS toxicity in the AHA rats." PUB_000645.

expected to be or is used widely in pregnancy.").[11] However, where dose levels (measured by Cmax or AUC) exceeded human exposure levels, malformations resulted. PUB_000648.

GSK could unquestionably have presented this evidence of fetal malformations in the Japanese study data, contextualized with data about both maximum and systemic exposure (Cmax and AUC), as ICH Guidelines suggest, to support a CBE label change from Pregnancy Category B to Category C. GSK could even have supported this application by re-evaluating the U.K. study data in terms of AUC and Cmax. No regulatory action taken by FDA would have prevented such a label change.

Moreover, as Dr. Danielsson explains, such a CBE application could also have been supported by other evidence of teratogenicity apart from the animal studies. Zofran's function as a hERG blocker, for example, has been known since at least 1994. JA_003592. Other hERG-blocking drugs, with similar mechanisms of action, including Corvert (ibutilide), dofetilide, and Dilantin (phenytoin), have all been shown to be teratogenic in animal studies. PUB_000658–59. And each carried

[11] This answers GSK's argument that the current FDA-approved labeling notes that the U.K. studies involved dosages "approximately 6 and 24 times the maximum recommended human oral dose . . . based on body surface area." GSK Br. 69 (quoting JA_11055). Measured by systemic exposure, most of the U.K. study dosages fell short of human exposure.

stronger warnings against use during pregnancy because of their teratogenicity.[12] GSK could have linked the evidence of birth defects in the Japanese animal studies to this well-recognized record of an association between hERG-blocking drugs and teratogenicity to establish "reasonable evidence of a causal association."

GSK contends that none of this matters, because FDA had already rejected evidence of birth defects from the U.K. animal studies and the one Japanese study it had previously submitted to FDA. GSK Br. 64-68. In its view, the Japanese studies are not "newly acquired information" because they do not "reveal risks of a different type or greater severity or frequency than previously included in submissions to FDA." *Id.* at 64 (quoting 21 C.F.R. § 314.3(b)).

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[12] "Pregnancy Category C. Ibutilide administered orally was teratogenic . . . and embryocidal in reproductive studies in rats. . . . CORVERT should not be administered to a pregnant woman unless clinical benefit outweighs potential risk to the fetus." (2000 label). www.accessdata.fda.gov/drugsatfda_docs/nda/2001/20-491S003.pdf.

"Pregnancy Category C. Dofetilide has been shown to adversely affect *in utero* growth and survival of rats and mice when orally administered during organogenesis . . . . Therefore, dofetilide should only be administered to pregnant women where the benefit to the patient justifies the potential risk to the fetus." https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/207058Orig1s000lbl.pdf.

"If this drug is used during pregnancy, or if the patient becomes pregnant while taking the drug, the patient should be apprised of the potential harm to the fetus. Prenatal exposure to phenytoin may increase the risks for congenital malformations and other adverse developmental outcomes." https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/008762s036lbl.pdf.

That is wrong as a matter of both law and logic. GSK had told FDA that the previously submitted studies contained no evidence of teratogenicity. *See, e.g.*, PUB_003139. So, by definition, a CBE application based on evidence of teratogenicity in the withheld Japanese animal studies would necessarily constitute evidence of "new or greater risks," *In re Celexa*, 779 F.3d at 41, than in previous submissions. Plus, as just explained, the Japanese studies involved higher dosing than the previously submitted studies. JA_003590 ("Compared to the studies evaluated by FDA, the doses in the Japanese oral and iv studies resulted in higher exposure margins in relation to the exposure in human pregnancy."). Especially when combined with the AUC and Cmax data that GSK *had not previously provided to FDA*, this would undoubtedly have amounted to "reasonable evidence of a causal association" with a "clinically significant hazard." 21 C.F.R. § 201.57(c)(6)(i).[13]

[13] *See, e.g.*, Br. of United States of America, *Merck Sharp & Dohme Corp. v. Albrecht*, 2018 WL 4562163, at *27-28 (U.S. 2018):

> To be sure, an actual FDA labeling decision might not in itself resolve preemption if, for instance, FDA did not consider certain safety information in approving name-brand drug labeling or in denying a labeling change because the information was not provided to FDA or because it arose after FDA's decision. In such a situation, a plaintiff could argue that information that FDA did not consider constitutes "newly acquired information," 21 C.F.R. 314.3(b), 314.70(c)(6)(iii)(A), showing that the drug caused a sufficiently serious hazard to have allowed the manufacturer to update its labeling under the CBE process.

Of course, on these facts, even if the withheld Japanese studies were merely cumulative of the studies FDA had previously considered, as GSK suggests—(they are not)—that would not lead to preemption. GSK's whole argument for discounting the birth defects found in the prior studies was that they were well within the expected "background rate" of naturally-occurring birth defects, *see* GSK Br. 3, 9–10, 66, conveniently ignoring the fact that the defects occurred only in the treated animals, not in the untreated controls.[14] Thus, evidence of additional studies in which only the treated animals had offspring with birth defects (the withheld Japanese studies)—especially if supported by the missing AUC and Cmax data, and information about the teratogenicity of other hERG-blocking drugs—would unquestionably weaken the argument for spontaneous occurrence and strengthen the

[14] GSK's argument also contradicts the testimony of its own Worldwide Director of Reproductive Toxicology, who acknowledged that for the rats in the U.K. studies there is a "lack of historical data for this strain to evaluate whether the incidences were above background or not." PUB_011947.

case for a causal relationship between the treatment drug and the resulting birth defects.[15] That is precisely the situation before the Court.[16]

If there were any doubt that FDA would have been interested in new information about an association between Zofran use during pregnancy and birth

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[15] As Dr. Danielsson explains:

> The causal relationship of ondansetron to the malformations seen in treated animals in the Glaxo studies is also strengthened in view of lack of malformations in concurrent controls, reproducibility of cardiovascular defects in the studies, and that malformations were only noticed in the studies with highest exposures.

PUB_000648. This is essentially Dr. Danielsson's application of the "'weight of the evidence' methodology . . . articulated by world-renowned epidemiologist Sir Arthur Bradford Hill in his seminal methodological article on inferences of causality," which this Court has endorsed. *Milward v. Acuity Specialty Prods. Grp., Inc.*, 639 F.3d 11, 17 (1st Cir. 2011) (citing *The Environment and Disease: Association or Causation?*, 58 Proc. Royal Soc'y Med. 295 (1965)).

[16] GSK attempts to mislead the Court by asserting that Plaintiffs' epidemiology expert, Dr. Carol Louik, agreed that there was no evidence of "an association—much less a causal association"—between Zofran and cardiac defects. GSK Br. 30; *see also id.* at 71–72. That is untrue. Dr. Louik conceded at deposition only that the "*epidemiologic literature* was not sufficient for me to say one way or the other whether or not there was a causal association." PUB_010444 Louik Dep. at 109:4–6 (Oct. 14, 2020)] (emphasis added). Nevertheless, the epidemiology was not inconsistent with a determination of causation based on other lines of scientific evidence; *i.e.*, a causal opinion would not contradict the epidemiology. As she wrote, "it is the generally accepted methodology that scientists like myself must consider the totality of the evidence, including the non-epidemiological studies, so long as there is not a demonstrated lack of association as inferred from the epidemiological studies." PUB_011510. Thus, Dr. Louik's testimony is entirely consistent with Dr. Danielsson's position that reasonable evidence of a causal association can be found from non-clinical animal study data, especially when combined with data on Cmax and AUC in those animal studies, and evidence of the teratogenic effect of other hERG-blocking drugs.

defects in animal reproduction studies—and would have considered it as "reasonable evidence of a causal association"— FDA provided a clear answer to that question in 2014. In response to a proposed labeling change submitted by GSK, FDA asked the company to "please provide *full details of animal reproduction studies*." PUB_003105 (emphasis added).[17] Yet, in responding, GSK made no reference to, let alone provided "full details of," the Japanese animal studies. PUB_003139. It simply described the same U.K. animal studies that it had previously submitted. *Id.* GSK now asserts that "FDA's comment referred to *the U.K. animal studies* summarized in the existing labeling," GSK Br. 61, but provides no basis for this claim.

In rejecting Defendant's impossibility preemption argument in *In re Taxotere (Docetaxel) Products Liability Litigation*, the court expressly took note of the fact that, years after plaintiff's use of the drug, FDA asked the manufacturer to analyze the risk of permanent alopecia, the adverse effect at issue. *Id.* at 84. The district court viewed this as evidence that the defendant had not previously "fully informed"

[17] Four years earlier, FDA had asked GSK to "[p]lease review and analyze available published and unpublished literature on the use of ondansetron during pregnancy and lactation, with a focus on the presence or absence of adverse pregnancy and/or neonatal outcomes." PUB_001140. GSK responded by telling the FDA that "the text in the 'Pregnancy and lactation' section of the [package insert for Zofran] accurately reflects the available data" and did not disclose the Japanese animal data. PUB_001144.

FDA about that risk. *Id.* Likewise, FDA's request to GSK in 2014 for "full details of animal reproduction studies," as well as its earlier request for GSK to analyze pregnancy risk with Zofran, affirm that FDA did not consider itself "fully informed" about those risks.

The case law cited by GSK does not support its argument that the Japanese animal studies would not meet the regulatory definition for "newly acquired information." In *Knight v. Boehringer Ingelheim Pharmaceuticals, Inc.*, 984 F.3d 329 (4th Cir. 2021), the medical article on which plaintiff relied as "newly acquired information" had not even been published until after the plaintiff's injury (and, in any event, was entirely consistent with information already possessed by FDA and reflected in the labeling). *Id.* at 338–39.[18] In *Drescher v. Bracco Diagnostics Inc.*, 2020 WL 1466296 (D. Ariz. Mar. 26, 2020), the court simply held that the plaintiff had not "state[d] a plausible claim that the Defendant manufacturers could have changed their labels [by CBE]," *id.* at *3, at least in part, because FDA, with full information, had expressly rejected the warning plaintiff claimed was required.[19]

[18] The real issue in *Knight* concerned statements that had been in a preliminary draft of the article but were withdrawn before publication; the court decided they were not "newly acquired information" because the authors had ultimately concluded that those statements were not scientifically warranted. *Id.* at 339–41.

[19] In any event, the *Drescher* court granted plaintiff leave to replead if she could allege reasonable evidence of a causal association. *Id.* at *4.

Finally, the animal studies at issue in *In re Incretin-Based Therapies* stand in stark contrast to the withheld Japanese animal studies here:

> Plaintiffs contend that Novo failed to provide evidence from five animal experiments. In particular, Plaintiffs point to a 2001 ZDF rat study which contained data that regeneration and acinar hyperplasia was observed in some of the rats. However, Plaintiffs do not explain how this data constitutes reasonable evidence of a causal association. There is no expert opinion that these observations provide reasonable evidence of a causal link, and *none of the rats in the study developed pancreatic cancer* [the adverse effect at issue].

524 F. Supp. 3d at 1026 (emphasis added) (internal citations omitted). Here, by contrast, Plaintiffs have everything that the *Incretin* court was looking for: the very injuries Plaintiffs allege were seen in the studies that they offer as newly acquired information, and Plaintiffs' experts explain how those studies provide reasonable evidence of causal association.

Thus, Plaintiffs have shown that the withheld Japanese animal studies, especially when placed in context with the additional evidence offered by Dr. Danielsson, constitute "newly acquired information" under 21 C.F.R. § 314.3(b). Therefore, GSK has not met its preemption burden of proving that "it fully informed the FDA of the justifications for the warning required by state law." *Albrecht*, 139 S. Ct. at 1678.

CONCLUSION

GSK argues that "Plaintiffs cannot defeat preemption by asking this Court to second-guess [FDA's] judgment." GSK Br. 3. Yet, as this Court has observed: "A

state law duty to initiate [a CBE label] change is . . . not by its nature a second guess of an FDA judgment." *In re Celexa*, 779 F.3d at 41. Plaintiffs do not seek to second guess the FDA; they only point out that GSK has failed to show that either it or Novartis "fully informed the FDA of the justifications for the warning required by state law and that the FDA, in turn, informed the drug manufacturer that the FDA would not approve changing the drug's label to include that warning." *Albrecht*, 139 S. Ct. at 1678. Because GSK could have initiated a CBE label change from Pregnancy Category B to Category C based on the withheld Japanese animal studies, Plaintiffs' claims are not preempted and the decision of the district court must be reversed.

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Respectfully submitted,

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June 15, 2022

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I hereby certify that on June 15, 2022 I electronically filed the foregoing with the Clerk of Court using the Court's CM/ECF system which will send notification of such filing to all counsel of record. I also certify that an unredacted copy of the foregoing will be sent by mail to the Clerk of Court and by e-mail to Counsel for Appellee.

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