UNITED STATES DISTRICT COURT
WESTERN DISTRICT OF NORTH CAROLINA
CHARLOTTE DIVISION
3:22-MD-03036-KDB

IN RE: GARDASIL PRODUCTS LIABILITY LITIGATION	)	**MDL No. 3036**
	)	**THIS DOCUMENT RELATES TO ALL BELLWETHER CASES**

ORDER

THIS MATTER is before the Court on Defendants Merck & Co., Inc. and Merck Sharp & Dohme LLC's (together, "Merck") Motion for Summary Judgment Based on Implied Preemption (Doc. No. 188). The Court has carefully considered this motion, the Parties' briefs and exhibits and oral argument on the motion from the Parties' counsel on February 25, 2025. For the reasons discussed below, the Court will GRANT the motion.

Gardasil is a Human Papillomavirus ("HPV") vaccine that has been widely administered since 2006 to effectively prevent cervical and other fatal cancers. The Bellwether Plaintiffs'[1] allege that in selling Gardasil, Merck violated state law by failing to include warnings related to Postural Orthostatic Tachycardia Syndrome ("POTS") or Primary Ovarian Insufficiency ("POI"), which they claim can be caused by the vaccine. In ruling on the pending motion, the Court must decide if Merck was permitted under federal law to add those warnings to the vaccine's label without prior approval from the Food and Drug Administration ("FDA") (which is typically required for

[1] The "Bellwether Plaintiffs" (sometimes referred to only as "Plaintiffs" in this Order) are Corinn McElerney, Kameron Hilton, Cooper Humphries, Madelyn Lipscomb, Savannah Flores, Nalon A. Soileau, Madelyn Malloy, Megan Marie Roeder, Sonja Wagner, Lakia Brayboy, Mary Ellouise Bond, Chaunna M. Lane, Kristen Linton, Logan T. Dunn, Jaden I. McTighe and Maeson Derr.

any changes to a vaccine's prescribing information). If Merck did not have that authority, state and federal law are in conflict and Plaintiffs' claims are, as a matter of law, preempted.

The governing federal regulations are complex; however, the question before the Court ultimately comes down to this: did Merck have enough "newly acquired information" (evidence that had not already been submitted to the FDA) that a qualified scientist could reasonably conclude that there was a causal association between taking Gardasil and contracting POTS or POI? This regulatory test is undoubtedly difficult to apply in many circumstances. Not so here. As of 2013, when Plaintiffs contend that the latest of the warnings should have been given, more than a hundred million doses of Gardasil had been administered worldwide. However, by that time, there had been only *one* published, verified case of POTS and *four* published case reports of POI. (In addition, there were scattered unverified reports of the illnesses, still totaling only a relatively miniscule handful). To the extent there were any broader studies or analyses before the relevant dates, they did not establish causal associations. Simply put, no scientist could reasonably conclude there is a causal association between POTS and POI and Gardasil based on this paucity of evidence, even putting aside the fact that the FDA was made aware of all these cases and studies (which raises a question whether they can even qualify as "newly acquired information"). Therefore, the Court concludes that Merck did not have the authority under federal law to unilaterally add Plaintiffs' requested warnings to the vaccine's label.[2] Bellwether Plaintiffs' state law failure to warn claims are thus preempted.

[2] Alternatively, a vaccine injury plaintiff's "failure to warn" claims are preempted if it is clear that the FDA would not have approved the proposed warnings. Here, there is substantial evidence that the FDA does not agree with Plaintiffs' allegations that there is a causal association between taking Gardasil and becoming sick with POTS and POI. The FDA has approved numerous Gardasil labels without any POTS or POI warnings from 2006 to the present; the department of Health and Human Services ("HHS") (FDA's parent agency) has consistently opposed allegations of a causal

I. LEGAL STANDARD

Merck's preemption defense raises a question of law, which must be decided by the Court. *Merck Sharp & Dohme Corp. v. Albrecht*, 587 U.S. 299, 303 (2019); *Knight v. Boehringer Ingelheim Pharms., Inc*., 984 F.3d 329, 337 (4th Cir. 2021). *Knight* is the leading Fourth Circuit case considering federal preemption in the context of a challenge to the adequacy of a drug's warnings under state law. In *Knight*, the court squarely holds that under *Albrecht* "a judge, not the jury," must decide the question of preemption, including the often-dispositive underlying issue of whether federal law allowed a vaccine manufacturer to unilaterally change the warnings in the vaccine's FDA-approved label. *Knight*, 984 F.3d at 337 & n.8. *See also Pietrantoni v. Corcept Therapeutics Inc*., 640 F. Supp. 3d 197, 210–13 (D. Mass. 2022) (summarizing preemption cases and concluding "the issue of FDA approval, like preemption in general, is a question of law for a judge, even where it subsumes significant factual disputes."). Questions of law that go to the heart of a case are best resolved prior to trial at summary judgment in the best interests of the litigants and judicial economy. *See United States v. Mashni*, 547 F. Supp. 3d 496, 506–07 (D.S.C. 2021).

II. FACTS AND PROCEDURAL HISTORY

Since August 2022, this Court has been the forum for a multi-district litigation ("MDL") in which more than two hundred cases asserting vaccine injury claims against Merck have been

connection in the "Vaccine Court"; and HHS / FDA has publicly stated its view that Gardasil does not cause POTS or POI in general communications and the federal register. *See* 82 Fed. Reg. 6294, 6298 ("CDC and FDA continue to evaluate vaccines to ensure their safety. To date [January 2017], there is no medical or scientific evidence that the HPV vaccine causes POTS and safety monitoring has not shown any other problems."). However, because the Court finds that Merck could not have unilaterally added warnings to the Gardasil label, the Court need not and does not decide if these facts are sufficient to find, as a matter of law, that the FDA would have rejected the proposed warnings if they had been suggested.

consolidated. (Doc. No. 2). Each Plaintiff alleges that he or she has suffered harm[3] caused by vaccination with Gardasil, an HPV vaccine manufactured and sold by Merck which seeks to prevent cervical and other cancers believed to be associated with HPV. (*See* Do. No. 190-3 (Gardasil Prescribing Information)). HPV, the most common sexually transmitted disease, is a viral infection that is estimated to cause nearly 36,500 cases of cancer in women and men every year in the United States, with more than 660,000 new cases of cervical cancer (and around 350,000 deaths) worldwide in 2022. (Doc. No. 190-8 (CDC, Reasons to Get Vaccinated) ("HPV vaccination can prevent 90% of these cancers by preventing the infections that cause them")); (Doc. No. 190-9 (World Health Organization ("WHO") statistics)). Since HPV vaccines have been used in the United States, they have been remarkably effective. "Among teen girls, infections with HPV types that cause most HPV cancers and genital warts have dropped 88 percent," and "[a]mong vaccinated women, the percentage of cervical pre-cancers caused by the HPV types most often linked to cervical cancer has dropped by 40 percent." (Doc. No. 190-13).

The Centers for Disease Control ("CDC") recommends HPV vaccination for both girls and boys through age 26 years. (Doc. No. 190-12 (CDC, HPV Vaccination Recommendations)). The initial formulation of Gardasil targeting four HPV strains was approved by the Food and Drug Administration ("FDA") in 2006, and a second version (Gardasil 9) adding five more strains associated with cervical and anal cancer was approved in 2014. Because it provides more comprehensive protection, only Gardasil 9 is currently sold in the United States. (*See* Doc. No. 190-4). HPV vaccines have been administered over 135 million times in the United States and 500

[3] To be clear, nothing in this Order is intended to cast aspersions on the fact or severity of any ailment alleged by the Plaintiffs. Rather, the Court is tasked with answering the legal questions posed by Plaintiffs' claims in the context of the highly regulated world of vaccines (which in turn reflects the government's attempt to carefully balance their considerable benefits and risks).

million times worldwide. (Doc. No. 190-3; Doc. No. 190-11 (WHO, Weekly Epidemiology Record) at 663 (Dec. 16, 2022)).

The Bellwether Plaintiffs (vaccinated at various dates from 2012 to January 2021) allege that Gardasil caused them to develop POTS or POI. They further allege that Merck should have added a POTS warning to Gardasil's FDA regulated labeling in 2011 and a POI warning in 2013. Merck responds that there is no evidence that Gardasil causes either POTS or POI, and the FDA has approved numerous Gardasil labels without any such warnings (as well as promoted the safety and efficacy of HPV vaccines, including with respect to POTS). As discussed in more detail below, all Parties have made lengthy scientific submissions which they contend support or argue against the need for Plaintiffs' requested warnings.

Gardasil is a childhood vaccine covered by the Vaccine Act, 42 U.S.C. §§ 300aa-1, *et seq*. As explained by the Supreme Court in *Bruesewitz v. Wyeth LLC*, 562 U.S. 223, 228–30 (2011), Congress enacted the Vaccine Act to "[t]o stabilize the vaccine market and facilitate compensation" to putative plaintiffs by establishing a no-fault compensation program "designed to work faster and with greater ease than the civil tort system." *Shalala v. Whitecotton*, 514 U.S. 268, 269 (1995). The program requires a person who claims to have been injured by a vaccine, or their legal guardian, to file a petition for compensation against the Secretary of Health and Human Services ("HHS") in the United States Court of Federal Claims prior to filing a civil action in State or Federal court. *See* 42 U.S.C. §§ 300aa–11, 12.

Each of the Bellwether Plaintiffs filed claims in the Vaccine Court. In its oppositions, HHS (which oversees both the FDA and CDC) argued against Plaintiffs' claimed association between HPV vaccination and POTS or POI. (*See* Doc. No. 190-1 (*Wagner*, Vaccine Court Doc. No. 42 at 11) ("[T]here is no known association between HPV vaccination and the development of POTS")));

(Doc. No. 190-2 (*Brayboy*, Vaccine Court Doc. No. 88 at 11) ("[T]he only reliable epidemiological evidence that exists on this issue demonstrates no causal association between the HPV vaccination and POI.")). Ultimately, all of the Plaintiffs' claims were either rejected or voluntarily withdrawn prior to a final adjudication. *See, e.g., Humphries v. Sec'y of Health & Hum. Servs.*, No. 17-288V, 2021 WL 1733512, at *3 (Fed. Cl. Apr. 9, 2021) (dismissing claim at Plaintiff's request but with prejudice "because this case is yet another Program case involving the HPV vaccine being dismissed largely to avoid the possibility of an adverse determination by the Office of Special Masters" and noting that the Special Master had "uniformly held that the HPV vaccine has not been demonstrated to cause POTS in numerous prior cases").[4]

Thereafter, Plaintiffs filed their claims in various federal district courts, which were then transferred to and consolidated into the MDL.[5] Early in the MDL proceedings and with the Parties' agreement, the Court created an "Initial Bellwether Pool" of sixteen plaintiffs who allege they have either POTS or POI as a result of their Gardasil vaccinations. (*See* Doc. Nos. 58, 77). Further, the Court and the Parties agreed to "prioritize discovery and dispositive motions on general causation and implied preemption." (Doc. No. 58 at 7). Since the creation of the Bellwether Pool, the Court has also narrowed the claims presented by the Plaintiffs. In March 2024, the Court granted in part and denied in part a "Bellwether" Motion for Judgment on the Pleadings as to two plaintiffs, later extending that ruling to all similarly asserted claims. (*See* Doc. Nos. 132, 158); *In re Gardasil*

[4] The Vaccine Act bars the use of the "finding[s] of fact or conclusion[s] of law" of the Vaccine Court in civil actions following the conclusion of Vaccine Court proceedings. *See* 42 U.S.C. § 300aa-23(e). Therefore, the Court cites the ruling of the Vaccine Court here not for any substantive conclusion, but rather because it reflects the knowledge of HHS (and its constituent agencies FDA and CDC) over many years of the same arguments and scientific support advanced here by Plaintiffs.

[5] The MDL was formed at the request of a number of plaintiffs, including some of the Bellwether Plaintiffs. *See* Doc. No. 257-1.

Prods. Liab. Litig., 724 F. Supp. 3d 474, 489–90 (W.D.N.C. 2024). Applying the Vaccine Act, the Court dismissed Plaintiffs' 1) "direct warning" claims that Merck failed to properly warn Plaintiffs and their parent(s); 2) "design defect" claims (including claims based on Gardasil's ingredients and clinical trials); 3) "manufacturing defect" claims; and 4) claims of fraud on medical providers. *In re Gardasil*, 724 F. Supp. 3d at 487-491. The Court allowed Plaintiffs' claims that Merck failed to properly warn and fraudulently concealed material facts from medical providers to proceed. *Id*. at 488, 492.

As earlier forecast, Merck has now filed a motion for summary judgment seeking to dismiss the Bellwether Plaintiffs' remaining claims on the grounds that those claims are impliedly preempted[6] by the FDA's ongoing approval and promotion of the vaccine and, specifically with respect to the requested POTS and POI warnings, its approval of the vaccine's "label," which provides comprehensive prescribing information to medical providers. Plaintiffs oppose the motion, contending that Merck's federal and state obligations are not in conflict because Merck could have added the POTS and POI warnings under its regulatory authority to make label changes without prior FDA approval based on "newly acquired information." *See* 21 C.F.R § 601.12(f)(2)(i). The motions have been extensively briefed by the Parties and oral argument on the motions was held on February 25, 2025. The motion is ripe for the Court's decision.

III. DISCUSSION

A. Governing Legal Principles for Preemption

Merck's summary judgment motion requires the Court to decide whether Plaintiffs' state law claims for failure to warn / fraudulent concealment are preempted by federal law. Merck, the

[6] Merck has also filed a motion for summary judgment on the grounds of "general causation." Doc. No. 217. The Court need not and does not decide that issue here because the threshold defense of preemption is independently dispositive of Bellwether Plaintiffs' remaining claims.

party asserting that federal law preempts state law, "bears the burden of establishing preemption." *In re Methyl Tertiary Butyl Ether (MTBE) Prod. Liab. Litig*., 725 F.3d 65, 96 (2d Cir. 2013).

The United States Constitution's Supremacy Clause provides that federal law "shall be the supreme Law of the Land; ... any Thing in the Constitution or Laws of any state to the Contrary notwithstanding." U.S. Const., art. VI, cl. 2. "[P]re-emption follows automatically by the operation of the Supremacy Clause" (*Wyeth v. Levine*, 555 U.S. 555, 624 (2009) (Alito, J. & Scalia, J., dissenting)), which "invalidates state laws that interfere with, or are contrary to, federal law." *Hillsborough Cnty. v. Automated Med. Labs., Inc.*, 471 U.S. 707, 712 (1985) (internal quotations and citation omitted). "Federal law can preempt state law in three ways: (1) express preemption, (2) field preemption, and (3) conflict preemption." *Farina v. Nokia Inc.*, 625 F.3d 97, 115 (3d Cir. 2010) (citing *Hillsborough Cnty.*, 471 U.S. at 713).

At issue here is "conflict preemption," which is "a demanding defense" in a federal system that supports independent state laws. *Wyeth*, 555 U.S. at 573.[7] Federal law impliedly preempts state law "where it is 'impossible for a private party to comply with both state and federal requirements.'" *Mutual Pharm. Co., Inc. v. Bartlett*, 570 U.S. 472, 480 (2013) (quoting *English v. Gen. Elec. Co.*, 496 U.S. 72, 79 (1990)); *Albrecht*, 587 U.S. at 315 ("the judge must simply ask himself or herself whether the relevant federal and state laws 'irreconcilably conflic[t].'"). Thus, in these circumstances, the "underlying question [becomes] whether federal law (including appropriate FDA actions) prohibited the drug manufacturer from adding any and all warnings to

[7] Plaintiffs incorrectly (but repeatedly) urge the Court to add a requirement that Merck establish preemption by "clear evidence" based on the use of those words in *Wyeth*. *See, e.g.*, Doc. No. 203 at 1. However, in *Albrecht* the Supreme Court made clear that the use of those words was not to be interpreted as an evidentiary standard (because the issue to be decided is a question of law, not fact). *Albrecht*, 587 U.S. at 315. Indeed, Justice Alito noted in concurrence that "the use of the phrase 'clear evidence' was merely a rhetorical flourish." *Id*. at 325.

the drug label that would satisfy state law." *Knight*, 984 F.3d at 337 (quoting *Albrecht*, 587 U.S. at 315). "A state-law challenge to FDA-approved warnings, including a tort action under state law, can thus proceed only when the defendant had the unilateral ability to change that labeling; otherwise, the claim is preempted." *Id.* Ultimately then, there are two ways a vaccine manufacturer may prevail on a preemption defense: if (1) it did not have the authority to make changes to the label, or (2) it establishes that the FDA would not have approved the changes to the label that the plaintiffs contend should have been made. *See Pietrantoni*, 640 F. Supp. 3d at 210–13 (explaining judicial development of preemption principles in this context).

There is a complex federal regulatory scheme governing pharmaceutical drugs and vaccines.[8] Congress enacted the Food, Drug, and Cosmetic Act ("FDCA") in 1938 "to bolster consumer protection against harmful products." *Wyeth*, 555 U.S. at 574; *see* 21 U.S.C. §§ 301 et seq. Pursuant to that statute, drug companies cannot sell or market a new pharmaceutical drug product without prior approval from the FDA. *See* 21 U.S.C. § 355(a). To obtain this approval, a manufacturer must submit comprehensive information about the safety and efficacy of a drug to the FDA in a "New Drug Application." *See id.* at § 355(b)(1). Also, before the FDA will approve the marketing of a new vaccine or other drug, the manufacturer must submit and the FDA must approve the exact text of the proposed label. *See* 21 U.S.C. § 355(b)(1)(A)(vi); *Wyeth*, 555 U.S. at 568; *Gibbons v. Bristol-Myers Squibb Co.*, 919 F.3d 699, 707 (2d Cir. 2019); *Herlth v. Merck & Co.*, No. 3:21-CV-438 (JAM), 2022 WL 788669, at *3 (D. Conn. Mar. 15, 2022).

The FDA extensively regulates the format and substance of the information that appears on a drug's label. *See, e.g.*, 21 C.F.R. §§ 201.56, 201.57; *In re Zofran*, 57 F.4th 327, 330 (1st Cir.

[8] Vaccines are considered "biologics" or "biological products," which are subject to regulatory oversight similar to pharmaceutical drugs. *See* 42 U.S.C. § 262(i).

2023). In formulating a vaccine's label, FDA regulations seek to provide what may be best described as the "Goldilocks" amount of information; that is, "just right" - not too little and not too much. In addition to seeking to include all necessary information, the FDA tries to "prevent overwarning, which may deter appropriate use of medical products, or overshadow more important warnings."[9] Supplemental Applications Proposing Labeling Changes for Approved Drugs, Biologics, and Medical Devices, 73 Fed. Reg. 49603, 49605–06 (Aug. 22, 2008). Thus, the regulations "allow only information for which there is a scientific basis to be included in the FDA-approved labeling," *id*. at 49604, guarding against the "[e]xaggeration of risk, or inclusion of speculative or hypothetical risks." Supplemental Applications Proposing Labeling Changes for Approved Drugs, Biologics, and Medical Devices, 73 Fed. Reg. 2848, 2851 (Jan. 16, 2008).

While the manufacturer always bears the responsibility for the content of its vaccine labels, federal regulations expressly bar manufacturers from changing their labels after the label has received FDA approval, with only limited exceptions. *Wyeth*, 555 U.S. at 567-68.[10] Most relevant here, a manufacturer is allowed to ship a vaccine with a "Special Labeling Supplement" amendment prior to FDA approval that notifies doctors of "Changes Being Effected" ("CBE"). *See* 21 C.F.R. § 601.12(f)(2)(ii); *Knight*, 984 F.3d at 337-38. For example, the CBE regulation allows a manufacturer to change a drug's label without prior FDA approval if it has "newly acquired information" that requires "add[ing] or strengthen[ing] a contraindication,

[9] The same Federal Register notice also states "State-law attempts to impose additional warnings can lead to labeling that does not accurately portray a product's risks, thereby potentially discouraging safe and effective use of approved products * * *." *See* Supplemental Applications Proposing Labeling Changes for Approved Drugs, Biologics, and Medical Devices, 73 Fed. Reg. 49603, citing 71 Fed. Reg. 3922 at 3935.

[10] Under FDA regulations, companies cannot unilaterally change the [label] without prior FDA approval because doing so is considered a "major" change. *See* 21 C.F.R. § 314.70(b) (explaining that "any change to a Medication Guide" requires "supplement submission and approval prior to distribution of the product made using the change").

warning, precaution, or adverse reaction for which the evidence of a causal association satisfies the standard for inclusion in the labeling under [21 C.F.R.] § 201.57(c)." *See* 21 C.F.R. § 314.70. Still, "manufacturers cannot propose a change that is not based on reasonable evidence." *Albrecht*, 587 U.S. at 315; *Mason v. SmithKline Beecham Corp.*, 596 F.3d 387, 392 (7th Cir. 2010) ("It is technically a violation of federal law to propose a CBE that is not based on reasonable evidence.").[11]

"Newly acquired information" is defined to include:

> 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.

In turn, 21 C.F.R. § 201.57(c)(6)(i) requires the "warnings and precautions" section of a drug's label to "describe clinically significant adverse reactions (including any that are potentially fatal, are serious even if infrequent, or can be prevented or mitigated through appropriate use of the drug)."[12] Further, under this regulation, "the labeling must be revised to include a warning about a clinically significant hazard as soon as there is reasonable evidence of a causal association with a drug; a causal relationship need not have been definitely established." 21 C.F.R. §

[11] In a Federal Register statement, the FDA emphasized that it "interprets the Act to establish both a 'floor' and a 'ceiling', such that additional disclosures of risk information can expose a manufacturer to liability under the act if the additional statement is unsubstantiated or otherwise false or misleading" … . *See* Supplemental Applications Proposing Labeling Changes for Approved Drugs, Biologics, and Medical Devices, 73 Fed. Reg. 49603-01.

[12] Underscoring the need for reasonable (and detailed) evidence to support the inclusion of a warning, the regulation requires that "the frequency of all clinically significant adverse reactions and the approximate mortality and morbidity rates for patients experiencing the reaction, if known and necessary for the safe and effective use of the drug, must be expressed as provided under paragraph (c)(7) of this section." 21 C.F.R. § 201.57(c)(6)(i).

201.57(c)(6)(i); Supplemental Applications Proposing Labeling Changes for Approved Drugs, Biologics, and Medical Devices, 73 Fed. Reg. 49603-01 ("A CBE submission may be made when the evidence meets the standard set forth in this rule, even if that evidence would not also support a higher evidentiary standard, such as a finding that there is a "preponderance" of evidence that a product actually causes a particular kind of adverse event."). However, "[t]he fact that a user of a drug has suffered an adverse event, standing alone, does not mean that the drug caused that event." *Matrixx Initiatives, Inc. v. Siracusano*, 563 U.S. 27, 44 (2011).

In sum, in order to qualify as "newly acquired information," the information must demonstrate "reasonable evidence of a causal association with a drug ...." 21 C.F.R. § 201.57. The FDA has consistently defined "reasonable evidence" as "when evidence exists on the basis of which experts qualified by scientific training and experience can reasonably conclude that the hazard is associated with the use of the drug." 44 Fed. Reg. 2848, 2851 (allowing a CBE amendment only for "known hazards and not theoretical possibility"); *id.* at 49604 (stating that this is how the FDA ensures "scientifically accurate information appears in the approved labeling"); *see also Gibbons*, 919 F.3d at 707 (holding that manufacturers are "limited in their ability to unilaterally change the labels on their products" because they must comply with the CBE regulation's causation thresholds).

Finally, although Merck bears the overall burden of proving preemption (for example, that the Gardasil labels that allegedly violated state law had been approved by the FDA), the burden falls on Plaintiffs to identify the "newly acquired information." *Herlth*, 2022 WL 788669, at *3–5; *Pfaff v. Merck & Co.*, 627 F. Supp. 3d 134, 143–44 (E.D.N.Y. 2022); *Gibbons*, 919 F.3d at 708 ("To state a claim for failure-to-warn that is not preempted by the FDCA, a plaintiff must plead a labeling deficiency that [defendants] could have corrected using the CBE regulation.") In other

words, Merck need not prove a negative, i.e., the absence of reasonable evidence of a causal association between the alleged harm and the administration of the vaccine.

B. Did Merck Have the Authority to Change the Gardasil Label?

As detailed above, a manufacturer may unilaterally add warnings to a vaccine's label if it has enough "newly acquired information" that qualified experts could reasonably conclude that there was a causal association between taking the vaccine and an adverse reaction. Here, Plaintiffs' contention is that Merck had the authority to add warnings to the Gardasil label related to two serious illnesses, POTS and POI, which they allege can be caused by taking the vaccine.

1. POTS

Based on the testimony of Plaintiffs' expert Dr. Stephen Amato,[13] Plaintiffs claim that Merck should have added the following warning for POTS by January 2011:

> Section 5 WARNINGS AND PRECAUTIONS 5.3 Serious adverse events can occur following the administration of GARDASIL. Gardasil may cause persistent headaches, fatigue, presyncope, tachycardia, gastrointestinal symptoms, and/or limb pain or weakness. This constellation of symptoms may relate to autoimmune conditions, such as postural orthostatic tachycardia syndrome (POTS). Careful history of any individual should be gathered before vaccination and if these symptoms present following vaccination, further doses should be avoided, and the patient should be referred for evaluation of autoimmune disease.

Doc. No. 186-2 at 146.

When a person moves from lying down to sitting or standing upright (called orthostasis), nearly a half-liter of blood moves to the lower extremities, causing a temporary reduction in blood flow to the brain. Normally, these changes activate the involuntary (autonomic) nervous system

[13] Stephen Amato, PhD, has been qualified by the Court as having general expertise in the FDA's regulation of drugs and medical devices. *See* Doc. No. 286. While he is not permitted to opine on the ultimate legal issues before the Court, Dr. Amato is the sole source of Plaintiff's expert evidence on the details and timing of the warnings that Plaintiffs contend should have been included on the Gardasil label, and the Court has carefully considered the factual information he has presented as discussed at length below.

leading to a temporary increase in heart rate. But in people with postural orthostatic tachycardia syndrome, something goes wrong with the body's response to upright posture. People with POTS suffer from an excessive increase in heart rate (tachycardia) and other symptoms that worsen upon standing or sitting up, such as light-headedness, shortness of breath, chest pain, and palpitations. NIH, National Heart, Lung, and Blood Institute, *Postural Orthostatic Tachycardia Syndrome (POTS): State of the Science, Clinical Care, and Research*, available at https://www.nhlbi.nih.gov /events/2019/postural-orthostatic-tachycardia-syndrome-pots-state-scienceclinical-care-and-research.

POTS can be a debilitating condition that affects routine activities such as working or attending school. POTS primarily affects women of child-bearing age, with most studies reporting >80-90% female predominance. The peak incidence is at age 14 years, but half of all individuals with POTS develop it in adulthood. While there are no precise data on the prevalence of POTS, it is estimated to affect 0.2-1% of the U.S. population. *Id*; Doc. 197-3 (Expert Report of Dr. David Feigal, Jr.)[14] at 46. Plaintiffs acknowledge that POTS occurs in young people who are unvaccinated and for reasons unrelated to Gardasil.[15] POTS is generally diagnosed after symptoms have persisted for at least six months, through either a standing test or a tilt-table test. Doc. Nos. 206-29 at 4; 190-46 at 3.

[14] Merck's expert witness Dr. David Feigal, M.D. has been qualified by the Court as having expertise in the FDA's regulation of drugs and medical devices. *See* Doc. No. 286 at pp. 9-10. As with Dr. Amato, the Court has carefully considered the factual information he has presented in response to Dr. Amato's opinions.

[15] Indeed, POTS was first described in the published literature in 1993, nearly a decade before HPV vaccines began to be tested in humans and 14 years before Gardasil was approved for use outside of clinical trials. *See* Doc. 197-3 at 46-47, citing Cleveland Clinic, *Postural Orthostatic Tachycardia Syndrome (POTS)*, available at https://my.clevelandclinic.org/health/diseases/ 16560-postural-orthostatic-tachycardia-syndrome-pots.

Dr. Amato summarized the evidence he found that suggests "a potential link between Gardasil vaccination and … (POTS)" as "several published case reports, case series, and internal data from Merck." *See* Doc. 186-2 at 137. Before describing that evidence, the Court notes the regulatory boundaries of its consideration. First, to support a unilateral change in the vaccine label based on the CBE regulations, the "reasonable evidence" of a "causal association" must be "newly acquired information." *See* 21 C.F.R. § 601.12(f)(2)(ii).

"Newly acquired information" is data, analyses and other information that has never been previously submitted to the FDA or reveal risks of a different type or greater severity or frequency than previously included in submissions to FDA. *See* 21 C.F.R. § 314.3. Therefore, data and analyses that the FDA already reviewed in connection with the initial approval of a vaccine, including but not limited to animal studies and clinical trials information, cannot by definition be "newly acquired information." *See In re Celexa and Lexapro Litig.*, 779 F.3d 34, 41 (1st Cir. 2015); *Mahnke v. Bayer Corp.*, No. 2:19-cv-07271, 2019 WL 8621437, at *5 (C.D. Cal. Dec. 10, 2019). Further, information related to post-marketing surveillance reports or scientific literature would similarly not be "newly acquired information" after its submission to the FDA. *See Pietrantoni*, 640 F. Supp. 3d 197, 210–13 (D. Mass. 2022) (adverse event reports failed to establish the existence of "newly acquired information").

Significantly, Dr. Amato and Plaintiffs do not claim that Merck failed to timely provide to the FDA any of the evidence they contend would have allowed Merck to add the requested warnings.[16] *See* Doc. No. 295 at 2, fn. 4, 5 (listing exhibits showing Merck communications with

[16] Dr. Amato and Plaintiffs instead argue that Merck failed to properly conduct its clinical trials or analyze its clinical data and that reports of POTS were listed as "new medical history" or "new medical conditions" rather than initial adverse reactions to the vaccine. However, allegations that Merck or the FDA should have conducted clinical trials differently, "misinterpreted" data (even

FDA and publication of its clinical trials and post-marketing safety data). This includes the clinical trials, post-marketing reports, case studies, literature review studies and other information Dr. Amato relies on for his opinions. Therefore, this evidence fails as "newly acquired information" under the regulatory definition.

Moreover, the regulatory structure limits the timeframe of the relevant "reasonable evidence." See *Herlth*, 2022 WL 788669, at *3–5 ("Herlth must allege that there was significant adverse risk information revealed to Merck at some point *after* the FDA's approval of Gardasil in June 2006… [and] plead facts to plausibly show that the newly acquired information was available to Merck *before* [the warning would have needed to be given]") (emphasis in original). Gardasil was first approved by the FDA in 2006, and Dr. Amato opines that Merck should have given its POTS warning by January 2011. Because evidence submitted to the FDA prior to approval would not be relevant nor would evidence that Merck did not possess until after the argued warning date, the Court must focus on whether Merck had reasonable evidence of a causal association between POTS and Gardasil from 2006 to January 2011.[17]

With respect to "published case reports" and "case series," Dr. Amato identifies only one published report of a POTS case during the relevant timeframe. In 2010, a foreign scientific journal published a case report describing a 20-year-old woman who developed POTS two weeks after

assuming Dr. Amato is qualified to diagnose POTS from reports of POTS symptoms – which he is not) and included information in the "wrong" section of reports to the FDA does not mean that the information was not "previously submitted to the FDA," for the purpose of determining if it is "newly acquired information." For example, the FDA was well aware of "new medical conditions," as clearly reflected in the revised Gardasil label the FDA approved in December 2010 (shortly before the date Plaintiffs claim that a POTS warning should have been added). *See* Doc. No. 190-80 at 285, 290-91 (describing "new medical conditions" related to Systemic Autoimmune Disorders evaluated in clinical trials follow-up as well as the clinical trials protocols).

[17] Also, before the relevant timeframe began, there were no cases of POTS reported in the clinical trials for Gardasil. Doc. No. 197-3 at 48.

her first Gardasil dose, showing symptoms like exercise intolerance, dizziness, and a significant heart rate increase during a tilt table test. *See* Doc. No. 204-15 (Blitshteyn 2010). Dr. Amato suggests, "[t]his case was notable for its temporal association between vaccination and POTS onset." Doc. No. 186-2 at 139. However, temporal association alone does not equate to "causal association," particularly in this context where tens of millions of young women and men received the vaccine prior to January 2011. *See Moberly ex rel. Moberly v. Sec'y of Health & Human Servs.*, 592 F.3d 1315, 1323 (Fed. Cir. 2010) (while "temporal proximity is a factor to be considered in the analysis of causation," it alone "does not suffice to show a causal link between the vaccination and the injury."); *In re Lipitor (Atorvastatin Calcium) Mktg., Sales Practices & Products Liab. Litig.*, 227 F. Supp. 3d 452, 479 (D.S.C. 2017), *aff'd sub nom. In re Lipitor (Atorvastatin Calcium) Mktg., Sales Practices & Products Liab. Litig. (No II) MDL 2502*, 892 F.3d 624 (4th Cir. 2018) (admissions or reports of temporal associations are "insufficient to create admissions of causation"); *Glastetter v. Novartis Pharms. Corp.*, 252 F.3d 986, 989–90 (8th Cir. 2001) (concluding that the temporal association upon which case reports are based is not "scientifically valid proof of causation"). Also, Dr. Amato himself acknowledges the limitations of case reports, which he states are "useful for identifying new or rare adverse events, but they lack a control group and cannot establish causality or incidence rates, limiting their generalizability." Doc. No. 186-2 at 28;[18] *see Herlth*, 2022 WL 788669, at *4 ("[C]ase reports from individual patients" did not satisfy CBE regulation).

[18] Dr. Amato also describes other case reports from 2014 and 2017 involving eight girls/women who were diagnosed with POTS (one is a duplicate from the 2010 report). None of the reports purports to find a "causal association" between Gardasil and POTS from only one or a handful of cases out of tens of millions of vaccine doses. *See* Doc. No. Doc. No. 186-2 at 139-140. Rather, they note the "temporal association" with the vaccine and suggest "further investigation" to determine whether or not there is any "causal relationship." *See* Doc. No. 206-4 at 5-6.

After a vaccine is approved, it becomes available for public use, but the manufacturer and FDA continue to monitor its safety and effectiveness through post-marketing surveillance. FDA and CDC jointly operate the Vaccine Adverse Event Reporting System ("VAERS"), which is a passive surveillance system designed to detect potential signals of safety issues with vaccines licensed in the United States. Healthcare providers, patients, and others may self-report adverse events, Doc. No. 186-2 at 26, and manufacturers must review all Adverse Event Reports ("AERs") they receive from any source. Doc. No. 197-3 at 21. FDA and CDC regularly monitor VAERS reports for any unexpected changes or patterns in rates of adverse events reported after administration of a vaccine. *Id*. at 42; Doc. No. 295 at 4, fn. 11(stating that FDA and CDC officials have performed numerous reviews of VAERS data related to POTS and POI at different times, citing Shimabukuro (2015), Arana (2017), Arana (2018) and Wodi (2023)).

However, post-marketing adverse event reporting systems, like VAERS, have significant limitations. *Id*.; Doc. No. 197-3 at 42-43; Doc. No 186-2 at 26 (Dr. Amato stating VAERS is "subject to limitations such as reporting bias, underreporting, and an inability to establish causality," while promoting its benefits). According to CDC, "VAERS data alone cannot determine if the vaccine caused the reported adverse event." This is because VAERS "accepts all reports of adverse events following vaccination without judging whether the vaccine caused the adverse event. Some VAERS reports might represent true vaccine reactions or side effects; others might be coincidental adverse events not related to vaccination." CDC, *About the Vaccine Adverse Event Reporting System (VAERS)*, https://www.cdc.gov/vaccinesafety-systems/vaers. In fact, adverse events are defined to include "[a]ny adverse event associated with the use of a biological product in humans, whether or not considered product related." 21 C.F.R § 600.80(a).

In the more than four years between June 2006 and January 2011, VAERS received fewer than 10 reports mentioning POTS and Gardasil (vaccination dates between December 2006 and May 2010). Doc. No. 197-3 at 48. During this same time period, Merck reported to the FDA approximately 10 cases of POTS in its periodic reports to the agency. *Id*. Even if all of these unverified reports were actually POTS cases, these reports would be far below the background rate for POTS given the tens of millions of individuals who had received Gardasil. *Id*.[19]

Finally, in addition to the case studies and adverse event reports relied on by Dr. Amato, other analyses or studies published in the scientific literature could potentially reflect "newly acquired information." At oral argument, Plaintiffs brought to the Court's attention two articles that were published in 2009, neither of which were discussed in Dr. Amato's report. However, even a cursory review of those studies makes clear that they don't establish any "causal association" between Gardasil and POTS.

Slade (2009) is a post-marketing review of 12,424 reports of AERs following administration of Gardasil. Doc. No. 203-58 at 2. The stated purpose and description of the study was to "review and describe adverse events following immunization … reported to VAERS from June 1, 2006, through December 31, 2008. *Id*. This study summarizes passive surveillance data from more than 23 million doses distributed in the United States. *Id*. at 3. As noted in the study, "such post licensure monitoring allows for the potential detection of rare [adverse events] as more people are vaccinated." *Id*. at 7. The review identified 51 reports of autoimmune disorders to the

[19] In their supplemental brief, Plaintiffs argue that their expert Dr. Miglis' background rate for POTS is overstated. *See* Doc. No. 293 at 4; Doc. No. 293-5 (Miglis Dep. 64:1014 stating the "incidence of POTS . . . in teenagers" is "[p]robably somewhere between .2 and 1 percent."). Yet, even at their newly suggested lower rates of .006% and .002%, it would still be expected that there would be tens and later hundreds of thousands of cases among the tens and hundreds of millions of doses of Gardasil administered. In other words, while POTS is relatively rare, the population of those taking Gardasil is massive.

VAERS system, including 26 reports of "autoimmune disorder (not otherwise specified)," but the study does not mention POTS. *Id*. The report concludes that most of the reported adverse events "did not meet the FDA definition of serious" and "the safety profile described by these data for frequent [adverse events] is consistent with prelicensure data, with the exception of syncope and [venous thromboembolic events]." *Id*.[20] Thus, not only does Slade not support Plaintiffs' position; it supports Merck's.[21]

The second article cited by Plaintiffs - Harper (2009) - is not a scientific study but is an "editorial" in a scientific journal. Like Slade (2009), it does not mention POTS, much less suggest evidence of a causal association with Gardasil. *See* Doc. No. 203-6. Instead, ignoring the conclusion in Slade (2009) that, with the two noted exceptions, the adverse effects were not serious and/or not occurring more than would be expected based on the relevant background rate, Dr. Harper suggests that doctors should more extensively discuss the possibility of adverse events of all kinds with patients because cervical cancer is most often not fatal. *Id*. at 4. Whatever the merits of Dr. Harper's editorial, it has no relevance to POTS (or POI) or the governing legal standards.

In summary, Bellwether Plaintiffs' alleged "newly acquired information" of any connection between POTS and Gardasil before January 2011 is one published case of POTS and less than 20 unverified reports of POTS. It is an understatement to conclude that such evidence does not rise to the level that qualified scientists could find a "causal association" between POTS and Gardasil. *See Gayle v. Pfizer Inc*., 452 F. Supp. 3d 78, 88 (S.D.N.Y. 2020), aff'd, 847 F. App'x

[20] The FDA's Pediatric Advisory Committee reviewed a copy of the Slade review in December 2010 along with other items related to Gardasil's safety and labeling and then voted unanimously to continue standard ongoing safety monitoring and make no other changes. *See* Doc. No. 197-3 at 44-45.

[21] Both of the issues noted in Slade (2009) were reflected in the Gardasil label as of December 2010, with the inclusion of a warning related to syncope and a listing of "deep venous thrombosis" as a post-marketing adverse reaction. *See* Doc. No. 190-80 at 1, 12,

79 (2d Cir. 2021) (holding that 6,000 "adverse reports" did not "demonstrate 'reasonable evidence of a causal association with a drug ....'"). With tens of millions of doses given, the Court cannot find that literally a single verified case and a few scattered reports of an illness that is most commonly found in the same young women typically vaccinated with Gardasil could be "reasonable evidence" sufficient to allow a warning on the vaccine's label. Indeed, to so find would effectively make the regulatory standard meaningless.

Further, in arguing for the imposition of a warning on such a slender reed of evidence, Plaintiffs ignore the real harm that is risked by adding unwarranted warnings to a vaccine. First, of course, anyone unnecessarily discouraged from taking a potentially lifesaving vaccine could suffer dire consequences. Also, adding "warnings" for every diagnosed malady that befalls a vaccine recipient within months or years after vaccination will crowd out the impact of those warnings that truly need to be given (much like the speed reading of possible side effects in a pharmaceutical commercial often becomes nothing more than an incomprehensible background to pleasant pictures of happy people). This may have equally devastating implications. Thus, the law reflects that it is critically important not just that needed warnings be added to vaccines but that those that are not required be avoided. On this record, Merck could not lawfully add a POTS warning to the Gardasil label in January 2011.

Plaintiffs argue that the FDA is too busy to independently evaluate the safety of vaccines, so Merck was required in this context to do more than "only" submit the information they had to the agency, presumably including some additional analysis of the data in the FDA's own VAERS database.[22] Beyond the absence of any support in the text of the rule (or case law) for this argument,

[22] Plaintiffs do not specify the further investigation or analysis that they argue Merck should have pursued. Instead, Plaintiffs in effect simply say that Merck should have somehow reached the same

which would significantly expand the governing regulation, Plaintiff's position undermines the FDA's statutory authority to require label changes of its own accord.[23] *See Albrecht*, 587 U.S. at 324–25 (concurrence of Justice Alito);[24] *see also Knight*, 984 F.3d at 339–40 (FDA continuing to approve labels with no warning "undermines the Knights' claim that [the evidence offered by plaintiff] made it immediately apparent, before the paper was published, that an optimal blood concentration range existed").

More fundamentally, there was nothing else to report. There was only one published case and fewer than 20 unverified reports of adverse events directly related to POTS. Plaintiffs suggest that disproportionality "signals" should have alerted Merck to the need for additional investigation. Even accepting that Merck had notice of any signals specifically related to POTS before January 2011 (which has not been established), Plaintiffs admit that a signal "does not prove reasonable

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conclusion as their litigation experts (a conclusion of course disputed by Merck's litigation experts as well as the FDA). Whether or not Plaintiffs can ultimately prove causation is a different question than the question of preemption, which turns on what information was actually available to Merck that was not already known by FDA. *See* Gayle, 452 F. Supp. 3d at 88 ("Under Plaintiffs' theory, any litigant could circumvent *Gibbons* by merely alleging that a manufacturer should have created the "newly acquired information."). In any event, as demonstrated by FDA's and its officials' numerous public communications and published studies cited in this Order, FDA has been actively involved with the issues raised by Plaintiffs since Gardasil's approval.

[23] The FDA regularly uses this authority. Very recently, the FDA, based on its own research on millions of doses of the Abrysvo and Arexvy RSV vaccines, ordered the manufacturers to add a warning related to Guillain-Barré Syndrome. *See* FDA, *FDA Requires Guillain-Barré Syndrome (GBS) Warning in the Prescribing Information for RSV Vaccines Abrysvo and Arexvy*, https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/fda-requires-guillain-barre-syndrome-gbs-warning-prescribing-information-rsv-vaccines.

[24] "Under 21 U.S.C. § 355(*o*)(4)(A), which was enacted in 2007, Congress has imposed on the FDA a duty to initiate a label change '[i]f the Secretary becomes aware of new information, including any new safety information ... that the Secretary determines should be included in the labeling of the drug.'* This provision does not relieve drug manufacturers of their own responsibility to maintain their drug labels, *see* § 355(*o*)(4)(I), but the FDA's "actions," *ante*, at 1678, taken pursuant to this duty arguably affect the pre-emption analysis. This is so because, if the FDA declines to require a label change despite having received and considered information regarding a new risk, the logical conclusion is that the FDA determined that a label change was unjustified." *Albrecht*, 587 U.S. at 324–25.

evidence of a causal association."[25] *See* Doc. No. 292 at 52; *see also Wells v. SmithKline Beecham Corp*., No. A-06-CA-126-LY, 2009 WL 564303, at *12 (W.D. Tex. Feb. 18, 2009), aff'd, 601 F.3d 375 (5th Cir. 2010) ("The Federal Drug Administration states … that '[d]ata mining can be used to augment existing signal detection strategies and is especially useful for assessing patterns, time trends, and events associated with drug-drug interactions. Data mining is not a tool for establishing causal attributions between products and adverse events.' FDA, *Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment*, at 112–13 (2005).").

Finally, in their arguments, Plaintiffs regularly and erroneously conflate discussions and references to broad "autoimmune" illness generally with POTS specifically. Indeed, the Gardasil label contains detailed information on "Systemic Autoimmune Disorders," *See* Doc. No. 190-80 at 290-92 (December 2010 label), and mentions "Autoimmune diseases" among the adverse events reported after Gardasil's approval. *Id*. at 293.[26] Therefore, it is incorrect to allege that Merck and the FDA ignored "autoimmune diseases," even though there was insufficient evidence of a causal association with POTS, a very specific condition. *See* Chao (2011), Doc. No. 203-12, (post-marketing study required by FDA evaluating the risk of new-onset autoimmune conditions following Gardasil vaccination and concluding that there was no evidence of an increased risk of autoimmune conditions associated with vaccination).

In sum, regardless of Merck's supposed duties to focus the FDA's attention on the evidence of a connection between POTS and Gardasil, the evidence of a causal association simply did not

[25] Also, Plaintiffs have not disputed that Merck analyzed rather than ignored any relevant EB05 scores. *See* Doc. Nos. 296-15; 296-16. Ex. 98, Dana Dep. 176-79; Ex. 99, Goss Dep. 202-04, 210.
[26] The label also mentions many of the symptoms of POTS cited by Plaintiffs (which are also symptoms of other conditions), including dizziness, headache, syncope, nausea, malaise, fatigue and gastrointestinal disorders. *See* Doc. No. 190-80 at 282, 293.

exist. Also, the question here is what Merck had the authority to do unilaterally, not what the FDA might do with additional information. *See Knight*, 984 F.3d at 337 & n.8.

The Court's conclusion that Merck could not unilaterally change the Gardasil label based on the CBE regulations to add a POTS warning is consistent with the finding of the other court that has considered whether a plaintiff's state law failure to warn claim against Gardasil is preempted. *See Herlth*, 2022 WL 788669, at *3–5. In *Herlth*, the court applied the same legal standards[27] and, based on similar facts and evidence from the plaintiff, granted a motion to dismiss. The court concluded, "… apart from [the] conclusory allegation [that "Gardasil has been linked to a myriad of autoimmune disorders, including ... POTS"] [plaintiff] does not allege newly acquired information containing 'reasonable evidence' as required under 21 C.F.R. § 201.57(c)(6)(i) of a causal association between Gardasil and POTS." *Id.* at *4. The court dismissed the plaintiff's claims as preempted by federal law to the extent they relied on a failure-to-warn theory of liability. *Id.* at *5. This Court agrees.

Perhaps recognizing the dearth of evidence in support of adding a POTS warning in January 2011, at oral argument and in a supplemental brief filed after oral argument, Bellwether Plaintiffs asked the Court for the first time to consider finding that Merck had sufficient information to unilaterally add a POTS warning at some time after January 2011. Plaintiffs don't request a specific date, but say vaguely that the Court can make a finding based on "the totality of the record at later dates." The Court must decline this invitation to error. It is plainly impractical

[27] In *Herlth*, the court explained that "[b]ecause Merck secured FDA approval of its label in the first instance, Herlth's failure-to-warn claim is therefore preempted by federal law unless she has pleaded a labeling deficiency that Merck could have unilaterally corrected in accordance with the requirements of the CBE regulation." *Herlth*, 2022 WL 788669, at *3, citing *Gibbons*, 919 F.3d at 708.

for the Court to separately rule on preemption for each day, month or even year between 2011 and January 2021 (the date of the last vaccination of a Bellwether Plaintiff). In fact, it is at least theoretically possible that Merck could have had reasonable evidence of a causal association based on the "totality of the record" on a given date and then later not have such evidence if the record evolved in favor of Merck's position. Thus, the Court cannot fairly act on such a broad, non-specific request. As noted above, Bellwether Plaintiffs (not the Court) bear the burden of establishing that Merck had sufficient "newly acquired information" to add a warning to the Gardasil label as of a particular date.

To the extent that Plaintiffs identified a specific alternate date for a POTS warning in their supplemental filing,[28] they focused on 2015. By June 2015, there were still only 83 cases of POTS reported worldwide out of well more than 100 million administered doses of the vaccine. *See* Doc. No. 207-23 at 72. However, of those reports, nearly half (40) did not meet the case definition for POTS upon further review. *Id*. at 73. In July 2015, in response to media reports and concerns raised by the Danish Health Authority, the European Medicines Agency ("EMA"), the agency responsible for regulating vaccines like Gardasil in Europe, conducted a "detailed scientific review" of the evidence regarding a possible association between Gardasil vaccination and POTS or complex regional pain syndrome ("CRPS"). *See European Medicines Agency, HPV vaccines: EMA confirms evidence does not support that they cause CRPS or POTS*, available at https://www.ema.europa.eu/en/medicines/human/referrals/humanpapillomavirus-vaccines-cervarix-gardasil-gardasil-9-silgard. Excerpts from the EMA review are instructive:

> **Symptoms of CRPS and POTS may overlap with other conditions, making diagnosis difficult in both the general population and vaccinated individuals.**

[28] While Bellwether Plaintiffs' supplemental brief mentions POI, all of their arguments are directed to POTS. Therefore, there are no newly argued grounds to consider a POI warning after November 2013, the lone date suggested by Plaintiffs' expert.

> However, available estimates suggest that in the general population around 150 girls and young women per million aged 10 to 19 years may develop CRPS each year, and at least 150 girls and young women per million may develop POTS each year. **The review found no evidence that the overall occurrence of these syndromes in vaccinated girls were different from expected occurrence in these age groups, even taking into account possible underreporting.**
> …
>
> **The Agency's review included published research, data from clinical trials and reports of suspected side effects from patients and healthcare professionals, as well as data supplied by Member States.** The Agency's Pharmacovigilance Risk Assessment Committee (PRAC) was responsible for the initial review. **In reaching its recommendations, it also consulted a group of leading experts in the field, and took into account detailed information received from a number of patient groups** that also highlighted the impact these syndromes can have on patients and families.
>
> The findings of the PRAC were passed to the Agency's Committee for Medicinal Products for Human Use (CHMP), along with further representations from patient groups. The CHMP concurred that the available evidence does not support that CRPS and POTS are caused by HPV vaccines. **It therefore did not recommend any changes to the terms of licensing or the product information for these medicines.**
>
> The review recognised that more than 80 million girls and women worldwide have now received these vaccines, and in some European countries they have been given to 90% of the age group recommended for vaccination. Use of these vaccines is expected to prevent many cases of cervical cancer (cancer of the neck of the womb, which is responsible for over 20,000 deaths in Europe each year) and various other cancers and conditions caused by HPV. The benefits of HPV vaccines therefore continue to outweigh the known side effects.

Id. (emphasis added).

Accordingly, in November 2015, EMA concluded that "the evidence does not support a causal link between the vaccines (Cervarix, Gardasil/Silgard and Gardasil-9) and development of CRPS or POTS. Therefore there is no reason to change the way the vaccines are used or amend the current product information." *Meeting highlights from the Pharmacovigilance Risk Assessment Committee (PRAC) 3-5 November 2015*,https://www.ema.europa.eu/en/news/meeting-highlights-pharmacovigilance-risk-assessment-committee-prac-3-5-november-2015. Thus, as of

the end of 2015, as reflected by a full review of the question by the EMA, the available evidence did not support a causal association between POTS and Gardasil.

Despite this major study, which Plaintiffs don't reference in their supplemental brief, Plaintiffs assert there was sufficient evidence of a causal association between Gardasil and POTS in 2015 based primarily on the testimony of their "causation" experts in this litigation. *See* Doc. No. 293 at 2.[29] However, neither those experts nor the Plaintiffs say that the FDA was unaware of any study or evidence cited – so their conclusions, whatever their merit, are not based on what might be considered as "newly acquired evidence."[30] Further, the governing regulations do not permit a plaintiff to present an expert report created for litigation – here well more than a decade after the plaintiff claims a warning should have been given – that in essence says that the manufacturer and the FDA got it wrong and then have that opinion be sufficient to avoid preemption. Preemption must be judged on the information actually available to the manufacturer at the relevant time which was "not submitted" to the FDA. *R.S.B. v. Merck & Co.*, 2021 WL6128161, at *4 (E.D. Wis. Dec. 28, 2021) (Plaintiffs "must point to the existence of newly acquired information that Merck possessed during the relevant time period."). In other words, the question of preemption (which asks "who gets to decide" not "did they get it right") is

[29] Yet, at oral argument, Plaintiffs conceded that Dr. Amato is their only expert opining on warning dates. Doc. No. 292 at 33-34. (Mr. PENNOCK: … Dr. Amato did not offer that opinion [when a warning should have been given] as to a later date in terms. THE COURT: And has any other expert offered by the plaintiffs pegged a different date -- MR. PENNOCK: No. THE COURT: -- upon which the Court should make a finding? MR. PENNOCK: No.).

[30] Plaintiffs also cited to the Court at oral argument a 2022 study from their expert Dr. Mehlsen, which not only could not be "newly acquired information" in 2015 but could not have been considered by Merck before the date of the last vaccination of a Bellwether Plaintiff in January 2021. Therefore, it has no relevance to the legal question of preemption. *See* Doc. No. 204-23.

fundamentally different than the question of substantive causation that Plaintiffs argue in their supplemental brief. Again, the ultimate question of causation is not before the Court at this time.[31]

The Court has also generally considered the time period after 2015. Merck's expert testified that in these later years independent researchers conducted real-world epidemiological studies to evaluate whether any association exists between HPV vaccination and POTS and those studies (some involving populations of more than a million) consistently found no association between HPV vaccination and POTS.[32] *See* Doc. No. 197-3 at 55, citing Thomsen (2019), Hviid (2020), Skufca (2018), Cameron (2016), Phillips (2020). Further, other studies after 2015 such as Arana (2017) do not find any causal association. *See* Doc. No. 190-32 ("Our safety review did not detect any unusual or unexpected patterns of reporting for POTS following HPV vaccination.").[33]

The Court understands that risk information may "accumulate over time," *Wyeth*, 555 U.S. at 569, and "newly acquired information" can include a new analysis of preexisting data "showing risks of a different type or of greater severity or frequency." *Id.* However, Plaintiffs conceded at argument that no study has ever shown a statistically significant increase in POTS or POI in those

[31] Echoing earlier arguments that the Court has already discussed (and rejected) above, Plaintiffs' Supplemental Brief also wrongly conflates "autoimmune illness" generally with POTS specifically and relies heavily on disproportionality analyses that, as admitted by Plaintiffs, cannot establish any causal association between a reported adverse effect and a vaccine. In any event, the FDA and its officials have studied autoimmune conditions and found no evidence of increased risk. *See* Doc. No. 295 at 5, fn. 13, citing FDA Information on Gardasil (2011), Gardasil Vaccine Safety (2009), Slade (2009), Shimabukuro (2015), Arana (2018), Shimabukuro (2019).

[32] The inconsistency in Plaintiffs' expert's view of various studies is striking. While Dr. Amato is willing to rely on less than a dozen (including unverified) reports of POTS in support of his conclusion that a warning was warranted in 2011, he criticizes a "systemic review and meta-analysis aimed at evaluating the risk of POI following HPV vaccination" that included "data from four cohort studies comprising of 1,253,758 female children and adolescents" because of the "small number of related studies." *See* Doc. No. 186-2 at 136, 139-140.

[33] Dr. Amato cites Chandler (2017), but he acknowledged that the research concluded that "a causal association between HPV vaccination and [possible POTS adverse events] remained uncertain [but] "the study authors believed that more extensive analysis of spontaneous reports can better identify relevant cases for thorough signal evaluation." *See* Doc. No. 186-2 at 105-106.

who have taken Gardasil versus those who have not; instead, comparative studies of vaccinated and unvaccinated persons demonstrate no increased risk.[34] *See* Doc. No. 292 at 78. Therefore, as with the period prior to January 2011, the Court finds that Merck did not have sufficient "newly acquired information" establishing a causal association between POTS and Gardasil that would have permitted it to unilaterally add a warning to the Gardasil label after January 2011.

2. POI

Based on the testimony of Dr. Amato, Plaintiffs claim that Merck should have added the following warning for POI by November 2013:

> Section 5 WARNINGS AND PRECAUTIONS 5.3 Serious adverse events can occur following the administration of GARDASIL. Gardasil may cause menstrual irregularities or change in menstrual function, difficulty conceiving, or primary amenorrhea. Such symptoms may relate to primary ovarian insufficiency (POI) or primary ovarian failure (POF). Careful history of any individual should be gathered before vaccination and if these symptoms present following vaccination, further doses should be avoided, and the patient should be referred for gynecological evaluation.

Doc. No. 186-2 at 146-47.

Premature ovarian insufficiency ("POI"), also known as premature menopause or premature ovarian failure ("POF"), is a clinical syndrome defined by loss of ovarian activity before the age of 40. Doc. Nos. 190-67 at 2; 206-46 at 2; 190-63 at 4. POI is generally diagnosed based

[34] *See*, e.g., Doc. No. 190-33, Anders Hviid et al., *Association between quadrivalent human papillomavirus vaccination and selected syndromes with autonomic dysfunction in Danish females*, 370 BMJ 1 (2020) ("[W]e observed no association between quadrivalent human papillomavirus vaccination and . . . postural orthostatic tachycardia syndrome"); Doc. No. 190-34, Reimar Thomsen, et al., *Hospital Records of Pain, Fatigue, or Circulatory Symptoms in Girls Exposed to Human Papillomavirus Vaccination*, 189 Am J Epidemiol. 277, 284 (2020) (using three different study designs, including comparison of 314,017 vaccinated girls to 314,017 unvaccinated girls, "HPV vaccination among girls was not associated with subsequent increased risk of pain, malaise, fatigue, tachycardia, hypotension, or syncope").

on symptoms reported,[35] including menstrual irregularities for at least three months, plus lab tests showing elevated FSH levels and low estradiol levels on at least two separate occasions. Doc. No. 204-46 at 2; 190-63 at 6. "Women with POI have little chance of spontaneous pregnancy, and no interventions could increase ovarian activity and natural conception rates." Doc. No. 190-67 at 2. POI impacts approximately 1% of women under age 40, 0.1% of women under age 30, and 0.01% of women under age 20. Doc. No. 197-3 at 56-57. For up to 90% of diagnosed POI cases, the cause is currently unknown. About 4% of POI cases are estimated to have an autoimmune etiology. Doc. No. 197-3 at 57, citing Christianson (2020).

As with POTS, Dr. Amato mentions preclinical animal studies, clinical trial data, case reports, literature, disproportionality signals and post marketing surveillance as the evidence he claims allowed Merck to add a POI warning to the Gardasil label. And, like POTS, this evidence falls far short of establishing that Merck had "newly acquired information" showing a causal association between POI and Gardasil.

Merck's preclinical animal studies are discussed on the Gardasil label used by Merck in November 2013. The company performed "reproductive studies" in "female rats at doses equivalent to the recommended human dose" that "revealed no evidence of impaired female fertility or harm to the fetus due to GARDASIL." *See* Doc. No. 190-80 at 81 (Gardasil label "Revised 9/2013"). Thus, to the extent they could be "newly acquired information" (which they are not) these studies support Merck's rather than the Plaintiffs' position. There was also no evidence of a causal association between POI and Gardasil in the clinical trials (which also cannot be "newly acquired information"). In the Gardasil clinical trials, no cases of POI were reported as

[35] Symptoms often include changes to menses, hot flashes, excessive sweating, hair loss, and skin and mucous membrane dryness. Doc. No. 206-46 at 2.

adverse events. Doc. No. 197-3 at 58. However, Dr. Amato again criticizes Merck for classifying clinical trial events as "new medical history."[36] Still, as to specifics, Dr. Amato's report states that "two ovarian failure cases were reported in the qHPV vaccine group, and four in the placebo group." This is clearly not evidence that would support a warning.[37]

With respect to "case reports," the first published case report of POI following Gardasil vaccination (a single case) was published in 2012. *See* Doc. No. 206-36 (Little (2012)). A series of three cases of POI following Gardasil vaccination was published in 2013. *See* Doc. No. 206-38 (Colafrancesco (2013)). As of November 2013, these two publications, covering four reported cases, were the only published literature of POI following Gardasil.[38] As discussed above, isolated case reports do not constitute evidence of a causal association between Gardasil and POI, as acknowledged even by Dr. Amato. Doc. No. 186-2 at 132 ("case reports cannot establish causation.").

There was also scant evidence of POI in Gardasil's post-marketing VAERS surveillance. In the more than six years between June 2006 and December 2013, VAERS received 12 reports mentioning ovarian failure or premature menopause and Gardasil. Through September 30, 2013, Merck reported 11 medically confirmed cases of POI following Gardasil vaccination in their periodic reports to the FDA. Doc. No. 197-3 at 58. None of these unverified reports, considered

[36] As discussed above, information classified as new medical history is still fully considered by FDA and may simply reflect the fact that some conditions aren't diagnosed until well after vaccination.

[37] Merck's expert similarly notes that ovarian failure or premature menopause were recorded as new medical history among 5 Gardasil recipients and 4 placebo recipients. Doc. No. 197-3 at 58.

[38] Dr. Amato also mentions a 2014 publication, Little (2014), that added two additional cases. Merck, of course, could not have considered this 2014 publication before November 2013. In any event, counting the case reports of POI following HPV vaccination published before November 2013, as of September 2024 there were still only six such case reports in the published literature. *See* Doc. No. 197-3 at 60.

on their own or in the aggregate, are reasonable evidence of a causal association between Gardasil and POI. Also, considering the background rate of POI in the population, these few cases of reported POI following tens of millions of Gardasil vaccinations are not sufficient to generate a safety concern. *Id.*

With respect to disproportionality "signals," Plaintiffs and Dr. Amato argue that Merck's 2012 and 2013 "EB05" data mining reports for "Cervical dysplasia" and menstrual disorder, delays or irregularities reflected a "signal" that should have caused Merck to further investigate any possible connection to the vaccine. *See* Doc. Nos. 186-2 at 125, 205-23, 205-24, 205-25. However, "Cervical dysplasia" and the various menstrual issues listed are not POI, and, as discussed above, disproportionality scores from data mining calculations are not evidence of causation. *See* Doc. No. 197-3 at 59.[39]

Finally, Dr. Amato's review of the relevant scientific literature does not support a finding that Merck had reasonable evidence of a causal association by November 2013 (or later). First, Dr. Amato cites Naleway (2018). In that study, the scientists conducted a population-based, retrospective cohort review using electronic health records from Kaiser Permanente Northwest. The objective was to evaluate the incidence of POI and estimate the risk of POI associated with HPV and other vaccines. The study population consisted of 199,078 female patients from 2006 to 2014. Only 46 cases were confirmed as diagnosed POI. The study concluded that the "ratios did not indicate a significant increase in risk." Doc. No. 186-2 at 134-135.

[39] Dr. Amato also references two "disproportionality assessments," one in 2020 that purported to detect a "signal" for "POI related events" for Gardasil 4 and "menstruation irregular" for Gardasil 9 and recommended "long-term reproductive safety studies" (which could not have been completed in time to provide timely evidence to support a warning) and a second published after January 2021, which would also be too late to be relevant here. (And, the authors of that study noted that their findings "may partly result from notoriety bias" and "further investigation is needed to confirm the association."). *See* Doc. No. 186-2 at 132-134.

Next, he discusses Hviid (2021), which was a retrospective cohort study aimed at evaluating the risk of POI following quadrivalent human papillomavirus (4HPV) vaccination. The study included 996,300 Danish-born girls and women aged 11 to 34 years, followed from 2007 to 2016. Out of 6,781,166 person-years of follow-up, 144 diagnoses of POI were identified (54 in vaccinated and 90 in unvaccinated individuals), which did not indicate a significant increase in risk. The authors concluded that the study found no significant association between HPV vaccination and POI. *See* Doc. No. 186-2 at 135-136.

Last, Dr. Amato discusses Torella (2022), a systematic review and meta-analysis aimed at evaluating the risk of POI following HPV vaccination. The study included data from four cohort studies comprising 1,253,758 female children and adolescents who received either the quadrivalent, bivalent, or 9-valent HPV vaccines. The study looked at the risk of POI after HPV vaccination, comparing vaccinated groups to unvaccinated groups or those vaccinated with other childhood vaccines. The meta-analysis did not find a significant increase in POI risk associated with Gardasil compared to unvaccinated controls or to other vaccines. As reported by Dr. Amato, "the authors concluded that HPV vaccination, specifically Gardasil, did not appear to increase the risk of POI compared to unvaccinated individuals or those receiving other childhood vaccines. The risk of POI post-vaccination was comparable to the general incidence of POI in the population." *See* Doc. No. 186-2 at 136. Therefore, not only were all these scientific studies published well after November 2013, they conclude that Gardasil does not appear to increase the risk of POI. [40, 41]

[40] Dr. Amato argues that the studies have several limitations, including that they are "underpowered" and "the small number of included studies." In light of Dr. Amato's willingness to rely on just a few cases of POI to support his opinions, these critiques, are, at best, incongruent.
[41] Merck's expert cites several additional analyses of adverse event reporting data by scientists at public health and regulatory authorities in the United States and around the world that have concluded there is no signal of concern for Gardasil and POI. *See* Doc. No. 197-3 at 60, citing Arana (2018), Shimabukuro (2019), Phillips (2020) and Wodi (2023).

In summary, Merck did not have sufficient "newly acquired information" to unilaterally add a POI warning to the Gardasil label in November 2013. Less than a handful of POI case reports, scattered unverified VAERS reports, and uncertain disproportionality "signals" related to various "menstrual" issues do not amount to the reasonable evidence of a causal association required to add a POI warning. Requiring such evidence is particularly important with respect to POI because a warning as to infertility in the absence of evidence of causal association is not only unauthorized, it would be plainly unwise. Raising the possibility of losing the ability to have children among a population of young women and their parents (who hope to be grandparents) might well significantly discourage use of a vaccine that has prevented innumerable deaths from cancer.

Federal law requires more than speculative inferences prior to adding dire warnings to lifesaving vaccines that discourage their use. The law requires reasonable scientific evidence of a causal association between the vaccine and the alleged harm. As described at length above, that evidence is lacking here. Therefore, Merck could not lawfully change the Gardasil label without prior approval from the FDA. Without that authority, federal and state law are in conflict and Bellwether Plaintiffs' state law failure to warn claims are all preempted. Summary judgment will be granted to Merck on those claims.

IV. ORDER

NOW THEREFORE IT IS ORDERED THAT:

1. Defendants' Motion for Summary Judgment Based on Implied Preemption (Doc. No. 188) is **GRANTED;** and
2. This Order shall be applied to Plaintiffs in the MDL other than the Bellwether Plaintiffs in accordance with the prior orders of the Court and/or the agreement of the Parties.

SO ORDERED ADJUDGED AND DECREED.

Signed: March 10, 2025

Kenneth D. Bell
United States District Judge