Legal Opinion Letter
Vol. 34 No. 4 March 24, 2025

Washington Legal Foundation
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FDA Labeling Preemption Precludes Plaintiffs' Failure-to-Warn Claims in MDL Targeting Vaccine

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The federal district court managing the nationwide Multidistrict Litigation targeting Merck & Company's Gardasil vaccine recently granted summary judgment to the defendant drug manufacturer based on federal labeling preemption, resulting in the resolution of hundreds of pending cases. *In re: Gardasil Products Liability Litigation*, No. 3:22-MD-03036-KDB (W.D.N.C. Mar. 11, 2025) (Bell, J.). Gardasil is FDA-approved to protect recipients from various forms of cancer and genital warts associated with the Human Papillomavirus (HPV). Plaintiffs, who received the Gardasil vaccine, alleged that it caused them to experience postural orthostatic tachycardia syndrome (POTS) or Primary Ovarian Insufficiency (POI), and that Merck had failed to warn them that use of the vaccine carried a risk that it could cause those conditions. In particular, the plaintiffs contended that Merck should have unilaterally amended its product label to add warnings regarding POTS by 2011 and to add a POI warning by 2013 under the Changes Being Effected (CBE) regulation. 21 C.F.R. § 601.12(f)(2)(i).

Legal Background

The Supreme Court has held that, where a sponsor or manufacturer can unilaterally change its label under the CBE regulation, there is no implied conflict preemption with FDA's decision to approve the prior labeling as safe and effective. *Wyeth v. Levine,* 555 U.S. 555, 569 (2009). While plaintiffs once hoped that decision would put an end to any labeling preemption defense for FDA approved drug and biologic products, the Supreme Court revisited the question several times since and confirmed that the *Wyeth* exception to labelling preemption only applies when FDA regulations provide the sponsor with ability to change its label unilaterally, without prior FDA approval. *See Mut. Pharm. Co., Inc. v. Bartlett*, 570 U.S. 472 (2013); *Merck Sharp & Dohme Corp. v. Albrecht*, 587 U.S. 299 (2019). The decision of whether conflict preemption applies is dedicated to the court as a question of law. *Albrecht*, 587 U.S. at 303.

FDA regulation 21 C.F.R. § 601.12(f)(2)(i) is the only regulation that permits a biologic sponsor to unilaterally change its labeling to address a safety issue without prior FDA approval (a similar provision, 21 C.F.R. § 314.70(c)(6)(iii), applies to drug products). That regulation allows the sponsor to change the label to strengthen a warning (among other things) only where there is "newly acquired information" (defined in 21 C.F.R. § 601.12(f)(6)) not previously known to FDA that reveals a new safety risk or an increased frequency or severity of a known safety risk. In the wake of *Albrecht*, in particular, several district and circuit courts have explored the meaning and limited the scope of the CBE regulation. *See, e.g., Knight v. Boehringer Ingelheim Pharm., Inc.*, 984 F.3d 329 (4th Cir. 2021); *Gibbons v. Bristol-Myers Squibb Co.*, 919 F.3d 699 (2d Cir. 2019); *Warner v. Amgen Inc.*, No. 1:24-CV-10632-JEK, 2025 WL 490720 (D. Mass. Feb. 13, 2025).

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Because the cases involved allegedly new risks not previously identified on the label that the plaintiffs alleged should have been in the warnings and precautions section, the court immediately turned its analysis to the regulatory standard for determining whether an adverse event should be identified in the warnings and precautions section of the label. 21 C.F.R. § 201.57(c)(6)(i). That regulation provides that adverse reactions that are "clinically significant … (including any that are potentially fatal, are serious even if infrequent, or can be prevented or mitigated through appropriate use of the drug)" must be listed in warnings and precautions. *Id.* It goes on to state that a warning and precaution must be added for an adverse reaction "as soon as there is reasonable evidence of a causal association," though it also states that a "causal relationship need not have been definitely established." *Id.*

No Newly Acquired Information Sufficient to Change the Label

The *Gardasil* court, held that, "in order to qualify as 'newly acquired information,' the information must demonstrate 'reasonable evidence of a causal association with a drug . . . ." *Gardasil*, slip op at 12. It then turned to the alleged "newly acquired information" proffered by the plaintiffs on the summary judgment for POTS and POI, noting that plaintiffs bore the burden of establishing the existence of satisfactory newly acquired information. *Id.* at 12.

POTS

POTS is a syndrome in which moving from lying down to standing or sitting, results in tachycardia and other symptoms (such as light-headedness, shortness of breath, chest pain and palpitations). *Id.* at 14. After noting that the relevant evidence for "newly acquired information" is information not previously submitted to the FDA that arises after the FDA's approval of a vaccine, *id.* at 15-16, the court noted that plaintiffs had offered only a single published report of POTS—a case report of a 20-year-old woman in a foreign medical journal—during the relevant time frame. During the same period, FDA's Vaccine Adverse Event Reporting System (VAERS) database for tracking adverse drug events after FDA approval had fewer than 10 reports of POTS associated with Gardasil, and Merck had reported about 10 cases to FDA. Two additional publications were identified by plaintiffs at oral argument.

Thus, the court summarized plaintiffs alleged "newly acquired information" regarding POTS consisted of "one published case of POTS and less than 20 unverified reports of POTS." The court held, "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." *Id.* at 20. The court also held that the 83 cases of POTS worldwide (out of more than 100 million administered doses of Gardasil), identified in plaintiffs supplemental briefing, did not satisfy the regulatory standard and concluded 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 label." *Id.* at 29.

POI

POI, also known as premature menopause or premature ovarian failure, is the loss of ovarian activity before the age of 40. *Id.* at 30. The court discussed alleged animal study data and clinical trial data evaluating ovarian failure in the clinical trials and dismissed that evidence as not constituting reasonable evidence of a causal association, but also of not being "newly acquired information," as that data was reported to FDA prior to vaccine approval. The court reviewed two case reports proffered by plaintiffs, covering four reported cases of POI (the only such reports in the medical literature at the relevant time), and concluded that they were insufficient to constitute evidence of a causal association. *Id.* at 31. The court also found "scant" evidence in the VAERS database and Merck's own

adverse event reporting, with only 12 reports of POI and 11 reports of POI respectively, to support a claim that there was evidence of a causal association. *Id.* at 32. The court also rejected plaintiffs' reliance on a retrospective cohort review of electronic health records, a Danish retrospective cohort review of Danish women, and a meta-analysis examining POI following HPV vaccination. Each of these papers failed to find a statistically significant relationship between vaccination and POI. The court concluded that "Merck did not have sufficient 'newly acquired information' to unilaterally add a POI warning to the Gardasil label." *Id.* at 34.

Preemption Applied

The court concluded that the CBE regulation did not empower Merck to unilaterally change its label to add safety information regarding POTS and POI and held that plaintiffs labeling claims were preempted. The decision was applicable directly to the bellwether case pool of sixteen plaintiffs but was ordered to be applied to the rest of the case inventory of approximately 200 cases to the extent applicable. The *Gardasil* court's approach of working backward from the regulatory threshold required for each section of the labeling to determine whether the alleged "newly acquired information" would meet that regulatory standard, provides an insightful approach to avoid considering the alleged "newly acquired information" in the abstract before turning to the heart of the preemption question.

