FDA Preemption and *Albrecht*'s Progeny

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ABSTRACT

In product liability cases, manufacturers have argued for years that failure-to-warn claims involving FDA-approved drugs should be preempted by federal law because manufacturers lack the ability to add certain warnings to an approved product label. In *Merck v. Albrecht*, the United States Supreme Court confirmed that preemption is a question of law properly decided by courts and provided additional guidance on the framework required for manufacturers to successfully raise this defense.[1] This Article examines how courts have applied this framework post-*Albrecht* and explores what potential litigants can do to better prepare to either raise a preemption defense or defend against it.

I. INTRODUCTION

It is well established that a state law in conflict with a federal law is without effect.[2] This is known as "impossibility preemption," because it is impossible to comply with both federal and state laws. In the context of product liability litigation, plaintiffs' legal theories typically, if not exclusively, arise under a variety of state tort law frameworks. One of the main theories advanced against prescription drug manufacturers is the manufacturer's "failure-to-warn" of specific risks associated with a drug product. These state common law or statutory duties to warn can, and often do, come into conflict with the federal statutory and regulatory scheme through which the U.S. Food and Drug Administration (FDA) regulates the information that appears on brand-name prescription drug labels.[3]

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[1] *See* Merck Sharp & Dohme Corp. v. Albrecht (*Albrecht*), 139 S. Ct. 1668, 1672 (2019).

[2] Mut. Pharm. Co. v. Bartlett, 570 U.S. 472, 479–80 (2013) (quoting Maryland v. Louisiana, 451 U.S. 725, 746 (1981)) (internal quotations omitted).

[3] *See Albrecht*, 139 S. Ct. at 1672.

In 2009, the Supreme Court recognized in *Wyeth v. Levine*[4] that state law failure-to-warn claims are preempted when there is "clear evidence" that FDA would not have approved the warning that state law requires.[5] The *Wyeth* holding led to a number of uncertainties and varying interpretations by lower courts. However, ten years later in *Albrecht*,[6] the Supreme Court 1) held that preemption is a question of law; 2) further defined the clear evidence standard; and 3) confirmed the appropriate framework for analyzing this type of preemption claim. *Albrecht* confirmed that in the context of prescription drug failure-to-warn claims, impossibility preemption is best thought of as a two-prong test, which asks: 1) does sufficient evidence exist to trigger a manufacturer's ability to add plaintiff's desired warnings to a product label? and 2) if so, does clear evidence exist that FDA would not have approved such changes?[7] This Article will discuss how courts have applied this analysis post-*Albrecht*.

II. PRESCRIPTION DRUG LABELS

FDA is the federal agency charged with regulating prescription drug products, including the regulation of safety information that appears on the labels of prescription drugs that are marketed in the United States.[8] FDA provides requirements for the content, format, and order of safety information on a drug product's label.[9] The specific location of where safety information is placed on a drug label indicates the likelihood and severity of a risk associated with the drug product.[10] The hierarchy of label information is purposely designed to "prevent over warning" so that less important information does not overshadow more important information.[11] Drug labels are also designed to exclude "[e]xaggeration of risk, or inclusion of speculative or hypothetical risks," that "could discourage appropriate use of a beneficial drug."[12]

For new drug products, manufacturers work with FDA to develop the initial drug label, and FDA must approve the final label.[13] Because safety information changes over time, additions or modifications to a drug label may become necessary. Drug manufacturers generally seek permission from FDA to make substantive changes to their drug labels.[14] However, pursuant to the Changes Being Effected (CBE) regulatory process, "drug manufacturers [may] change a label without prior FDA approval if the change is designed to 'add or strengthen a . . . warning' where there is

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4 *See* Wyeth v. Levine, 555 U.S. 555 (2009).

5 *Albrecht*, 139 S. Ct. at 1675–76.

6 *See generally id.* at 1670–71.

7 *See id.*

8 *Albrecht*, 139 S. Ct. at 1672 (citing 21 U.S.C. § 355(b); 21 C.F.R. § 201.57(a) (2018)).

9 *Albrecht*, 139 S. Ct. at 1673 (citing 21 C.F.R. § 201.57(c) (2021)).

10 *See Albrecht*, 139 S. Ct. at 1673.

11 *Id.* at 1673 (quoting Supplemental Applications Proposing Labeling Changes for Approved Drugs, Biologics, and Medical Devices, 73 Fed. Reg. 49,603, 49,605–06 (Aug. 22, 2008) (to be codified at 21 C.F.R. pt. 314, 601, and 814)).

12 *Albrecht*, 139 S. Ct. at 1673.

13 *Id.* at 1673.

14 *Id.*

'newly acquired information' about the 'evidence of a causal association' between the drug and a risk of harm."[15]

III. MERCK V. ALBRECHT

Merck Sharp & Dohme Corporation (Merck) manufactured Fosamax®, a drug for the prevention of osteoporosis in women.[16] "Fosamax . . . slows the breakdown of old bone cells and thereby helps postmenopausal women avoid osteoporotic fractures."[17] "However, the mechanism through which Fosamax decreases the risk of osteoporotic fractures may increase the risk of a different type of fracture"—atypical femoral fractures (AFF).[18]

At the time of Fosamax's approval in 1995, Merck's scientists were aware of "at least a theoretical risk of [AFF]."[19] Merck brought those concerns to FDA's attention prior to Fosamax's approval, but FDA did not require an AFF warning in the initial Fosamax label.[20] After 1995, evidence connecting Fosamax to AFF developed.[21] In 2008, Merck applied to FDA for preapproval to change Fosamax's label to add the risk of stress fractures.[22] FDA did not approve the "stress fracture" language because FDA found the proposed terminology of "stress fractures" to be inadequate, explaining that the "identification of 'stress fractures' may not be clearly related to the atypical subtrochanteric fractures that have been reported in the literature."[23] FDA invited Merck to address the deficiencies and resubmit its application for the changes.[24] Merck withdrew its application and did not add a warning related to stress fractures or AFF.[25] In early 2011, FDA ordered Merck to add a warning to the Fosamax label regarding the risk of AFF based on the agency's own analyses.[26] During negotiations with FDA, Merck suggested that the new warning should consist of its previously suggested language regarding stress fractures.[27] FDA rejected that suggestion as not adequately representing the "seriousness of [AFF]" and required a specific warning aimed at AFF.[28]

In late 2011, more than 500 plaintiffs brought suit against Merck, arguing that the company had a duty to warn patients and their doctors about the risks of AFF.[29] Merck

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[15] *Id.* at 1673 (citing 21 C.F.R. § 314.70(c)(6)(iii)(A)).

[16] *Albrecht*, 139 S. Ct. at 1673.

[17] *Id.*

[18] *Id.*

[19] *Id.* at 1674.

[20] *Id.*

[21] *Id.*

[22] *Id.*

[23] *Id.*

[24] *Id.*

[25] *Id.*

[26] *Id.*

[27] *Id.* at 1674–75.

[28] *Id.* at 1675.

[29] *Id.*; In re Fosamax (Alendronate Sodium) Prods. Liab. Litig., No. 2243, 2011 U.S. Dist. LEXIS 135006 (D.N.J. Nov. 21, 2011).

argued that these state law failure-to-warn claims should be dismissed as preempted by federal law.[30] Merck conceded that the CBE process was available to request an AFF warning prior to the FDA-mandated warning in 2010. Merck argued, however, that "for some period of time between 1995 [when FDA first approved a drug label for Fosamax] and 2010 . . . both Merck and FDA were unsure whether the developing evidence of a causal link between Fosamax and [AFF] was strong enough to require adding a warning to the Fosamax drug label."[31] Merck pointed to FDA's rejection of its 2008 attempt to add a stress fracture warning as "clear evidence" that FDA would not have allowed the plaintiffs' desired warning at that time.[32]

The Supreme Court did not reach the substantive question of whether clear evidence of FDA disapproval existed.[33] Instead, the Supreme Court's holding was limited to a determination that preemption is a question of law for the court—not a jury— to decide.[34] In so doing, the Court did provide additional informative commentary on the impossibility preemption framework and the clear evidence standard previously articulated in *Wyeth v. Levine*. The Court explained that there must first be an available mechanism for manufacturers to add the desired warning.[35] In cases like *Albrecht* and *Wyeth* where warnings could be added via the CBE process, for preemption to apply, there must also be clear evidence that FDA was "fully informed" of the justifications for the proposed warning and that the agency would not have approved the inclusion of the desired warning.[36] Importantly, the Court added that any such FDA action disapproving of a label change must be done "carrying the force of law" in exercising the agency's authority as delegated by Congress; essentially, only official agency actions can result in preemption.[37]

IV. MANUFACTURER'S ABILITY TO ADD THE DESIRED WARNING

The first step of the *Albrecht* preemption analysis is to determine whether the manufacturer had the ability to unilaterally add the desired warning. In prescription drug cases, this analysis centers on whether there is sufficient evidence to trigger a manufacturer's ability to change its label under the CBE regulatory process.[38] The CBE process requires that: 1) the manufacturer knew or should have known of the newly acquired information about its drug; 2) the newly acquired information about the drug showed a causal association between the drug and an effect; and 3) such causal association warrants a new warning.[39] Courts must consider the above three

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[30] *Albrecht*, 139 S. Ct. at 1675.

[31] *Id.*

[32] *Id.* at 1675–76.

[33] *See id.* at 1676, 1680–81.

[34] *See id.* at 1675.

[35] *See id.* at 1678.

[36] *See id.* at 1677–78.

[37] *Id.* at 1679.

[38] *See generally* Knight v. Boehringer Ingelheim Pharm., Inc., 984 F.3d 329 (4th Cir. 2021).

[39] *See* Dolin v. GlaxoSmithKline L.L.C., 951 F.3d 882, 885 (7th Cir. 2020) (quoting Dolin v. GlaxoSmithKline L.L.C., 901 F.3d 803, 805 (7th Cir. 2018)).

elements in determining whether the ability to change the label under the CBE process exists.[40] In so doing, courts weigh different forms of data and medical evidence to evaluate if newly acquired information existed to allow a manufacturer to unilaterally make a label change.[41] Establishing the first step of the *Albrecht* framework is essential; if a plaintiff is unable to demonstrate that a manufacturer had the ability to add the desired warning via the CBE process or otherwise, then a failure-to-warn claim is preempted, and courts need not even consider the second clear evidence step articulated in *Albrecht*.[42]

A. Newly Acquired Information

In *Knight v. Boehringer Ingelheim Pharmaceuticals, Inc.*, the Fourth Circuit Court of Appeals discussed factors to be evaluated in the analysis of "newly acquired information."[43] In *Knight*, plaintiffs brought claims against Boehringer Ingelheim Pharmaceuticals (Boehringer), the manufacturer of Pradaxa®—a blood thinner used by the plaintiffs' deceased mother.[44] The plaintiffs alleged that their mother suffered a gastrointestinal bleed from Pradaxa and died following subsequent complications.[45] The FDA-approved label for Pradaxa warned that it "can cause serious and, sometimes, fatal bleeding."[46] However, the plaintiffs asserted that Boehringer should have changed Pradaxa's label to provide a warning "recommend[ing] that patients with impaired kidney function taking Pradaxa undergo blood testing to check Pradaxa concentration levels" because the risk of bleeding increases as Pradaxa concentration levels increase.[47] As evidence of Boehringer's duty to warn, plaintiffs pointed to Boehringer's re-analysis of Pradaxa's original clinical trials (referred to as the "Reilly Paper").[48]

Citing *Albrecht*, the Fourth Circuit recognized that a failure-to-warn claim may proceed "only [if] the defendant had the unilateral ability to change [FDA-approved] labeling [in the way the plaintiffs demand]; otherwise, the claim is preempted."[49] The Fourth Circuit explained that the first step in a preemption analysis is determining whether the manufacturer had the ability to unilaterally make the desired label change without FDA approval through the CBE process.[50] The CBE process requires all modifications to add or strengthen warnings can only be made where there is newly acquired information about the evidence of a causal association between the drug and a risk of harm.[51] The court explained that, for purposes of the CBE regulatory process, newly acquired information is information that "reveals risks of a different type or

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[40] *Id.*

[41] *See Knight*, 984 F.3d at 338.

[42] *Id.* at 337

[43] *See id.* at 338.

[44] *Id.* at 332.

[45] *Id.*

[46] *Id.* at 334.

[47] *Id.* at 336–39.

[48] *Id.* at 334.

[49] *Id.* at 337.

[50] *Id.*

[51] *Id.* at 338 (quoting Merck Sharp & Dohme Corp. v. Albrecht, 139 S. Ct. 1668, 1673 (2019)).

greater severity or frequency than previously included in submissions to FDA."[52] Newly acquired information is not limited to only newly generated data, but also includes re-analysis of historical data.[53] Regardless of form, the defining hallmark of newly acquired information is that it must show "risks of a different type or of great severity or frequency" than what was previously known.[54]

In determining the plaintiffs' claims were preempted because there was insufficient newly acquired information to trigger Boehringer's ability to utilize the CBE regulatory process to add plaintiffs' desired warning, the Fourth Circuit provided a number of notable factors to be considered when evaluating newly acquired information.[55] First, newly acquired information should have existed before the patient's exposure or injury as the information could have prevented the harm in question.[56] Data generated or published after the plaintiffs' use of the product or injury cannot constitute newly acquired information in the context of a particular claim.[57]

Second, the Fourth Circuit confirmed that a re-analysis of historical data may constitute newly acquired information.[58] However, when evaluating the re-analysis of data previously submitted to FDA, the court considered whether the re-analysis actually found "risks of a different type or greater severity or frequency" than what was already known to FDA at the time the drug product was approved.[59] Here, the court concluded that even though the Reilly Paper "discusses the correlation between Pradaxa blood concentration levels and bleeding risk . . . FDA was already aware of this correlation" at the time of Pradaxa's approval and did not require the warning plaintiffs sought.[60] Consequently, the Reilly Paper's conclusion could not constitute newly acquired information.[61]

Third, open-ended conclusions or conclusions that require additional research do not constitute newly acquired information because they "plainly [do] not establish any new risks."[62] In addition, the "regulatory and scientific community['s]" accept[ance] of conclusions should be considered in evaluating whether a specific conclusion is newly acquired information.[63] The fact that FDA has reviewed the data in question and continues to approve a label without plaintiffs' desired warning undermines a claim that the data was sufficient to trigger a manufacturer's CBE ability.[64]

The *Knight* court emphasized the need for an individualized inquiry into the preemption question and concluded that "there is no bright-line, one-size-fits-all line

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[52] *Knight*, 984 F.3d at 338.

[53] *Id.*

[54] *Id.*

[55] *See id.* at 338–40.

[56] *Id.* at 338.

[57] *Id.*

[58] *Id.* at 338–41.

[59] *Id.* at 338.

[60] *Id.*

[61] *Id.*

[62] *Id.* at 339.

[63] *Id.*

[64] *Id.*

marking the moment when an analysis reveals new information. A careful review of the record is needed to determine whether a conclusion has been reached."[65]

B. Burden of Proof for Newly Acquired Information

Courts are divided on which party has the burden of demonstrating the existence of newly acquired information. Some courts have adopted a burden-shifting framework that requires plaintiffs to establish the existence of newly acquired information before shifting to defendants to demonstrate clear evidence of FDA rejection.[66] However, other courts treat preemption strictly as an affirmative defense in which the manufacturer alone bears the burden of proof as to all aspects.[67] Regardless of approach, the practical takeaway seems to be that regardless of whose burden it is to show that specific information is in fact newly acquired information, a plaintiff must first identify what is alleged to be newly acquired information.

In *Gibbons v. Bristol-Myers Squibb Co.*, the Second Circuit utilized the burden-shifting framework in which a plaintiff must prove the existence of newly acquired information to establish a manufacturer's ability to utilize the CBE regulation and then the burden shifts to the manufacturer to demonstrate clear evidence of FDA rejection.[68] Eliquis® is an FDA-approved blood-thinning drug used to reduce the risk of stroke in certain patients.[69] Due to its blood-thinning properties, Eliquis has, since its approval, included "warnings about the risk of serious, and possibly fatal, bleeding events."[70] Plaintiffs in *Gibbons* alleged that these warnings were insufficient, and the lack of appropriate warning resulted in serious and sometimes fatal injuries.[71] As evidence of the necessity for an additional warning, plaintiffs alleged that defendants were aware of numerous adverse event reports involving serious hemorrhaging in patients taking Eliquis. Additional post-approval studies confirmed this risk.[72]

The Second Circuit explained that the first prong of the preemption analysis is to examine whether "a plaintiff [has] plead a labeling deficiency that [Defendants] could have corrected using the CBE regulation."[73] Only then does the burden shift to the manufacturer to demonstrate clear evidence that FDA would not have approved the proposed label change.[74] The Second Circuit confirmed that dismissal is appropriate at the motion to dismiss stage where the plaintiff's complaint fails to point to any information which would suggest a manufacturer could utilize the CBE mechanism.[75]

The Second Circuit scrutinized the operative complaint and held that the plaintiffs failed to plead any newly acquired information that would allow defendants to modify

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[65] *Id.* at 341.

[66] Gibbons v. Bristol-Myers Squibb Co., 919 F.3d 699, 708 (2d Cir. 2019).

[67] In re Zofran (Ondansetron) Prod. Liab. Litig., No. 1:15-MD-2657-FDS, 2021 WL 2209871, at *27 (D. Mass. June 1, 2021).

[68] *See Gibbons*, 919 F.3d. at 708.

[69] *Id.* at 702.

[70] *Id.*

[71] *Id.*

[72] *Id.* at 708.

[73] *Id.*

[74] *Id.*

[75] *Id.*

the Eliquis label pursuant to the CBE process.[76] The court found that the plaintiffs' pleadings included only "conclusory and vague" allegations and did not plausibly allege any newly acquired information of a new or heightened risk.[77] The Second Circuit rejected that adverse event reports of hemorrhaging and publications confirming the risk of bleeding cited in the plaintiffs' complaint could constitute newly acquired information because these reports and studies failed to reveal risks of a "different type or greater severity, or frequency" than previously included in a submission to FDA.[78] Keeping in mind that the Eliquis label consistently warned of serious (and even fatal) risks of bleeding, the Second Circuit reasoned that the complaint provided no basis to conclude that the cited reports and studies revealed a risk that differed from what FDA already knew.[79]

Other courts have recently confirmed that dismissal at the pleading stages is appropriate where the operative complaint does not identify newly acquired information. For example, in *Zamfirova v. Amag Pharmaceuticals*, the court explained that plaintiffs must first identify newly acquired information sufficient to allow defendants to utilize the CBE process in their pleadings.[80] Amag Pharmaceuticals, Inc. (Amag) manufactured Makena®, a drug approved for use during pregnancy to prevent preterm births.[81] Plaintiffs claim that Amag misrepresented the efficacy of Makena to doctors, patients, and FDA.[82] Makena was initially approved by FDA on the condition that a follow-up clinical trial called the PROLONG study be completed to confirm the drug's efficacy.[83] FDA recommended that Makena be withdrawn from the market after the results of the PROLONG study showed no significant differences in birth outcomes between patients on Makena and those on placebo treatments.[84] The plaintiffs identified both the Meiss study (which FDA evaluated before approving Makena) and the PROLONG study in their complaint as support of the ineffectiveness of Makena in preventing birth defects.[85]

The court focused on the first step of the *Albrecht* framework and evaluated whether the ability to make the label change under the CBE process was present as part of Amag's preemption defense.[86] The court recognized that there must be newly acquired information of significant risk or harm for a manufacturer to unilaterally change a label.[87] It found that a plaintiff's complaint must allege a deficiency in labeling that

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[76] *Id.*

[77] *Id.*

[78] *Id.*

[79] *Id.*

[80] Zamfirova v. Amag Pharms., Inc., No. 20-CV-00152, 2021 WL 2103287, at *7 (D.N.J. May 25, 2021).

[81] *Id.* at *1.

[82] *Id.*

[83] *Id.* at *2.

[84] *Id.*

[85] *Id.*

[86] *Id.* at *7.

[87] *Id.*

the manufacturer could fix under the CBE process.[88] The court established that plaintiffs must include in their pleadings what the newly acquired information is that requires the manufacturer to change the label to comply with state law.[89]

In analyzing the ability to make the label change under the CBE process, the court found that the plaintiffs failed to "allege specific facts" in support of their claims that Amag was aware of the efficacy of Makena.[90] It first found that the Meiss study could not be considered newly acquired information, as FDA fully reviewed the study in their initial approval process.[91] Therefore, the PROLONG study was the only evidence that could be considered newly acquired information.[92] However, the court noted that the plaintiffs failed to provide any evidence that Amag was or could have been aware of the results of the PROLONG study before its finalization.[93] The court questioned how Amag could have known the results of a double-blinded, placebo-controlled clinical trial before the data was processed.[94] Thus, the court could not find any basis for the newly acquired information element of the CBE process as there was insufficient evidence that Amag could have been aware of the results of the clinical trial.[95]

In contrast to the burden-shifting approach, other courts treat impossibility preemption strictly as an affirmative defense with the burden placed entirely on the manufacturer. Illustrative of this approach is *In re Zofran Products Liability Litigation*, where the court found that the burden of proof is held exclusively by the defendant to establish that the CBE mechanism was unavailable, and/or that there is clear evidence that FDA would have rejected the proposed warning.[96] GlaxoSmithKline (GSK) manufactured Zofran®, a drug approved for preventing nausea caused by radiation therapies. However, the drug was often prescribed by physicians to pregnant women to treat nausea associated with pregnancy.[97] In 2010, FDA became aware of the frequent off-label use of Zofran and requested that GSK provide information concerning Zofran's safety when used during pregnancy.[98] GSK provided an analysis of all available safety data, and in response, FDA did not require any label changes.[99] The plaintiffs were women who took Zofran during their pregnancies and whose children suffered birth defects.[100] The plaintiffs claimed that GSK failed to provide

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[88] *Zamfirova*, 2021 WL 2103287, at *7 (quoting In re Celexa & Lexapro Mktg. & Sales Pracs. Litig., 779 F.3d 34, 41 (1st Cir. 2015)).

[89] *See Zamfirova*, 2021 WL 2103287, at *7–8 (quoting Goodell v. Bayer Healthcare Pharms., Inc., No. 18-CV-10694-IT, 2019 WL 4771136, at *4 (D. Mass. Sept. 30, 2019)).

[90] *Id.* at *8.

[91] *Id.*

[92] *Id.* at *7–8.

[93] *Id.*

[94] *Id.*

[95] *Id.*

[96] *See generally In re* Zofran (Ondansetron) Prod. Liab. Litig., No. 1:15-MD-2657-FDS, 2021 WL 2209871, at *27 (D. Mass. June 1, 2021).

[97] *See id.* at *1.

[98] *Id.*

[99] *Id.*

[100] *Id.*

adequate warning on Zofran's label of the risk of birth defects when pregnant women take the drug.[101] Plaintiffs also alleged that all FDA rejections of the proposed labels were based on incomplete information and misrepresentations by GSK.[102] GSK pointed to several citizen petitions which FDA rejected that were submitted by GSK and Zofran's former manufacturer, Novartis, as clear evidence of FDA's rejection of the proposed warning.[103]

The court outlined the *Albrecht* test stating that a drug manufacturer must demonstrate that it fully informed FDA of the justifications for the proposed warning and that FDA would have rejected such warning.[104] The court found that a drug manufacturer may only successfully claim the preemption defense if the CBE process was unavailable to the manufacturer, or if it proves by clear evidence that FDA would not have approved the proposed warning.[105] In addressing the question of who bears the burden of proof, the *Zofran* court acknowledged that the Second Circuit recently found a two-stage burden-shifting framework requiring the plaintiff to first show newly acquired information, as set by *Gibbons*.[106] Here, however, the court found that preemption is an affirmative defense, and as such, the manufacturer carries the burden of proof.[107] The court looked to *Albrecht* and found that the court supported its assertion that, to be successful in a preemption defense, a manufacturer must show that it was prohibited from changing the label.[108] The court pointed to previous treatments of preemption defenses by the First Circuit and found that the court consistently treated preemption like any other affirmative defense. Thus, both the First Circuit and Supreme Court suggest that the burden of proof lies only with the defendant.[109]

Despite finding that GSK was solely responsible for showing that the CBE process was unavailable, the court declined to decide whether the CBE process was available to the manufacturer and assumed, for purposes of the motion for summary judgment, there was newly acquired information.[110] The court then moved on to the question of whether there was clear evidence of FDA rejection of the proposed label change.[111] Further, the court rejected the plaintiff's claim that GSK did not provide all material information in their requests, because FDA's rejection of GSK's final requested change included all the information that the plaintiff alleged was omitted from prior submissions. However, FDA still rejected the proposed change despite being fully informed (as required by *Albrecht*).[112]

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[101] *Id.*

[102] *Id.* at *2.

[103] *Id.* at *1–2.

[104] *Id.* at *24.

[105] *Id.* at *25.

[106] *Id.* at *27.

[107] *Id.*

[108] *See id.* at *27 (quoting Merck Sharp & Dohme Corp. v. Albrecht, 139 S. Ct. 1668, 1678 (2019)).

[109] *In re Zofran*, 2021 WL 2209871, at * 27.

[110] *Id.* at *28.

[111] *Id.*

[112] *Id.* at *29–30.

The court expressly rejected the notion of shifting the burden of proof in the *Albrecht* framework.[113] The court looked to the evidence alleged by the plaintiff of the omitted information in the defendant's submissions to FDA when evaluating the presence of clear evidence of FDA's rejection.[114] Its holding is easily applied when evaluating the clear evidence prong of *Albrecht*. However, requiring a manufacturer to prove a lack of newly acquired information as required by the CBE process is analogous to being required to prove a negative. The court didn't provide much insight, as it only evaluated the evidence provided in the context of there being clear evidence of FDA's rejection of the warning. It's unclear how the court would consider this burden of proof to address the inability to make the label change under the CBE process and the presence of newly acquired information required therein.

While courts have varied articulations of which party has the burden of demonstrating the existence of newly acquired information, all courts seem to, at minimum, expect a complaint to identify the newly acquired evidence with specificity. The *Gibbons* and *Zamfirova* cases are illustrative of how a lack of newly acquired information can bring about early and efficient case resolution. Both the plaintiffs' and defense bar would be well served to understand the nuances of these concepts. The defense bar should aggressively attack any complaint that fails to identify, with specificity, the information that plaintiffs assert reveals risks of a different type or greater severity, or frequency than what was previously known by FDA. Merely pointing to evidence of causation is not sufficient; the plaintiff must provide new information of a greater risk. The plaintiffs' bar would be equally well served to evaluate all potential causes of action through this lens, as well.

C. Newly Acquired Information Must Predate the Harm

While it may seem obvious, newly acquired evidence must be evaluated in the context of a specific claim. As explained by the Fourth Circuit in *Knight*, newly acquired information must have existed at the time of a patient's exposure or injury.[115] Accordingly, data generated or published after the plaintiff's use of the product or injury cannot constitute newly acquired information in the context of a particular claim.[116] The district court in *Rayes v. Novartis Pharmaceuticals* provided additional insight into this analysis. The *Rayes* plaintiff brought failure-to-warn claims against Novartis, the manufacturer of Beovu®, a drug approved for the treatment of certain eye disorders.[117] The plaintiff's claim originated from two injections of Beovu in December 2019 and January 2020.[118] As a result of these injections, the plaintiff claimed to have developed retinal vascular occlusion.[119] Beovu was originally approved in October 2019 without any warning related to retinal vasculitis or retinal vascular occlusions, but from November 2019 to February 2020, Novartis received ten reports of patients suffering from retinal vasculitis and/or retinal vascular

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[113] *Id.* at *27.

[114] *Id.* at *16–18.

[115] *See generally* Knight v. Boehringer Ingelheim Pharm., Inc., 984 F.3d 329 (4th Cir. 2021).

[116] *Id.*

[117] Rayes v. Novartis Pharms. Corp., No. EDCV21201JGBKKX, 2021 WL 2410677, at *1 (C.D. Cal. June 11, 2021).

[118] *Id.* at *2.

[119] *Id.*

occlusions.[120] In February 2020, the American Society of Retina Specialists issued an alert to physicians that it had received fourteen reports of "retinal vasculitis and occlusive retinal vasculitis,"[121] adverse events that occurred subsequent to Beovu injections.[122] After the alert, Novartis commissioned an external safety review committee to review the safety of Beovu.[123] Based on a safety signal identified by the review committee, Novartis revised the Beovu label to include a warning detailing the risk of retinal vasculitis and/or retinal vascular occlusions in June 2020.[124]

In explaining the *Albrecht* preemption framework, the court concluded that "a plaintiff must plead a labeling deficiency that the defendant could have corrected using the 'changes being effected' (CBE) regulation."[125] The court added that the newly acquired information in question must have been present before the injury in question.[126] The court reasoned that any information acquired after the plaintiff's harm could not have prevented the harm.[127] The court evaluated the evidence and found that only the information between the original October 2019 approval of Beovu and the plaintiff's second injection in January 2020 could be considered as to whether sufficient newly acquired information existed for Novartis to use the CBE process.[128] Thus, the only new pieces of information the plaintiff could offer as evidence were the three reports of patients suffering from retinal vasculitis from November 2019 to December 2019, and the seven reports dated between the plaintiff's two injections.[129] The court found that the handful of reports between the approval of Beovu and the plaintiff's final injection was insufficient to demonstrate causation to allow Novartis to change its labeling under the CBE process.[130]

The *Knight* and *Rayes* cases illustrate that the mere existence of newly acquired information is insufficient. Litigants must demonstrate that the newly acquired information existed at time points relevant to their claims (i.e., at the time a plaintiff used a particular product). Courts often constrain the newly acquired information analysis to the time period relevant to each plaintiff's claims.

V. CLEAR EVIDENCE OF FDA REJECTION

Even where sufficient newly acquired information exists to allow a CBE label change, a failure-to-warn claim is still preempted where there is clear evidence that

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[120] *Id.*

[121] Retinal vasculitis and occlusive retinal vasculitis are inflammatory or infective disorders which pose a significant risk of blindness.

[122] *Rayes*, 2021 WL 2410677, at *2.

[123] *Id.*

[124] *Id.*

[125] *Id.*

[126] *Id.*

[127] *Id.*

[128] *Id.* at *5.

[129] *Id.*

[130] *See id.* at *6: Plaintiff also claimed that Novartis learned of the risk of retinal vasculitis during phase 3 clinical trials but failed to disclose the risk to FDA. However, under *Buckman Co. v. Plaintiffs' Legal Comm.*, 531 U.S. 341, 353 (2001), claims against a manufacturer for alleged misrepresentations to FDA are preempted. Thus, the court expeditiously dismissed this claim.

FDA would have rejected the proposed warning.[131] Clear evidence, as defined by *Wyeth* and refined by *Albrecht*, requires: 1) evidence that FDA was fully informed of the justifications for the warning required by state law; 2) that FDA informed the manufacturer or interested parties that FDA would not approve a change to the drug's label to include the proposed warning; and 3) FDA's refusal to approve a change is done through agency action taken pursuant to FDA's congressionally delegated authority.[132] Evaluation of clear evidence is highly fact-specific and numerous factors may be pertinent in any particular case.[133] These factors may include the completeness of data submitted to FDA for approval, the availability of new data after submission, interested parties petitioning for FDA action, the formality of agency communication, evidence of class-wide product mandates by FDA, and the dispositive nature of agency determinations.[134]

A. A Fully Informed FDA and FDA's Rejection of Proposed Label

Defining when FDA is fully informed, and identifying when FDA would reject a change, is vital to understanding the clear evidence prong of *Albrecht*. In *In re Avandia Marketing, Sales and Product Liability Litigation*, the Third Circuit expanded on what it means to fully inform FDA. In *Avandia*, the plaintiffs, two health benefit plans, levied false marketing state law claims against GSK, the manufacturer of the prescription drug Avandia®.[135] Plaintiffs claimed Avandia's labeling failed to disclose the cardiovascular risks associated with Avandia at the time it was part of plaintiffs' formularies.[136] Avandia was approved in 1999, and in 2006 GSK submitted a Prior Approval Supplement (PAS) to FDA seeking to add to the Avandia label the results of a recent meta-analysis demonstrating that Avandia may be associated with a significant increase in "myocardial ischemic events."[137] In 2007, GSK submitted an update to the PAS in an attempt to make the proposed warning more "prominent and clear."[138] Shortly after that submission, the Nissen Study was published, finding that Avandia was associated with a "significant increase in the risk of myocardial infarction and with an increase in the risk of death from cardiovascular causes that had borderline significance."[139]

After the Nissen Study was published, GSK spoke with an FDA official to inform FDA that GSK was considering a label change under the CBE regulations.[140] The

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[131] *See generally* In re Avandia Mktg. Sales & Prod. Liab. Litig., 945 F.3d 749 (3d Cir. 2019).

[132] *See generally* Merck Sharp & Dohme Corp. v. Albrecht, 139 S. Ct. 1668, 1668 (2019).

[133] *See generally Avandia*, 945 F.3d at 759; Cerveny v. Aventis, Inc., 783 F. App'x 804, 808 n.9 (10th Cir. 2019); Dolin v. GlaxoSmithKline L.L.C., 951 F.3d 882, 890–91 (7th Cir. 2020); Hardeman v. Monsanto Co., 997 F.3d 941, 957–58 (9th Cir. 2021).

[134] *See Avandia*, 945 F.3d at 759; *Cerveny*, 783 F. App'x at 808 n.9; *Dolin*, 951 F.3d at 890–91; *Hardeman*, 997 F.3d at 957–58.

[135] *Avandia*, 945 F.3d at 752.

[136] *Id.* at 752–53.

[137] *Id.* at 753. Myocardial ischemic events limit the blood flow to an individual's heart, thus depriving the heart of oxygen.

[138] *Id.*

[139] *Id.*

[140] *Id.* at 753–54.

official strongly advised GSK not to begin the CBE process but concluded the conversation by reminding GSK that the drug manufacturer is ultimately responsible for making the decision to pursue a labeling change under the CBE process.[141] Afterward, FDA sent a letter to GSK stating that the PAS was "not approvable" and requested additional information.[142] FDA later directed GSK to add a black-box warning to Avandia's label to address the risk of myocardial ischemic events.[143] In 2014, FDA directed GSK to remove only the black-box warning regarding the increased risk of myocardial infarction, despite finding a "small amount of residual uncertainty remains" over the link between Avandia and cardiovascular risks.[144]

The Third Circuit explained that according to *Albrecht*, "in order to prove impossibility preemption, the drug manufacturer must show that the 'FDA would not approve changing the drug's label' and that the FDA was 'fully informed . . . of the justifications for the [proposed] warning' at the time that the FDA rejected the proposed warning."[145] GSK asserted that FDA was fully informed when it sent the letter informing GSK that the PAS was not approvable. However, the Third Circuit rejected GSK's claim because in the letter, FDA "indicated that GSK needed to submit various data and information 'in order to address the deficiency of [the PAS].'"[146] The court further rejected GSK's argument that the information requested by FDA was not material and therefore unnecessary to fully inform FDA.[147] The court explained that it is FDA, not the manufacturer, that is the "arbiter of which data . . . is or is not material to FDA's decision to approve or reject a labeling change, not GSK.[148]

Next, the Third Circuit found that GSK failed to demonstrate that FDA informed GSK that the agency would not approve the proposed label change, as required by *Albrecht*.[149] The court explained that the text of the letter made clear "that FDA did not consider GSK's [PAS] 'not approvable' because it was unconvinced of the need for a strong warning . . . rather, FDA considered the [PAS] 'not approvable' because it contained various 'deficiencies' that FDA required GSK to ameliorate prior to FDA's making a final determination."[150] This, the court reasoned, was sufficient to preclude preemption premised on the letter.[151] Additionally, according to the court, the fact that FDA required a boxed warning shortly after issuing the letter and reviewing the additional data "undermines" the position that FDA would have rejected the proposed label change if it were fully informed.[152]

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[141] *Id.* at 754.

[142] *Id.*

[143] *Id.*

[144] *Id.* at 755.

[145] *Avandia*, 945 F.3d 749, 759 (3d Cir. 2019) (citing Merck Sharp & Dohme Corp. v. Albrecht, 139 S. Ct. 1668, 1672 (2019)).

[146] *Avandia*, 945 F.3d at 758.

[147] *Id.* at 758–59.

[148] *Id.*

[149] *Id.* at 759–60.

[150] *Id.*

[151] *Id.* at 760.

[152] *Id.* at 759.

Finally, the court held that informal and unofficial agency actions or communications could not constitute clear evidence of FDA's rejection of a proposed warning.[153] The court reasoned that GSK's informal phone conversations with an FDA official were not official agency actions and as such, could not constitute the necessary clear evidence.[154] The court also rejected GSK's claim that the closing of the FDA letter in which FDA informed GSK that Avandia might be considered misbranded if it was marketed with the proposed label changes before approved as part of the Prior Approval Supplement application constituted clear evidence of FDA's rejection.[155] The Third Circuit found that this language was mere "stock language" included in many FDA communications and was insufficient to constitute agency action taken pursuant to FDA's congressionally delegated authority.[156] It reasoned that the stock language was merely a warning; it did not fully evaluate the facts and did not represent official agency determination.[157]

The Third Circuit provided some clarity as to what constitutes a fully informed FDA.[158] The court suggested that the determination of whether the information is material belongs exclusively to FDA, and any relevant data available after submission to the agency is still a consideration when determining whether FDA was provided all material data at the time.[159] The court's actions show that courts may look at FDA rejections or approvals occurring after the harm in question to determine whether there is clear evidence that FDA would reject a CBE label change.[160] Notably, the court rejected a simple informal communication between GSK and FDA as constituting agency action under the CBE process.[161] The rejection must be done under the formal decision-making processes of the agency body.[162]

B. What Constitutes Evidence of FDA Rejection

The *Albrecht* framework requires that FDA provide notice that the agency would reject the proposed warning, but the notice need not be directly addressed to defendants.[163] One example is the *Zofran* case. As noted, GSK manufactured Zofran and was defending a failure-to-warn claim. GSK offered three FDA-rejected Citizen Petitions as evidence, as required by *Albrecht*'s second prong.[164] The first Citizen Petition, submitted in 2013, requested that FDA change the Zofran label to include a warning concerning the risks of birth defects if ingested during pregnancy, but FDA

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[153] *Id.* at 760.

[154] *Id.*

[155] *Id.*

[156] *Id.*

[157] *Id.*

[158] *See id.* at 759.

[159] *See id.* at 758–60.

[160] *See id.* at 760.

[161] *Id.* at 760–61.

[162] *See id.*

[163] *See* In re Zofran (Ondansetron) Prod. Liab. Litig., No. 1:15-md-2657-FDS, 2021 WL 2209871, at *1 (D. Mass. June 1, 2021).

[164] *See id.* at *1–2.

rejected the petition.[165] In 2015, Novartis (the manufacturer of Zofran at the time) submitted a proposed label change to FDA to include a warning that it should not be used during pregnancy.[166] FDA rejected this proposed label change.[167] In 2019, GSK filed a Citizen Petition requesting that FDA review information about the safety of Zofran, but FDA again did not require a label change.[168] In 2020, Novartis submitted a proposed label change with a pregnancy warning based on newly published epidemiological studies, but FDA rejected the proposed warning.[169]

The court found that the series of proposed label changes and the Citizen Petitions from 2013 to 2020 served as clear evidence that FDA would have rejected any proposed changes under the CBE process.[170] In addition, it found that treating Novartis' actions and GSK's actions differently would be arbitrary and served no "rational policy goal."[171] FDA's rejection of either party's request for label changes served as the clear evidence required under *Albrecht*, regardless of which manufacturer in fact requested the label change.[172]

Dolin v. GlaxoSmithKline provides an example of how FDA's notification of a CBE regulatory change request can be based on public notice and does not specifically need to be addressed to the defendant manufacturer or any related parties.[173] In *Dolin*, the plaintiff sued GSK for failing to include warnings concerning the risk of adult suicide on its branded paroxetine drug, Paxil®.[174] In 2010, the plaintiff's husband began taking a generic version of Paxil and subsequently committed suicide.[175] The plaintiff sued GSK on the theory that GSK was responsible for the warning labeling of all paroxetine products due to the regulatory framework concerning branded and generic drugs.[176] The Seventh Circuit began its opinion by highlighting FDA's CBE standard.[177] The court next applied the *Wyeth* framework, determining that the plaintiff's claim was preempted because:

> there is clear evidence that FDA would have rejected the warning in 2007 (when [FDA] ordered GSK to remove its Paxil-specific adult-suicidality warning and instead use a class-wide SSRI warning) and . . . GSK lacked new information after 2007 that would have allowed it to add an adult-suicidality warning under the CBE regulation.[178]

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[165] *Id.* at *1.

[166] *Id.*

[167] *Id.*

[168] *Id.* at *2.

[169] *Id.*

[170] *See id.* at *32–33.

[171] *Id.* at *34.

[172] *Id.*

[173] *See generally* Dolin v. GlaxoSmithKline L.L.C., 951 F.3d 882 (7th Cir. 2020).

[174] *Id.* at 885.

[175] *Id.*

[176] *See id.* The plaintiff's claims would be preempted due to established case law surrounding the labeling of generic drugs.

[177] *Dolin*, 951 F.3d at 885 (citing 21 C.F.R. § 314.70(b)(2)(v)(A)).

[178] *Dolin*, 951 F.3d at 886.

The court found that *Albrecht* clarified the impossibility standard set by *Wyeth* and provided a general definition of clear evidence, which was absent in *Wyeth*; however, *Albrecht* cannot be interpreted as a rejection of *Wyeth*.[179] Thus, the *Albrecht* decision did not change the standard for preemption, but instead gave the doctrine a "sharper focus."[180] Outlining the *Albrecht* standard, the Seventh Circuit defined *Albrecht*'s clear evidence requirement as evidence showing that the manufacturer "fully informed FDA of the justifications for the warning required by state law," and that FDA "informed the drug manufacturer that FDA would not approve a change to the drug's label to include that warning."[181] The Seventh Circuit rejected the defendant's argument that their informal "exchanges of correspondence" with FDA were actions taken "pursuant to FDA's congressionally delegated authority."[182]

Finally, the court held that its decision remains the same even after applying the *Albrecht* framework.[183] The court, citing its previous opinion on the matter, held that GSK disclosed all relevant data underlying its requested suicide warning to FDA in 2006,[184] before the patient's suicide; thus, such a warning would not have prevented the patient's death. The court went on to add that FDA rejected the warning in 2007 when it "formally mandated that all SSRIs carry a uniform, class-wide warning label."[185] Ultimately, the plaintiff failed to offer evidence that GSK was aware of, or should have been aware of, new material information after 2007 when FDA rejected the manufacturer's proposal to add an adult-suicidality warning to the Paroxetine label that would have "justified a change in the label and thus undermine GSK's preemption defense."[186] The court found that FDA's requirement that all SSRIs have the same warning label is a clear example of "agency action taken pursuant to FDA's congressionally delegated authority," despite not being directed specifically to GSK.[187]

The Seventh Circuit clarified the implications of the *Albrecht* decision. The court recognized the standard as a layered approach, which first requires evaluation of the ability to make the label change under the CBE process; then it must determine whether the manufacturer fully informed FDA of the justifications for a warning change and that FDA would have rejected said warning through official agency action.[188] The court determined that drug class-wide determinations of labeling can function as the required notification by FDA to manufacturers; the notification need not be specific to the manufacturer claiming the preemption defense.[189]

Despite *Albrecht*'s vague language to the contrary, courts have not required manufacturers to be the only permissible entity to inform FDA about a request for a

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[179] *See id.* at 889–91 (responding to plaintiffs filing a Rule 60(b)(6) Relief of Judgment motion).

[180] *Id.* at 891.

[181] *Id.* at 890.

[182] *Id.*

[183] *Id.* at 888.

[184] *Id.* at 891.

[185] *Id.*

[186] *Id.*

[187] *Id.*

[188] *See id.* at 885–91.

[189] *See id.* at 891.

product label change. In *Cerveny v. Aventis*, the court interpreted *Albrecht* to not require a manufacturer to fully inform FDA and upheld the court's prior ruling that FDA's denial of a citizen petition submitted by a third-party is sufficient to meet the requisite element of clear evidence.[190] In *Cerveny*, the plaintiffs brought fraud and negligent misrepresentation claims against Aventis, the manufacturer of the fertility drug Clomid®, for the birth defects of their children born after they had used Clomid prior to becoming pregnant in 1992.[191] The plaintiffs claimed Aventis failed to warn patients and doctors of the risk of birth defects associated with pre-pregnancy usage of Clomid.[192] However, since receiving FDA approval, Clomid has had a warning that the drug should not be taken during pregnancy due to the possibility of birth defects.[193] In 2012, a Citizen Petition was filed to order Aventis to add the proposed pre-pregnancy warning to Clomid's label, but FDA rejected the petition.[194]

The court found that the claims relating to pre-pregnancy usage of Clomid were preempted, as there was clear evidence that FDA would have rejected the proposed warning for pre-pregnancy usage.[195] It reasoned that FDA's rejection of the 2012 Citizen Petition served as clear evidence that FDA would reject the label change.[196] However, the plaintiffs filed a Rule 28(j) letter after *Albrecht* was decided, suggesting that the case was in opposition to the court's previous ruling.[197] The court did not find that *Albrecht* changed their previous decision.[198] It reasserted that FDA's rejection of the 2012 Citizen Petition advocating for the warning for pre-pregnancy risks was clear evidence that FDA would have rejected a label change under the CBE regulation.[199] This served as clear evidence of FDA rejection of any such proposed warning, despite the fact that the manufacturer had no role in "fully inform[ing]" FDA, and the agency didn't notify Aventis of their determination.[200] The Tenth Circuit found that there is "nothing in *Wyeth* or *Albrecht* excluding Aventis from justifying preemption" based on FDA's rejection of a petition by an entity that is unrelated to the manufacturer in question.[201]

Here, the Tenth Circuit adds to the *Albrecht* framework, suggesting clear evidence does not necessarily need to be evidence of the manufacturer fully informing FDA. Instead, a third party receiving a response as part of formal agency action can provide the necessary showing of FDA's rejection of the proposed warning.[202]

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[190] *See generally* Cerveny v. Aventis, Inc., 783 F. App'x 804 (10th Cir. 2019).

[191] *Id.* at 805.

[192] *Id.*

[193] *Id.* at 805–06.

[194] *Id.* at 808.

[195] *Id.*

[196] *Id.*

[197] *Id.* at 808 n.9.

[198] *Id.*

[199] *Id.*

[200] *Id.*

[201] *Id.*

[202] *See id.*

C. Agency Action

Finally, the third *Albrecht* requirement that FDA rejection must be taken through agency action pursuant to FDA's congressionally delegated authority has been considered by the lower courts. In *Avandia*, the court rejected the argument that informal phone conversations with an FDA official and stock language in an FDA letter in response to GSK seeking approval for labeling changes (warning GSK that changing the label before approval will be considered misbranding) constituted formal agency action.[203] The *Avandia* court, however, did not define how official agency action should be evaluated.[204] It only held that these communications were insufficient to constitute agency action "taken pursuant to FDA's congressionally delegated authority."[205] One such court provides a working definition, despite relating to the Environmental Protection Agency (EPA). In *Hardeman v. Monsanto*, the court clarified a few examples of non-agency action carried out by congressional authority and provided a baseline for how courts should evaluate the authority of agency action.[206] In *Hardeman*, the plaintiff sued the Monsanto Company (Monsanto), the manufacturer of Roundup® pesticide with the active ingredient glyphosate, which the plaintiff alleges caused Non-Hodgkin's lymphoma, under state law failure-to-warn theories.[207] Monsanto claimed that the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and EPA's authority therein preempted the plaintiff's claim, as the statute prevented any state from "impos[ing] or continu[ing] in effect any requirements for labeling or packaging in addition to or different from those required by FIFRA."[208] After appealing the District Court's verdict, Monsanto argued that EPA action had shown clear evidence of the agency's rejection of the proposed label change.[209] Monsanto relied on EPA's approval of the original labeling, FIFRA's language preventing labeling changes, and EPA's letters written in 2017 and 2019 determining that "glyphosates are not likely to be carcinogenic to humans" to show clear evidence that EPA would not accept the label warning.[210]

The Ninth Circuit, in deciding Monsanto's appeal, outlined the *Albrecht* framework. The court recognized that for Monsanto to prevail on their attempts to benefit from the impossibility preemption defense, it must offer clear evidence that the agency was fully informed of all justifications for the proposed warning, that the agency has informed the manufacturer that it would not approve the label change, and that the agency's action "carries the force of law."[211] The court interpreted the prohibition on changes to labeling "in addition to or different from those required by FIFRA" as only applicable to dispositive determinations by EPA.[212] It found that EPA's regulatory approval of the original product labeling did not constitute agency action carrying the

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[203] *See* In re Avandia Mktg., 945 F.3d 749, 760 (3d Cir. 2019).

[204] *See generally id.* at 749.

[205] *Id.*

[206] *See generally* Hardeman v. Monsanto Co., 997 F.3d 941 (9th Cir. 2021).

[207] *Id.* at 950.

[208] *Id.* at 957 (citing 7 U.S.C. § 136v(b)).

[209] *Hardeman*, 997 F.3d at 951–52.

[210] *Id.* at 952, 958.

[211] *Id.* at 957 (citing Merck Sharp & Dohme Corp. v. Albrecht, 139 S. Ct. 1668, 1678–79 (2019)).

[212] *Hardeman*, 997 F.3d at 950 (citing 7 U.S.C. §136v(b)).

force of law.[213] The court, citing FIFRA, recognized that EPA's decision to approve a label during the registration process raises a rebuttable presumption that the products labeling complies with FIFRA.[214] The Ninth Circuit found that a rebuttable presumption fails to carry the force of law required for impossibility preemption.[215]

The court then turned to the letter sent by EPA to all manufacturers of products containing glyphosates, stating that EPA "believes any label with a cancer warning due to the presence of glyphosate will be misbranded."[216] The court found that the letter also did not carry the force of law because the letter did not follow any formal administrative procedure—it lacked notice and an opportunity to respond, and merely expressed an informal policy opinion of EPA.[217]

Here, the Ninth Circuit applied the *Albrecht* standard to the labeling of products under the purview of EPA and illuminated what constitutes agency action.[218] As previously shown in *Hardeman* and *Avandia*, the agency action must be executed under the authority given to the agency by Congress, thus carrying the force of law.[219] However, the court here provided greater insight into what actions have said authority or carry the weight of the law.[220] The court rejected EPA's letter and asserted that agency action should follow formal procedures, provide notice and an opportunity to be heard, or represent a dispositive determination by the agency.[221] The defendant's reliance on written communication and baseline labeling approval was insufficient to determine that EPA would not have permitted the proposed label change as required by *Albrecht*.[222] Manufacturers should not think the risk of litigation is mitigated after receiving such informal communications with FDA; only formal dispositive determinations make for a successful preemption defense.

VI. CONCLUSION

The practical implications flowing from *Albrecht* are actually quite robust despite the limited holding that clear evidence of FDA disapproval of a proposed warning is a question of law to be decided by the court and not a question of fact to be determined by a jury.

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[213] *Hardeman*, 997 F.3d at 956.

[214] *Id.* at 957 (citing 7 U.S.C. §136a(f)(2)); The court found that EPA's decision is a rebuttable presumption based on language in the statute governing EPA's authority, thus does not apply to FDA's decision-making process.

[215] *Hardeman*, 997 F.3d at 957.

[216] *Id.*

[217] *Id.*

[218] *See generally id.* at 941.

[219] *See Hardeman*, 997 F.3d at 957–58; *see also* In re Avandia Mktg., 945 F.3d 749, 760 (3d Cir. 2019) (citing Merck Sharp & Dohme Corp. v. Albrecht, 139 S. Ct. 1668, 1679 (2019)).

[220] *See Hardeman*, 997 F.3d at 957.

[221] *Id.* at 957–58; *Cf.* In re Incretin-Based Therapies Prod. Liab. Litig., No. 13-MD-2452-AJB-MDD, 2021 WL 880316, at *17 (S.D. Cal. Mar. 9, 2021) (finding that both FDA's active monitoring of the risks associated with incretin-based drugs by approving other such drugs after the defendant fully informed the agency and their rejection of a Citizen Petition served as sufficient agency action to meet the clear evidence standard).

[222] *See generally Hardeman*, 997 F.3d. at 941.

In the post-*Albrecht* world, there are still numerous areas of uncertainty, though areas of greater clarity have emerged. Courts appear to consistently examine impossibility preemption in the prescription drug failure-to-warn context via a two-part test, which asks: 1) does sufficient evidence exist to trigger a manufacturer's ability to add plaintiff's desired warnings to a product label? and 2) if so, does clear evidence exist that FDA would not have approved such changes? As to the first prong, the most common mechanism for manufacturers to add a warning to a product label is via the CBE regulatory pathway. While courts remain split on who bears the ultimate burden of proof in establishing the manufacturer's ability to utilize the CBE process, all courts require that plaintiffs, at minimum, identify the information giving rise to the manufacturer's ability to modify the product label. Even if the first prong of the analysis is satisfied, a claim is still preempted where a manufacturer demonstrates clear evidence that FDA, after being fully informed of all material information by the manufacturer or a third party, would have rejected the proposed state-law warning.

Before incurring prohibitive costs working up a case only to be dismissed at the pleading stage, a plaintiff should ask: Is there newly acquired information suggesting a new or heightened risk? Has FDA been fully informed of all material information on the subject? Did FDA reject any suggested changes through their formal decision-making process? Conversely, manufacturers should provide all possible pertinent information to FDA when seeking product approval and label changes. Manufacturers should ensure that their documentation practices are sufficient to evidence what information was provided to FDA and when. Manufacturers should be aware that informal communications with FDA suggesting FDA's rejection or uncertainty as to the sufficiency of data to support a warning will be insufficient to support a preemption defense. Instead, manufacturers should seek to formalize FDA feedback via formal requests to encourage dispositive FDA action. In the event a change is approved, the best interests of the manufacturer and the public are met, and if FDA rejects the proposed change, a manufacturer may be able to successfully assert a preemption defense in future litigation.

This Article focused on how the *Albrecht* standard applies in the pharmaceutical products liability context, but as *Hardeman* has shown, this framework applies to any industry in which product information or warnings are regulated by federal agencies. Practitioners in these industries should consider the above case law and evaluate how the evidence applies in their respective contexts.