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A PRESCRIPTION FOR PHARMACEUTICAL PREEMPTION

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Determining liability over prescription drugs is a balancing act. For some people, medicine can save their lives or enhance their well-being. But, as medicines can also come with side effects, some people will have unavoidable and perhaps serious adverse reactions. The United States Food and Drug Administration (FDA) works with manufacturers of prescription drugs to manage known public risks. The FDA assesses the benefit-risk analysis for each drug and must approve the design and warnings before the drug can be made, marketed and sold. Once on the market, the FDA continues to work with the manufacturers to identify risks and assure the warnings that accompany the drugs continue to provide adequate information about these risks. Physicians then manage a patient's personal risk by deciding, often through informed consent by the patient or responsible person, whether a drug's benefit-risk profile is appropriate for that patient.

Personal injury litigation over the use of a prescription drug generally involves individuals alleging injury from a side effect of a drug and that the drug's labeling failed to adequately inform their prescribing physicians about the risk of that side effect.[1] Accordingly, a lawsuit tends to focus on the private risks and injuries of that individual. However, any assessment of the adequacy of a drug's warnings must also focus on public health risks, and it must do so within the context of the benefits the medication provides to the public—which is what the FDA and manufacturer assess when developing the label. When a jury finds liability in a prescription drug failure-to-warn case, it is telling the FDA and manufacturer that they got the label wrong.

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[1] *See* RESTATEMENT (THIRD) OF TORTS, PRODS. LIAB. § 6 (AM. L. INST. 1998) (establishing general principles for manufacturing, design and warning defect for prescription drugs, where liability is generally focused on the adequacy of warnings); *see also* Aaron Twerski, *The Demise of Drug Design Litigation: Death by Federal Preemption,* 68(1) AM. UNIV. L.R. 281-304 (2018) (explaining that design defect liability for prescription drugs has largely been preempted by federal approval of a drug's design and the inability of a manufacturer to change a drug's design without pre-approval from the FDA).

Juries, though, generally have little or no scientific expertise, no line of sight to the people who benefit from the drug, and cannot assess the potential negative impact that changing the warnings to address the plaintiff's situation in the case may have on others.[2] This tension between state law personal injury claims and the federal regulatory regime for prescription drugs has been the focus of significant debate and concern in the legal and medical communities.

In just the last fourteen years, the United States Supreme Court has issued several consequential decisions regarding the interplay between state tort liability and the FDA regulatory regime.[3] Two of them address failure-to-warn liability involving brand-name prescription drugs—which is the focus of this article. In *Wyeth v. Levine*, the Supreme Court held that patients alleging injury from a drug generally could maintain a failure-to-warn claim against a brand-name manufacturer of an FDA-approved drug, but not when there is "clear evidence" the FDA would not have approved the labeling change the plaintiff claims was needed to prevent his or her injury.[4] In those cases, the federal FDA regulatory regime preempts the state tort claims.[5] This ruling, though, led to questions about when such "clear evidence" exists. In 2019, the Court provided more guidance in *Merck Sharp & Dohme Corp. v. Albrecht*, holding that federal law preempts the state claims when the plaintiff has presented no new evidence of a causal association between the drug and injury alleged or the FDA was "fully informed"

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[2] *See* Riegel v. Medtronic, Inc., 552 U.S. 312, 325 (2008) (observing a jury sees "only the cost of a more dangerous design, and is not concerned with its benefits; the patients who reaped those benefits are not represented in court.").

[3] *See, e.g.*, Wyeth v. Levine, 555 U.S. 555 (2009); Mutual Pharmaceutical Co. v. Bartlett, 570 U.S. 472 (2013); PLIVA, Inc. v. Mensing, 564 U.S. 604 (2011); and Merck Sharp & Dohme Corp. v. Albrecht, 139 S. Ct. 1668 (2019).

[4] Wyeth v. Levine, 555 U.S. 555, 580 (2009).

[5] *See id.*

of the justification for the warning change and had already communicated that it would not approve that change.[6]

The lower courts have been applying *Levine* and *Albrecht* over the past few years, developing a body of law that is instructive for when these failure-to-warn claims are preempted. Several key issues have arisen, for example, what constitutes "new evidence" supporting a labeling change;[7] what does it mean that the FDA was "fully informed";[8] and how must FDA communicate that it would not have approved the change?[9] This article examines these rulings to clarify when preemption can be established in prescription drug failure-to-warn cases. Part I of this article discusses the drug approval process, including how a manufacturer can change a drug's labeling. Part II examines the recent Supreme Court preemption rulings in pharmaceutical failure-to-warn cases. And, part III analyzes key post-*Albrecht* rulings, identifying the questions courts are asking and answering when making decisions about whether the FDA regulatory regime preempts state failure-to-warn claims.

I. THE FEDERAL DRUG APPROVAL PROCESS

Until the early twentieth century, regulation of medicine had been left to the states, although, in practice, drugs were generally unregulated.[10] In 1938, that changed when Congress enacted the Federal Food Drug & Cosmetic Act (FDCA) and required companies to demonstrate the safety of new drugs before marketing them.[11] This

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

[7] *See* discussion on "newly acquired information" in Section IIIA, *infra*.

[8] *See* discussion on cases assessing whether the FDA was "fully informed" in Section IIIB, *infra*.

[9] *See* discussion on cases assessing how FDA must communicate it would not have approved the change in Section IIIB, *infra*.

[10] Federal Food Drug & Cosmetic Act, Pub. L. No. 75-717, 52 Stat. 1040 (1938) (codified as amended at 21 U.S.C. §§ 301-392).

[11] 21 U.S.C. § 355 (the 1938 law, while requiring manufacturers to prove the safety of the drug to the FDA before marketing, did not require an evaluation of its effectiveness).

system required the manufacturers to provide pre-market notice to the FDA of the safety profile of its drugs, but it did not require FDA approval before the drugs could be marketed.[12] The FDCA also established the requirement that manufacturers adequately label their drugs and identify which medicines are available only through a physician's prescription.[13] In 1962, Congress transformed this system to require the FDA to approve "the safety and effectiveness of every new drug" before the drug could be marketed.[14] The FDA had oversight of all clinical testing, could inspect facilities, established good manufacturing practices, and could govern advertising.[15] The new law also required manufacturers to report adverse reactions, along with imposing other post-market obligations to assure the ongoing safety and effectiveness of a drug after it is on the market.[16] This general

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[12] *See id.*

[13] In 1951, the Durham-Humphrey Amendment clarified the legal distinction between prescription and nonprescription drugs. Durham-Humphrey Drug Prescription Act, ch. 578, 65 Stat. 648 (codified at 21 U.S.C. §§ 333, 353 (1951)).

[14] PETER BARTON HUTT & RICHARD A. MERRILL, FOOD AND DRUG LAW CASES AND MATERIALS (2d ed. 1991) (observing the role of the FDA in preventing the thalidomide outbreak in Europe from occurring in the United Sates); *see also* Jeffrey Shuren, Essay, *The Modern Regulatory Administrative State: A Response to Changing Circumstances*, 38 HARV. J. ON LEGIS. 291, 301-303 (2001) (stating that the 1962 Act changed the system from pre-market notification to pre-market approval, which effectively "transformed the FDA's role from a review of data to an active participant in the drug development process").

[15] *See* Arthur H. Hayes, Jr., *Food and Drug Regulation After 75 Years*, 246 J. AM. MED. ASS'N 1223, 1224 (1981).

[16] *See id.*

framework has remained in place since then, though this regulatory regime has been regularly updated and improved.[17]

Today, the FDA administers "the most comprehensive drug regulatory system in the world."[18] It is often considered the gold standard.[19] Under this regulatory regime, the FDA seeks to optimize the benefit-risk balance of prescription medicine by allowing drugs on the market only if they are reasonably safe for a class of consumers.[20] The

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[17] *See generally id.*; *see also* FDA, *Milestones of Drug Regulation in the United States*, (Jan. 20, 2023) https://www.fda.gov/media/109482/download.

[18] Bert W. Rein et al., *Addressing the Conflict: FDA vs. Torts*, PHARM. & MED. DEVICE L. BULL. May 2003, at 1 https://www.lawjournalnewsletters.com/sites/lawjournalnewsletters/2003/11/10/addressing-the-conflict-fda-vs-torts/?slreturn=20230314113315.

[19] Catherine M. Sharkey & Kevin M.K. Fodouop, *AI and the Regulatory Paradigm Shift at the FDA*, 72 DUKE L.J. ONLINE 86, 98 (Nov. 2022) ("The FDA emerges as the most stringent ex ante safety regulator of any U.S. federal agency; moreover, its 'gold standard' is higher than that of foreign medical product regulatory agencies." *Merck and Vioxx: Putting Patient Safety First?*: *Hearings Before the S. Comm. on Fin.*, 108th Cong. 1 (2004) (statement of Sandra L. Kweder, Deputy Dir., FDA Off. of New Drugs)); Jacob S. Sherkow, *Regulatory Sandboxes and the Public Health*, 2022 ILL. L. REV. 357, 374 ("FDA approval remains . . . the 'gold standard' of agency approval worldwide."); Brett Samuels & Morgan Chalfant, *White House faces new obstacles in COVID-19 fight*, THE HILL (Apr. 16, 2021, 6:00 AM) https://thehill.com/homenews/administration/548561-white-house-faces-new-obstacles-in-covid-19-fight/ ("White House press secretary Jen Psaki described the FDA process as the 'gold standard' during a Thursday briefing . . ."); *see also* S. REP. NO. 104-284, at 97 (1996) ("FDA is by no means perfect, but it is still renowned as one of the most effective consumer protection agencies in the world. . . . [I]ts record of excellence in protecting the health of the American public remain[s] unmatched.").

[20] "A principal focus of the Food and Drug Administration, apart from safety, is efficacy. Since every drug includes some risks, the Food and Drug Administration regards efficacy as essential – if one is to take risks, he or she should obtain the desired result." Victor E. Schwartz, *Unavoidably Unsafe*

Center for Drug Evaluation and Research (CDER), which began as a one-desk operation a hundred years ago, now employs doctors, toxicologists, pharmacologists, epidemiologists, chemists and statisticians to analyze pre- and post-market data, assess warnings, and find the appropriate benefit-risk balance for each drug before and after they are marketed.[21] Overall, the Congressional Budget Office recently reported, the FDA has approved through the CDER, on average, 38 new drugs per year over the past decade and only 12% of drugs entering clinical trials are ultimately approved.[22]

A. Pre-Market Approval

The current framework for pre-market approval of prescription drugs[23] was established in 1984, when Congress enacted the Drug Price Competition and Patent Term Restoration Act, which is commonly referred to as the Hatch-Waxman Amendments.[24] This law established two types of drug applications: (1) new drug applications for brand-name prescription drugs, or NDAs, and (2) abbreviated new drug applications for generic drugs, or ANDAs.[25] When a brand-name drug manufacturer develops a new drug and wants to bring it to market, it must seek FDA approval by submitting an NDA, which is a rigorous formal rule-making process.[26] This process includes an independent assessment that the drug is safe and effective for its intended use and that the proposed labeling is accurate and adequate.[27] In order to approve the drug for market, the FDA must determine that it "meets the

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Products: Clarifying the Meaning and Policy Behind Comment K, 42 WASH. & LEE L. REV. 1139, 1142 (1985).

[21] *See* Daniel Carpenter & A. Mark Fendrick, *Accelerating Approval Times for New Drugs in the U.S.*, 15 REG. AFFS. J. 411 (2004), http://people.hmdc.harvard.edu/~dcarpent/acceleration-raj.pdf.

[22] *See* CONGRESSIONAL BUDGET OFFICE, RESEARCH AND DEVELOPMENT IN THE PHARMACEUTICAL INDUSTRY 1-2 (April 2021).

[23] 21 U.S.C. § 355(a).

[24] *See* Pub. L. No. 98-417, 98 Stat. 1585 (1984).

[25] *See* 21 U.S.C. § 355(b), (c), (j).

[26] 21 U.S.C. § 355(b)(1), (d).

[27] *Id.*

statutory standards for safety and effectiveness, manufacturing and controls, and labeling."[28] These drugs are referred to as "brand-name" drugs because they are generally marketed and sold by the company that developed and brought the drug to market.

Generic drugs, on the other hand, generally go through the ANDA process, which provides a simpler, less demanding and faster process for approval. The manufacturer seeks approval to sell a drug that is the same in all relevant respects as a previously approved brand-name drug, which is referred to in FDA parlance as the "reference listed drug" (RLD).[29] The generic drug manufacturer must show that its drug has the same active ingredients as the RLD, "the route of administration, the dosage form, and the strength of the new drug are the same" as the RLD, and its product is "bioequivalent" to the RLD.[30] The FDA allows manufacturers of generic drugs to use different "inert" or "inactive" ingredients, such as release mechanisms, binders, and preservatives while still maintaining bioequivalence.[31] Because of these similarities, the ANDA process permits the manufacturer to incorporate the safety and efficacy data submitted in the NDA of the RLD, eliminating the need for the ANDA applicant to duplicate clinical trials performed on the RLD. [32] Additionally, an ANDA applicant must "show that the

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[28] 21 C.F.R. § 314.105(c). "In fulfilling its mission to monitor and control the safety and efficacy of drugs, the Agency continually walks a razor's edge between two opposing risks – premature approval of dangerous drugs and undue delay in making safe, effective, and medically useful drugs available to the public." Steven R. Salbu, *The FDA and Public Access to New Drugs: Appropriate Levels of Scrutiny in the Wake of HIV, AIDS, and the Diet Drug Debacle*, 79 B.U. L. REV. 93, 96 (1999).

[29] 21 U.S.C. § 355(j).

[30] 21 U.S.C. § 355(j)(2)(A)(ii), (iii), (iv).

[31] *See* 21 C.F.R. § 320.1(c) (2012); *see also Drugs@FDA Glossary of Terms*, FDA, http://www.FDA.gov/Drugs/informationondrugs/ucm079436.htm#G (last updated Nov. 11, 2017) (defining pharmaceutical equivalents).

[32] PLIVA, Inc. v. Mensing, 564 U.S. 604, 612 (2011) (citing 21 U.S.C. § 355(j)(2)(A), (j)(2)(A)(v), (j)(4)(G)).

[safety and efficacy] labeling proposed" in the ANDA "is the same as the labeling approved for the [RLD]." [33]

Another pathway for drug approval is available to brand-name manufacturers, but only when it makes changes to the design of an RLD that are "so slight that a manufacturer may rightly rely on the 'full reports of investigations' of the [listed] drug to establish the new drug's safety and efficacy." [34] These manufacturers file an NDA but generally use the investigations and data from the RLD, along with additional data, demonstrating that any differences between the originally approved drug and the proposed drug do not affect safety or efficacy.[35] However, there is no statutory or regulatory requirement under this pathway for the proposed drug to contain the same labeling as the RLD.[36]

Regardless of which pathway is used, the FDA approves the exact text that will be included in the drug's labeling.[37] The labeling contains basic information, such as a description of the drug and its ingredients,[38] directions for its intended use including any necessary preparation, dosage, frequency and duration of use,[39] and a description of any situation where the drug should not be used because the risk would outweigh the benefit.[40] The labels must also include information on potential side effects, which the FDA breaks down into three categories: (1) "contraindications," describing any situation in which the drug should not be used because the risk of use outweighs any therapeutic benefit; (2) "warnings," which are serious risks known to

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[33] *Id.* at 612-13 (citing § 355(j)(2)(A)(v), (j)(4)(G); 21 CFR §§ 314.94(a)(8), 314.127(a)(7)).

[34] Ethypharm S.A. France v. Abbott Labs., 707 F.3d 223, 227 (3d Cir. 2013) (quoting 21 U.S.C. § 355(b)(1)).

[35] *Id.* (quoting 21 U.S.C. § 355(b)(2)).

[36] *See* 21 U.S.C. § 355(j)(2)(A)(v); *cf*. 21 U.S.C. § 355(b)(2) (containing no such provision).

[37] *See* 21 U.S.C. § 355(d), (j)(4)(H).

[38] 21 C.F.R. §§ 201.1, 201.50, 201.10, 201.51, 201.17.

[39] 21 C.F.R. §§ 201.5, 201.55, 201.57.

[40] 21 C.F.R. § 201.57.

occur in some patients; and (3) "precautions," which are risks that arise less frequently.[41] A drug may be required to have a prominent "boxed" warnings if it has risks that may lead to death or serious injury.[42]

Finally, each label must follow the FDA required content, format, and order of how the safety information is to be listed on the label.[43] "The hierarchy of label information is designed to 'prevent overwarning' so that less important information does not 'overshadow' more important information."[44] "It is also designed to exclude '[e]xaggeration of risk, or inclusion of speculative or hypothetical risks,' that 'could discourage appropriate use of a beneficial drug.'"[45] In 2006, the FDA added a new requirement that drug labels highlight the most important prescribing information, including concise summaries of the most significant contraindications, warnings, and precautions, and the most frequently occurring adverse reactions.[46] In short, the goal for each label is to "portray the drug's safety profile with accuracy, balance, and brevity" to help physicians prescribe drugs in ways that maximize a drug's effectiveness and minimize risks.[47]

B. After-Market Responsibilities

The FDA and NDA-holder, which is typically the brand drug manufacturer, also work together on post-market surveillance to assess the drug's safety and efficacy results and determine whether any new

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[41] 21 C.F.R. § 201.57(a).

[42] *See* § 201.57(a), (c).

[43] Merck Sharp & Dohme Corp. v. Albrecht, 139 S. Ct. 1668, 1673 (2019).

[44] *Id.* (citing 73 Fed. Reg. 49605–49606 (2008)).

[45] *Id.* (citing 73 Fed. Reg. 2851 (2008)).

[46] *See* Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products, 71 Fed. Reg. 3922 (Jan. 24, 2006) (to be codified at 21 C.F.R. pt 201.56).

[47] Kip W. Viscusi et al., *Deterring Inefficient Pharmaceutical Litigation: An Economic Rationale for the FDA Regulatory Compliance Defense*, 24 SETON HALL L. REV. 1437, 1440 (1994) [hereinafter "Viscusi"]; *see generally* 21 C.F.R. pt. 201 (2004) (stating the substantive and stylistic requirements for labels, including that labels and warnings have proper prominence, typeface and text size).

drug safety information emerges that requires changes to the drug label.[48] The manufacturers conduct epidemiological studies or review such studies conducted by others, report and assess adverse drug reactions, and review actions that physicians took in response to adverse drug reactions.[49] Manufacturers must submit to the FDA these post-marketing actions, including any scientific literature on the drug and experiences with the drug in other countries.[50] They also must file summary reports with the FDA highlighting any "significant new information . . . that might affect the safety, effectiveness, or labeling of the drug product" and describes the actions taken as a result of the new information.[51] The FDA has many tools at its disposal to gather new information on the drug, including requiring the NDA-holder to undertake further clinical studies to better understand adverse events.[52]

If these after-market results indicate the benefit-risk analysis included in the labeling is no longer adequate, the FDA can send warning letters to physicians, require labeling changes, urge the manufacturer to recall the drug, or withdraw the drug's approval altogether.[53] In addition, if the NDA-holder learns of a "clinically significant hazard," it must revise a drug's labeling to include appropriate warnings for that hazard "as soon as there is reasonable evidence of a causal association with a drug."[54] The NDA-holder can

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[48] *Albrecht*, 139 S. Ct. at 1673 (citing 21 C.F.R. §§ 314.80(c), 314.81(b)(2)(i)).

[49] *See* 21 C.F.R. § 314.80(b), (c) (2023).

[50] *See* 21 U.S.C. § 355(k)(3).

[51] *See* 21 C.F.R. § 314.81(b)(2)(i).

[52] 21 U.S.C. § 355(o)(3) (discussing a type of Phase IV study known as a postmarketing requirement); *see also* DANIEL R. LEVINSON, U.S. DEP'T OF HEALTH & HUM. SERVS., OFF. OF INSPECTOR GEN., OEI-01-04-00390, FDA'S MONITORING OF POSTMARKETING STUDY COMMITMENTS ii (2006), http://oig.hhs. gov/oei/reports/oei-01-04-00390.pdf (finding that 48% of NDAs approved between fiscal years 1990 and 2004 involved at least one postmarketing study commitment).

[53] *See* 21 U.S.C. § 355(e), (o)(4).

[54] 21 C.F.R. § 201.57(c)(6)(i) (2023).

change its FDA-approved labeling in one of two ways. The typical way is for the manufacturer to seek advance permission from FDA to make a label change through a Prior Approval Supplement application (PAS).[55] If the manufacturer seeks such advance permission, it may not change the label until and unless it receives FDA approval. [56] Alternatively, the manufacturer can change the label on its own, without FDA preapproval, by submitting a Changes Being Effected application (CBE), which is considered an exception to the PAS process.[57] It is not a shortcut.

To make a labeling change under the CBE process, the alteration must be necessary to accomplish at least one of five objectives: (1) to add or strengthen a contraindication, warning, precaution, or adverse reaction for which the evidence of a causal association satisfies the standard for inclusion in the labeling; (2) to add or strengthen a statement about drug abuse, dependence, psychological effect, or over-dosage; (3) to add or strengthen an instruction about dosage and administration intended to increase the safe use of the drug; (4) to delete false, misleading, or unsupported indications for use or claims for effectiveness; or (5) any change the FDA specifically requests under this provision.[58]

With respect to labeling, which is the focus of this article, the CBE option is available only in limited circumstances, namely, when "the changes add or strengthen a contraindication, warning, precaution, or adverse reaction" or "add or strengthen an instruction about dosing and administration that is intended to increase the safe usage of the drug product in order to reflect newly acquired information."[59] Thus, in order to make a labeling change under the CBE process, the change must "reflect newly acquired information" providing "reasonable evidence of

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[55] *See* 21 C.F.R. § 314.70(b)(ii)(v)(C), (c)(6)(iii) (2023).

[56] § 314.70(a).

[57] *See* § 314.70(c)(6)(iii)(A)-(D).

[58] *See* § 314.70(c)(6)(iii)(A)-(E).

[59] 21 C.F.R. §§ 314.70(c)(6)(iii)(A), (C) (CBE regulation), 314.3(b) (defining "newly acquired information").

a causal association of a clinically significant adverse reaction linked to a drug."[60] A clinically significant adverse reaction is defined as one that has a "significant impact on therapeutic decision-making, such as a risk that is potentially fatal or otherwise serious."[61] At bottom, the FDA contemplated the CBE regulation would be used sparingly, noting it "would not allow a change to labeling to add a warning in the absence of reasonable evidence of an association between the product and an adverse event."[62] The FDA can also reject a labeling change made pursuant to the CBE process.[63]

In addition, in 2007, Congress gave the FDA an independent obligation to assess safety information provided to the agency, regardless of how received—from the manufacturer or a citizen petition.[64] Under this regulatory regime, if the agency believes the safety information "should be included in the labeling of the drug," it must "promptly notify" the RLD holder and work with it on such changes.[65] The manufacturer may propose the labeling changes or explain why it believes the changes are not warranted.[66] Either way, the FDA is obligated to impose any labeling language it believes is needed:

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[60] 21 C.F.R. § 314.3(b) (defining "newly acquired information"); 21 C.F.R. § 201.57(c)(6)(i).

[61] McGrath v. Bayer Healthcare Pharms., Inc., 393 F. Supp. 3d 161, 167 (E.D.N.Y. 2019) (citation omitted).

[62] Supplemental Application Proposing Labeling Changes for Approved Drugs, Biologics, and Medical Devices, 73 Fed. Reg. 2848, 2851 (Jan. 16, 2008) (allowing a unilateral change based only on "known hazards and not theoretical possibility," "sufficient evidence of a causal association," or "reasonable evidence of an association"); *see also* Wyeth v. Levine, 555 U.S. 555, 571 (2009) ("requiring a manufacturer to revise its label to include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug").

[63] *In re* Avandia Mktg., Sales & Prod. Liab. Litig., 945 F.3d 749, 758 (3d Cir. 2019).

[64] *See* 21 U.S.C. § 355(o)(4).

[65] § 355(o)(4)(A).

[66] § 355(o)(4)(B)(i)-(ii).

> If the [FDA] disagrees with the proposed changes in the supplement or with the statement setting forth the reasons why no labeling change is necessary, the Secretary shall initiate discussions to reach agreement on whether the labeling for the drug should be modified to reflect the new safety or new effectiveness information, and if so, the contents of such labeling changes.[67]

Under the regulations, the discussion period is fairly short, after which the FDA decides the outcome.[68] The FDA can direct the RLD holder to make the labeling change that it deems appropriate to address the new information.[69]

Courts have recognized that the FDA has a high standard for when to allow or impose a labeling change because of the need to optimize the safe use of medications.[70] Putting scientifically unfounded warnings on a label could harm patient care. Physicians and consumers may ignore or not be able to discern important warnings.[71] Also, excessive warnings could discourage the beneficial use of medications.[72] The concern is that "labeling that includes theoretical

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[67] § 355(o)(4)(C).

[68] *See* § 355(o)(4)(D)-(F).

[69] *See id*. § 355(o)(4)(E).

[70] *See, e.g.*, Albrecht, 139 S. Ct. at 1673; Perham v. GlaxoSmithKline LLC (*In re* Zofran Ondansetron Prods. Liab. Litig.), 57 F.4th 327, 330 (1st Cir. 2023).

[71] *See generally* Robinson v. McNeil Consumer Healthcare, 615 F.3d 861, 869 (7th Cir. 2010) ("The resulting information overload [from describing every remote risk] would make label warnings worthless to consumers."); Thomas v. Hoffman-LaRoche, Inc., 949 F.2d 806, 816 n.40 (5th Cir. 1992) (explaining that including "every possible risk" on a drug's labeling could lead physicians "to ignore or discount the warnings").

[72] *See, e.g.*, Mason v. SmithKline Beecham Corp., 596 F.3d 387, 391-92 (7th Cir. 2020) ("[O]verwarning can deter potentially beneficial uses of the drug by making it seem riskier than warranted."); Dowhal v. SmithKline Beecham Consumer Healthcare, 88 P.3d 1, 16 (Cal. 2004) ("[A] truthful warning of an uncertain or remote danger may mislead the consumer into misjudging the dangers stemming from use of the product, and consequently making a medically unwise decision.").

hazards not well-grounded in scientific evidence can cause meaningful risk information to lose its significance,"[73] harming the ability of physicians to make proper prescribing decisions.

This post-market regime, including the CBE process, does not apply to generic drugs. Generic drug manufacturers must obtain FDA approval *before* making any safety changes to their drugs' labeling.[74] In part, this distinction between brand-name and generic drug manufacturers' responsibilities is due to the fact that generic drug manufacturers must have "the same" labeling as their brand-name counterparts.[75] If the generic drug's manufacturer were to change its product's labeling, the FDA could charge the manufacturer with misbranding or even withdraw the manufacturer's ANDA.[76] If a generic manufacturer "believes that new safety information should be added" to its drug's labeling, it must "provide adequate supporting information to FDA, and FDA will determine whether the labeling for the generic and listed drug should be revised."[77]

This federal regulatory regime, and specifically, when federal law bars a manufacturer from unilaterally changing its drug's labeling, has proven determinative for when courts have ruled that a state failure-to-warn claim is preempted by federal law.[78]

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[73] McGrath v. Bayer Healthcare Pharms., Inc., 393 F. Supp. 3d 161, 167 (E.D.N.Y. 2019).

[74] Abbreviated New Drug Application Regulations, 57 Fed. Reg. 17950, 17961 (Apr. 28, 1992).

[75] *See* 21 U.S.C. § 355(j)(4)(G); 21 C.F.R. § 314.94(a)(8)(iii) (2023).

[76] *See* PLIVA, Inc. v. Mensing, 564 U.S. 604, 615 (2011) (stating that the FDA's position is "if generic drug manufacturers, but not the brand-name manufacturer, sent [Dear Health Care Provider] letters, that would inaccurately imply a therapeutic difference between the brand and generic drugs and thus could be impermissibly 'misleading'").

[77] Abbreviated New Drug Application Regulations, 57 Fed. Reg. at 17961.

[78] *See, e.g.*, PLIVA, Inc. v. Mensing, 564 U.S. 604, 614 (2011).

II. CONFLICT PREEMPTION IN FAILURE-TO-WARN CASES

Failure-to-warn cases against pharmaceutical manufacturers allege that the manufacturer did not maintain adequate warnings on the drug's label and that the plaintiff's proposed label change would have prevented the injury being claimed..[79] Generally speaking, the plaintiffs allege the manufacturer did not sufficiently act on new risk information, though sometimes they allege the manufacturer failed to provide certain risk information to the FDA when the FDA approved the labeling. As discussed above, when a manufacturer knows or should know about new risk information, there are specific federal standards and processes the manufacturers must adhere to with respect to when and how to adjust a drug's labeling to be compliant with federal law and regulations. A prescription drug manufacturer is not authorized to change a drug's labeling merely because it *could have* avoided a plaintiff's specific injury. This potential conflict between state failure-to-warn liability and federal drug labeling law has led to three Supreme Court cases over the past fourteen years. The Court has held that, under constitutional preemption principles, when such a conflict arises, the federal regulatory regime controls and the state claims are preempted.

The first case was *Wyeth v. Levine*. The plaintiff, Diana Levine, was intravenously administered the brand-name drug Phenergan, an antihistamine used to treat nausea, through a process known as "IV-push" instead of an "IV-drip."[80] A surgeon had to amputate her forearm after she developed gangrene.[81] A jury found the drug manufacturer liable for not adequately warning of the dangers of administering Phenergan by IV-push.[82] The Supreme Court assessed the federal regulatory regime to determine whether federal law prohibited the brand-name manufacturer from changing its labeling to provide stronger

[79] *See* Wyeth v. Levine, 555 U.S. 555 (2009).

[80] Wyeth v. Levine, 555 U.S. 555 (2009).

[81] *Id.*

[82] *Id.* at 562.

warnings about the IV-push method of administration.[83] In a 6-3 ruling, the Court allowed the claim, reasoning it was not *impossible* for Wyeth to comply with both federal labeling law and the state law warning requirements derived from the litigation.[84]

The Court explained that Wyeth *could have* used the CBE process to add the safety information required by the jury's determination and then seek FDA approval for that change afterwards.[85] Wyeth had showed that the FDA approved Phenergan's label and worked with the company to update it several times. But, the Court said Wyeth did not show that the FDA would have *prohibited* the required change if the warning was deemed inadequate under state tort law.[86] "[W]hen the risk of gangrene from IV-push injection of Phenergan became apparent, Wyeth had a duty to provide a warning that adequately described that risk, and the CBE regulation permitted it to provide such a warning before receiving the FDA's approval."[87] The Court continued, stating that the state law claims would be preempted by the federal regulatory regime if the brand-name drug manufacturer provided "clear evidence that the FDA would not have approved" the change to the drug's label required by the state claim.[88] Under such a circumstance, it would be "impossible . . . to comply with both federal and state requirements."[89]

Two years later, in *PLIVA, Inc. v. Mensing* the Supreme Court heard a preemption challenge to state failure-to-warn liability in a case

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[83] *Id.* at 565-68.

[84] *Id.* at 581.

[85] *See Levine*, 555 U.S. at 573.

[86] *Id.* at 561-62, 577-78-73; *see supra* Part I.B. (discussing the CBE process).

[87] *Levine*, 555 U.S. at 571.

[88] *Id.* at 571. Some defendants have met this standard. *See, e.g.*, Dobbs v. Wyeth Pharm., 797 F. Supp. 2d 1264, 1277 (W.D. Okla. 2011) (finding a failure-to-warn claim preempted where the regulatory history of Effexor presented "clear evidence" that, had the defendant submitted a stronger warning about adult suicide to the FDA, the FDA would have rejected it).

[89] *Dobbs*, 797 F. Supp. at 1269 (quoting *Levine*, 555 U.S. at 571).

involving a generic prescription drug.[90] In this case, two patients who took generic metoclopramide (brand-name drug Reglan) claimed the generic drug manufacturer failed to adequately warn of the risk of developing tardive dyskinesia, a movement disorder that causes involuntary repetitive muscle movements in the face, neck, arms, and legs.[91] As in *Levine*, the Court applied the "impossibility preemption" test, concluding by a 5-4 majority that it would be impossible for the generic drug manufacturer to adhere to both its federal labeling requirements, which requires that it use the "same" warning approved for the branded drug, and change those warnings in an effort to cure any defect a jury in the state failure-to-warn suit determined to exist.[92] The Court explained that "[t]he question for 'impossibility' is whether the private party could independently do under federal law what state law requires of it."[93] Here, unlike with brand-name drug manufacturers, "the CBE process was not open to" generic drug manufacturers.[94] So, there was no pathway for the manufacturer to change its labeling without prior FDA approval.[95] If the manufacturer cannot "of its own volition . . . strengthen its label in compliance with its state tort duty[,]" then the claim is preempted by the federal drug regulatory regime.[96] Thus, state law failure-to-warn claims over generic prescription drugs are generally preempted by the FDCA.

Finally, in 2019, the Court heard *Merck Sharp & Dohme Corp. v. Albrecht*, which helped elucidate the "clear evidence" standard as to when it would be similarly impossible for brand-name manufacturers to change its warning labels unilaterally.[97] The case involved claims from some 500 individuals who took the brand-named drug Fosamax, which

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[90] PLIVA, Inc. v. Mensing, 564 U.S. 604 (2011).

[91] *Id.* at 609-10.

[92] *Id.* at 613.

[93] *Id.* at 620 (citing *Levine*, 555 U.S. at 573).

[94] *Id.* at 615.

[95] *See id.* at 616.

[96] *Mensing*, 564 U.S. at 624.

[97] Merck Sharp & Dohme Corp. v. Albrecht, 139 S. Ct. 1668 (2019).

was approved to treat and prevent osteoporosis in postmenopausal women.[98] The plaintiffs asserted failure-to-warn claims of the risk of certain types of bone fractures, including atypical femoral bone fractures.[99] The plaintiffs took Fosamax at some point between 1999 and 2010, before the labeling was updated to warn of these risks.[100]

Merck argued the "clear evidence" standard was met in this case because the FDA had rejected its efforts to add warnings about the risk of such bone fractures before 2011.[101] Specifically, during the drug's development Merck brought concerns to the FDA about potential bone fractures, and the FDA found the concerns theoretical and did not approve labeling referring to this risk.[102] By 2008, Merck believed there was sufficient post-market evidence to support these warnings, and submitted a Prior Approval Supplement (PAS) application to support the labeling changes.[103] The FDA approved changes only to the Adverse Reactions section that highlighted incidents of bone fractures, but rejected Merck's proposed change to the Warnings and Precautions section of the labeling, saying those changes lacked justification.[104] In 2010, the FDA issued a Drug Safety Communication that data the FDA reviewed "have not shown a clear connection between bisphosphonate [Fosamax] use and a risk of atypical sub trochanteric femur fractures."[105] It was not until 2011 that the FDA agreed to new warning language on these fractures.[106] Based on this history, the District Court ruled that the claims were, in fact, preempted.[107] Merck had established

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[98] *Id.* at 1675.

[99] *Id.* at 1674.

[100] *Id.*

[101] *Id.* at 1674-75.

[102] *Id.*

[103] *Id.*; see *also* 21 C.F.R. § 314.70(b) (2018) (discussing Prior Approval Supplement (PAS) criteria).

[104] *Albrecht*, 139 S. Ct. 1674.; *see also In re* Fosamax Alendronate Sodium Prods. Liab. Litig., 852 F.3d 268, 277 (2017).

[105] *In re Fosamax*, U.S. Dist. LEXIS 42253, *16 (2014).

[106] *See id.*

[107] *Albrecht*, 139 S. Ct. at 1675 (2019).

"clear evidence" the FDA would not have approved the labeling change during the time in question.[108] But, the Court of Appeals vacated that ruling and urged Supreme Court to provide clarity on how to apply the "clear evidence" standard, and the Court granted review.[109]

In issuing its ruling, the Supreme Court provided guidance as to how lower courts should apply the "clear evidence" standard for preemption in brand-name drug failure-to-warn cases. As a threshold matter, the Court clarified the "clear evidence" reference in *Levine* was not a heightened evidentiary standard, as some suggested, but a need for clarity that FDA would not have approved the labeling change.[110] It also stated that whether the "clear evidence" standard has been met is a legal question for the judge, not a fact question for juries.[111] The Court reasoned that "judges are better suited than are juries to understand and to interpret agency decisions in light of the governing statutory and regulatory context."[112] The issue of preemption does not lend itself to a battle of experts, where lay juries can be improperly influenced into overturning an agency's scientific determinations. Also, giving judges this responsibility "should produce greater uniformity among courts; and greater uniformity is normally a virtue when a question requires a determination concerning the scope and effect of federal agency action."[113] As a result, brand-name drug manufacturers can raise a preemption defense in motions to dismiss, at summary judgment, or in

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[108] *See id.*

[109] *See id.* at 1675-76.

[110] *Id.* at 1672, 1676.

[111] *Id.* at 1676, 1679.

[112] *Id.* at 1680.

[113] *Albrecht*, 139 S. Ct. at 1680.

post-trial motions—whenever it can establish that the clear evidence standard has been met.[114]

With regard to the substantive determination of clear evidence, the Court defined "clear evidence" to mean evidence showing that the drug manufacturer "fully informed the FDA of the justifications for the warning required by state law and that the FDA, in turn, informed the drug manufacturer that the FDA would not approve a change to the drug's label to include that warning."[115] The Court also recognized that federal law permits the FDA to communicate disapproval of a warning in multiple ways, including notice-and-comment rulemaking setting forth labeling standards, formally rejecting a warning label, or other agency action carrying the force of law.[116] "[T]he judge must simply ask himself or herself whether the relevant federal and state laws 'irreconcilably conflic[t]'" in reviewing whatever "method" the FDA expressed disapproval.[117]

One of the questions that played out in duel concurring opinions was what constitutes an agency communication that a labeling change would not have been permitted. The majority opinion itself acknowledged only that "[t]he question of disapproval 'method' is not now before us. And we make only the obvious point that, whatever the means the FDA uses to exercise its authority, those means must lie within the scope of the authority Congress has lawfully delegated."[118] In one concurrence, Justice Thomas suggested that a final agency action would be needed.[119] In an opposing concurring opinion, Justice Alito, joined by Chief Justice Roberts and Justice Kavanaugh, emphasized the "real world" nature of a branded drug manufacturer's dealings with the

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[114] *See, e.g.*, Gibbons v. Bristol-Myers Squibb Co., 919 F. 3d 699 (2nd Cir. 2019) (ruling where preemption was granted at the motion to dismiss stage in Eliquis cases).

[115] *Albrecht*, 139 S. Ct. at 1678.

[116] *Id.* at 1679.

[117] *Id.* (quoting Rice v. Norman Williams Co., 458 U.S. 654, 659 (1982)).

[118] *Id.*

[119] *See id.* at 1681-83 (Thomas, J., concurring).

FDA, whereby "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."[120]

For instance, in 2008, during a telephone conversation, an FDA official purportedly told Merck that "[t]he conflicting nature of the literature does not provide a clear path forward, and more time will be need[ed] for FDA to formulate a formal opinion on the issue of a precaution around these data."[121] A week later, another FDA official sent an email stating "the FDA would 'close out' Merck's applications if Merck 'agree[d] to hold off on the [Precautions] language at this time.'"[122] Although these were not final agency actions, they presented "clear evidence" that the FDA would not have approved labeling changes regarding bone fractures that would have been required if the jury found that not including this information in the labeling constituted a state law failure-to-warn defect.[123]

The Court also took notice that the FDA, through the Solicitor General, filed a brief in support of preemption in the case to guard against over-warning.[124]

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[120] *Id.* at 1684.

[121] *Albrecht*, 139 S. Ct. at 1685 (quoting internal Merck memorandum describing call provided as part of case record).

[122] *Id.* at 1685-86 (quoting case record).

[123] *Id.* at 1686 (quoting Brief of United States as *Amicus Curiae*).

[124] *See* Brief for the United States as Amicus Curiae at *13-24, Merck Sharp & Dohme Corp. v. Albrecht, 139 S. Ct. 1668 (2019) (No. 17-290). The Supreme Court invited the Solicitor General to file a brief expressing the views of the United States on Dec. 4, 2017. Docket Entry, Merck Sharp & Dohme Corp. v. Albrecht, 139 S. Ct. 1668 (2019) (No. 17-290). The United States filed a brief on September 20, 2018 in support of Merck. *See* Brief for the United States as Amicus Curiae Supporting Petitioner at *1, Merck Sharp & Dohme Corp. v. Albrecht, 139 S. Ct. 1668 (2019) (No. 17-290). On Dec. 3, 2018, the Solicitor General participated in oral argument after the Court granted leave. Docket Entry, *Albrecht*, 139 S. Ct. 1668 (No. 17-290).

III. PREEMPTION: A DEMANDING YET ATTAINABLE DEFENSE

Since 2019, courts have been applying *Albrecht*, raising important considerations for when state failure-to-warn claims involving brand-name drugs are preempted by the federal regulatory process. They generally follow the burden shifting approach the Second Circuit developed in *Gibbons v. Bristol-Myers Squibb Co.*[125] The first inquiry under this analysis looks at whether the brand-name manufacturer can use the CBE process to change the labeling in order to be consistent with a state jury finding that the current labeling is inadequate.[126] This requires the plaintiff to show that the requirements for making a labeling change under the CBE regulations have been met: which, as discussed earlier, requires, among other things, proof that there was "newly acquired information" of a "causal association" between the drug at issue and the alleged injury.[127] Only once this burden of proof has been met does the burden shift to the manufacturer to assert a valid preemption defense, namely by showing that the FDA was fully informed of any such new information and that there is clear evidence the FDA would not have approved the labeling change.[128] The following cases include important discussions on these and other key issues for determining whether preemption exists in state failure to warn claims.

A. No Newly Acquired Information

As discussed above, a brand-name drug manufacturer can make a labeling change before receiving FDA approval under the CBE regulation only when the change reflects "newly acquired information" that provides the manufacturer with "reasonable evidence of a causal association of a clinically significant adverse reaction linked to a

[125] 919 F.3d 699 (2d Cir. 2019).

[126] *Id*. at 708.

[127] *See id*.; *see also* discussion on CBE requirements, *infra*.

[128] *See id*.

drug."[129] Thus, in order to prevail in a failure-to-warn claim, the plaintiff has the burden to show such newly acquired information existed at the time of the alleged injury such that the manufacturer could have changed the labeling.[130] Newly acquired information can include new data, as well as "new analyses of previously submitted data."[131] Because "risk information accumulates over time . . . the same data may take on a different meaning in light of subsequent developments."[132] Conversely, information that was before the FDA at the time of the label's approval is not newly acquired information.[133]

The U.S. Court of Appeals for the Fourth Circuit applied the "newly acquired information" standard in *Knight v. Boehringer Ingelheim Pharms, Inc.*[134] In *Knight*, the plaintiffs alleged that Boehringer Ingelheim failed to warn of the risk of bleeding associated with a 75mg dose of the anticoagulant drug Pradaxa and that the 75mg dose was never tested in patients.[135] The Fourth Circuit explained that this "state law challenge to FDA-approved warnings" can proceed "only when the defendant had the unilateral ability to change that labeling" under the CBE process because there was "'newly acquired information' about the 'evidence of a causal association' between the

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[129] 21 U.S.C. § 314.3(b) (defining "newly acquired information"); 21 C.F.R. § 201.57(c)(6)(i).

[130] *See, e.g.*, Zamfirova v. AMAG Pharms., Inc., No. 20-CV-00152, 2021 WL 2103287, at *8, *24 (D.N.J. May 25, 2021) (dismissing all of the consumer-fraud based claims without prejudice because plaintiffs failed to provide sufficient facts for the court to determine whether or not their claims are preempted).

[131] *Wyeth*, 555 U.S. at 569 (internal quotation marks omitted).

[132] *Id.*

[133] *See In re* Celexa & Lexapro Mktg. & Sales Pracs. Litig., 779 F.3d 34, 42-43 (1st Cir. 2015) (holding that plaintiffs' failure-to-warn claims preempted because the complaint identified only information that had been before FDA at the time of approval; in other words, the complaint did not identify any newly acquired information).

[134] *See* 984 F.3d 329, 340 (4th Cir. 2021).

[135] *See id.* at 336.

drug and a risk of harm."[136] The plaintiffs argued that a draft study published *after* the alleged injuries could constitute such newly acquired information.[137] The Fourth Circuit disagreed, stating because the "finalized version" of the paper "was not sent to the publisher until" after the alleged injury, it "would not have made any difference" to the plaintiffs.[138] Further, the paper's analyses did not meet the standard for CBE labeling changes because it did not "reveal risks of a different type or greater severity or frequency than previously included in submissions to [the] FDA."[139] Further, the FDA "was already aware" of the correlation raised in the study and the label warned of these risks, so the paper's conclusions did not "establish any new risk."[140]

The *Knight* court cautioned, however, that its decision "should not be construed to require final, peer-reviewed publication of an analysis to constitute newly acquired information."[141] At the same time, courts should not have "a quick trigger in determining the existence of newly acquired information."[142] The substance should guide the decision-making:

> It is imperative for the scientific process that open dialogue and exchange of ideas take place during an analysis and drafting of a paper. That, along with airing and testing opposing opinions, results in better decisions. That is why hypotheses, differing viewpoints and even preliminary conclusions are not 'reliable evidence of new risks. If they were, companies might discourage the open dialogue needed to reach the best results. Or, unnecessary warnings might flood labels and distract

[136] *Id.* at 332, 337-38 (citing *Albrecht*, 139 S. Ct. at 673).

[137] *Id.* at 338.

[138] *Id.*

[139] *Id.* at 338 (quoting 21 C.F.R. § 314.3(b)).

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

[141] *Id.* at 340. On the other hand, the Third Circuit has held that the CBE process was available upon a "completed" study, not preliminary assessments. *In re* Avandia Mktg., Sales & Prod. Liab. Litig., 945 F.3d 749, 760 (3d Cir. 2019).

[142] *Knight*, 984 F.3d at 340.

> from real risks. . . . In sum, there is no bright-line, one-size-fits-all line marking the moment when an analysis reveals new information.[143]

Accordingly, courts need to carefully review the record on a case-by-case basis.

Courts analyzing the *Albrecht* factors in the cases before them reflect such a rigorous assessment of the scientific evidence. For example, in *McGrath v. Bayer Healthcare Pharms., Inc.*, a federal district court in New York held a woman's failure-to-warn claims were preempted because she did not show new information demonstrating a causal association between the drug and a clinically significant adverse reaction at the time she was administered the medication.[144] The plaintiff alleged injuries from exposure to Magnevist, an FDA-approved gadolinium-based contrast agent administered to patients to enhance the quality of MRIs.[145] The plaintiff claimed defendants knew or should have known of risks associated with gadolinium retention for certain patients and failed to include a corresponding warning.[146] Two years after plaintiff's treatments, the FDA's medical advisory committee voted to add a warning that gadolinium can be retained in some organs, including the brain, in patients with healthy kidneys.[147] The plaintiff based her failure-to-warn claim on the fact that this risk was not disclosed earlier.[148]

In a lengthy ruling analyzing the scientific questions at issue, the court dismissed the claims as preempted because the reports and studies the plaintiffs cited "discuss the fact of gadolinium retention but do not reach any conclusions regarding the *adverse effects* or *risks* associated

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[143] *Id.* at 340-341 (internal citations omitted).

[144] McGrath v. Bayer Healthcare Pharms., Inc., 393 F. Supp. 3d 161, 167-68 (E.D.N.Y. 2019).

[145] *See id.* at 164-65.

[146] *See id.* at 165-66.

[147] *Id.* at 165.

[148] *Id.*

with gadolinium retention in patients with normal renal function."[149] Rather, the new studies were "inconclusive regarding the risks, if any, associated with gadolinium retention and would not justify a unilateral labeling change" through the CBE process.[150] The court also looked into a study published *after* the injury occurred that alleged an adverse reaction in mice. It found that "[a] single study performed on mice does not make a risk 'apparent' or otherwise constitute 'reasonable evidence of an association'" authorizing a change to the labeling through the CBE process.[151] The court noted that "the FDA prefers a more cautious approach" to labeling that does not include warning of risks that are "not *well-grounded* in scientific evidence."[152]

Following this same type of detailed approach, a federal court in New York held that adverse event reports, themselves, "do not constitute 'newly acquired information.'"[153] Here, plaintiffs alleged that "some 6,000 adverse event reports" the manufacturer sent to the FDA constituted newly acquired information.[154] But, the court explained, adverse event reports are required "whether or not considered drug related" and courts have "rejected the notion that analyses based on adverse event reports—much less the reports standing alone—can constitute 'newly acquired information.'"[155] Similarly, a federal district court in Wisconsin rejected an expert's analysis purporting to find newly acquired information because the conclusions were "litigation-driven and unsupported by any published research."[156] "A single report, unaccompanied by any significant analysis, does not demonstrate the

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[149] *Id*. at 169 (emphasis in original).

[150] *McGrath*, 393 F. Supp. 3d at 169.

[151] *Id.* at 170.

[152] *Id.* at 169 (internal citation omitted).

[153] Gayle v. Pfizer, Inc., 452 F. Supp. 3d 78, 88 (S.D.N.Y. 2020).

[154] *Id.*

[155] *Id.* (emphasis in original); *see also*, 21 C.F.R. § 314.80(a) (2023); Utts v. Bristol-Myers Squibb Co., 251 F. Supp. 3d 644, 663 (S.D.N.Y. 2017); *McGrath*, 393 F. Supp. 3d at 169.

[156] R.S.B. *ex rel.* Hammar v. Merck & Co., Inc., No. 20-C-1402, 2022 WL 3927868, at *4 (E.D. Wis. Aug. 31, 2022).

existence of a risk that is of a different type or greater severity or frequency, such that a manufacturer can invoke the CBE regulation."[157] The standard for using the CBE process is intended to be high, as is the standard for newly acquired information.

Courts have also discarded creative plaintiff arguments that try to circumvent this high bar. A federal district court in Connecticut explained that plaintiffs must allege "there was significant adverse risk information revealed" to the manufacturer related to the injuries alleged.[158] The plaintiff alleging injuries from a vaccine presented studies purportedly showing increased risk of infertility and cancer, but those were not the injuries she alleged.[159] The court rejected the claim, stating the studies "bear no relation" to her claims.[160] In California, a federal district court found for preemption where the plaintiff alleged the drug manufacturer and FDA, in fact, "had prior knowledge of the link between" the medication and the alleged injuries and that the "label was approved despite this known link."[161] The court stated this case "alleges the opposite of what is required to overcome preemption" and did not demonstrate newly acquired information.[162] And, a federal district court in Georgia rejected an argument that "while the Judge must decide the factual question of whether the FDA would not have approved a change under *Albrecht*, the newly acquired information is an issue of fact for the jury."[163] The court affirmed that both prongs constitute the two-part test and "are for a Judge to decide, not a jury."[164]

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[157] *Id.*

[158] Herlth v. Merck & Co., Inc., No. 3:21-CV-438 (JAM), 2022 WL 788669, at *4 (D. Conn. Mar. 15, 2022).

[159] *Id.*

[160] *Id.*

[161] Roshkovan v. Bristol-Myers Squibb Co., No. ED CV 21-8590-FWS-AGR, 2022 WL 3012519, at *11 (C.D. Cal. June 22, 2022).

[162] *Id.* at *10.

[163] Lyons v. Boehringer Ingelheim Pharms., Inc., 491 F. Supp. 3d 1350, 1363 (N.D. Ga. 2020).

[164] *Id.*

Unlike juries, judges can dive into the medical science issues through detailed briefings and hearings.

Finally, most courts have reinforced the *Gibbons* burden-shifting approach in response to arguments that *Albrecht* shifted this burden onto defendants "to show the *non*-existence of newly acquired information."[165] Plaintiffs in these cases have argued, among other things, that the burden should be on the manufacturer because it would require the manufacturers to seek out information "that allowed it to invoke the CBE regulation."[166] The courts, however, have explained that it would be unfair to make the manufacturer "prove a negative—that it acquired no new information" to justify a CBE modification.[167] This burden-shifting argument "upends" the preemption framework by allowing litigants to circumvent it by merely alleging that a manufacturer should have created the "newly acquired" information.[168] Accordingly, the courts stated, this argument "cannot stand."[169] In accordance with *Gibbons*, most courts have found that the burden to show the CBE process was available due to newly acquired information remains on the plaintiff, and shifts to defendants only *after* plaintiffs establish such new information existed.[170]

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[165] Herlth v. Merck & Co.,Inc., No. 3:21-CV-438 (JAM), 2022 WL 788669, at *5 (D. Conn. Mar. 15, 2022).

[166] R.S.B. *ex rel.* Hammar v. Merck & Co., Inc., No. 20-C-1402, 2022 WL 3927868, at *4 (E.D. Wis. Aug. 31, 2022).

[167] Silverstein v. Boehringer Ingelheim Pharms., Inc., 2020 U.S. Dist. LEXIS 188176 (S.D. Fla. Oct. 7, 2020).

[168] *R.S.B. ex rel. Hammar*, 2022 WL 3927868, at *4 (internal citation omitted); *but see In re* Zofran (Ondansetron) Prods. Liab. Litig., 541 F. Supp. 3d 164, 196-97 (D. Mass. 2021) (rejecting this burden shifting approach, stating, "[n]onetheless, this Court will continue to treat preemption as an affirmative defense, for which the manufacturer alone bears the burden of proof.").

[169] *Id.*

[170] *R.S.B. ex rel. Hammar*, 2022 WL 3927868, at *4; *see also* Gayle v. Pfizer, Inc., 452 F. Supp. 3d 78, 88 (S.D.N.Y. 2020).

B. Clear Evidence the FDA Would Not Have Approved Labeling

The second prong of the two-part preemption test is the burden on the defendant to prove the affirmative defense that there is "clear evidence" that, even with this newly acquired information, the FDA would not have approved the labeling change needed for the defendant to cure a ruling that its labeling failed to adequately warn of the risks at issue.[171] As the Supreme Court set forth in *Albrecht*, this prong, itself, has two parts: that the FDA was "fully informed" of the justifications for the warnings required by the failure-to-warn claim, and the FDA communicated that it would not have approved changing the drug's label to include the warning.[172]

The *Albrecht* case itself provides a valuable guide for how these issues play out in real life. The Supreme Court remanded the case, *In re Fosamax*, to the Third Circuit, which in turn, sent the case to the district court to determine whether there was clear evidence the FDA would not have approved the labeling change.[173] The first question was whether the FDA was fully informed of the risk of atypical femoral fractures. As the district court explained, "the basic inquiry . . . is whether the FDA had 'all of the information it deemed necessary to decide whether to approve or reject'" a proposed warning.[174] The district court conducted an in-depth assessment of the communications between the manufacturer and the FDA: "Between its formal safety updates, periodic emails, and PAS, Defendant clearly and fully informed the FDA of the panoply of risks associated with long-term Fosamax use and the justifications for its proposed label change."[175] In this case, the court had the benefit of an *amicus* brief filed by the FDA stating it was fully informed. In that instance, the court concluded, "the

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[171] *See Albrecht*, 139 S. Ct. at 1678.

[172] *Id*.

[173] *In re* Fosamax (Alendronate Sodium) Prod. Liab. Litig., 593 F. Supp. 3d 96, 120 (D.N.J. 2022).

[174] *Id.*

[175] *Id.*

FDA's view of the evidence matters" because the FDA is the "arbiter of which data and information is or is not material to its decision to approve or reject a change to a drug's label."[176]

The next set of questions involved what actions the manufacturer and FDA needed to take in order for the district court to conclude that the FDA would not have approved the warnings at issue in the case. Here, the plaintiffs argued that only a final agency action rejecting the specific wording at issue should carry this weight: "a manufacturer must have *actually requested* a label change that the FDA then *expressly rejected*."[177] The district court rejected this formalistic approach, explaining that such a rule would be impractical because a decision on whether to even submit a proposed or revised warning often reflects ongoing discussions between the manufacturer and the FDA.[178] Generally, the FDA would have already communicated whether it would accept a warning change before the warning would have been submitted, so the court needs to look at the communications between the manufacturer and FDA as a whole in determining whether the FDA conveyed it would have rejected the warning.[179] As a result, "a drug manufacturer may prove preemption without showing that it ever proposed or pursued a label change"—it need not submit a PAS or CBE to preserve its preemption defense.[180] The court also noted that no court post-*Albrecht* established a standard for impossibility preemption requiring such a specific action.[181]

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[176] *Id.* at 125.

[177] *Id.* at 117.

[178] *See id.* at 126 ("The preemption question turns on whether Congress delegated to the agency the authority to act in such a manner in the first instance, not on whether the agency's action is necessarily a 'final' one.").

[179] *In re Fosamax*, 593 F. Supp. 3d at 120 (citing Justice Alito's concurrence that information communications between the FDA and drug manufacturers should be considered in the preemption analysis).

[180] *Id.* at 117.

[181] *Id.*

Similarly, the district court stated that the FDA does not need to reject the specific warning language sought in the case.[182] The key, the court stated, is that FDA was fully informed of the type of injury at issue and did not require a warning that would have covered the harm alleged in the case, even if the plaintiff's wording is slightly different from what it communicated it would have rejected.[183] To this end, "the FDA's *raison d'etre* [is] to regulate drug safety [and has] and independent legal duty to notify a manufacturer as soon as it 'becomes aware of new safety information that [it] believes should be included in the labeling of a drug' and 'initiate discussions to reach an agreement . . . on labeling."[184] Here, armed with sufficient information, the FDA "did not believe there was reasonable scientific evidence of a causal association between bisphosphonate use and atypical femoral fractures, or else it would have suggested edits to that end, or simply mandated a warning using language that the FDA thought was more appropriate."[185]

For these reasons, the district court held that Merck had "fully informed the FDA of the justifications for its proposed warning" and that "the FDA's rejection was predicated on insufficient evidence of a causal link between Fosamax and atypical femoral fractures."[186] Accordingly, the FDA's Complete Response Letter with the other communications constituted clear evidence that the FDA would not have approved a warning on atypical femoral fractures.[187]

As indicated, the Fosamax ruling relied on several cases decided since *Albrecht*, including the U.S. District Court of Massachusetts ruling *In re Zofran (Ondansetron) Products Liability Litigation*.[188] In *Zofran*, the district court issued a similarly thorough ruling, holding the

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[182] *See id.* at 137.

[183] *See id.*

[184] *Id.* (citing 21 U.S.C. § 355(o)(4)(A)).

[185] *In re Fosamax*, 593 F. Supp. 3d at 138.

[186] *Id.* at 145.

[187] *See id.*

[188] *In re* Zofran (Ondansetron) Prod. Liab. Litig., 541 F. Supp. 3d 164 (D. Mass. 2021).

plaintiffs' state failure-to-warn claims were preempted by the federal regulatory regime.[189] The plaintiffs alleged the manufacturer of anti-nausea drug Zofran did not provide adequate warnings of potential risks related to birth defects of the off-label use of the drug during pregnancy.[190] The FDA had become aware of such off-label uses and, in 2010, had asked GSK, the manufacturer at the time, to provide supplemental information on the safety of Zofran during pregnancy.[191] In 2013, a citizen petition was filed with FDA by a third party requesting the labeling "indicate an increased risk to fetal safety."[192] And in 2015 and 2020, Novartis, who bought the rights to market Zofran from GSK, submitted proposed label changes related to use during pregnancy.[193] The FDA rejected all of these requests, finding no causal link established between the drug and birth defects.[194] In response to the 2020 submission, the FDA not only rejected the proposed warning, it added the statement: "All pregnancies have a background risk of birth defect, loss, or other adverse outcomes."[195]

In finding for preemption, the district court rejected several arguments by plaintiffs that could impact other cases. For example, plaintiffs alleged that GSK had withheld certain information and mischaracterized other information related to birth defects when the drug was first approved in the 1990s.[196] In setting these allegations aside, the district court stated that all of these purported omissions and mischaracterizations were put before the FDA in a 2019 citizen petition by GSK and the Novartis submissions, so by 2020 at the very least, the FDA was fully informed of the alleged justifications for the warning

[189] *See id.* at 206.
[190] *See id.* at 167.
[191] *Id.*
[192] *Id.*
[193] *See id.*
[194] *In re Zofran*, 541 F. Supp. 3d at 167.
[195] *Id.* at 181.
[196] *Id.* at 168.

label that plaintiffs contend was required.[197] The FDA's rejection of the warning labels after that submission means that this information, even assuming *arguendo* that it was new to the FDA, was not material to its rejection of the warning language suggested by plaintiffs. So, the rejection in 2021 had a retroactive effect for all allegations before then. Similarly, the district court rejected the allegation that, even though it had this information, the FDA did not properly consider it because Novartis had not affirmatively requested that it be added to the label: "the Court will not assume that the FDA failed to perform, in fact blatantly ignored, its statutory duties to review and monitor the drug for human safety."[198] Finally, the district court held that it is not determinative how the information was provided to the FDA, *i.e.*, through the manufacturer or a citizen petition, or whether the FDA communicated to the specific defendant.[199] Here, communications to Novartis in response to its 2020 submission applied equally to claims against GSK; the key is that the FDA was fully informed and communicated that it would not have approved the required warnings.[200]

The First Circuit upheld this preemption ruling in early 2023, but approached the case differently.[201] It held that the information plaintiffs argued should have led to the labeling changes did not even constitute newly acquired information. It stated that, under *Albrecht*, the CBE process is "unavailable if there is no reasonable basis for treating the information identified by plaintiffs as newly acquired information."[202] It then conducted a detailed scientific analysis and concluded the studies "do not appear to 'reveal risks of a different type or greater severity or frequency than previously included in submissions to FDA,' as required to meet the definition of 'newly acquired

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[197] *Id.* at 200.

[198] *Id.* at 202.

[199] *Id.* at 204-06.

[200] *In re Zofran*, 541 F. Supp 3d at 204-06.

[201] Perham v. GlaxoSmithKline LLC (*In re* Zofran Ondansetron Prods. Liab. Litig.), 57 F.4th 327 (1st Cir. 2023).

[202] *Id.* at 336.

information.'"[203] Although it could have ended the inquiry there, the First Circuit also found clear evidence the FDA would not have approved the labeling change. It suggested the required "demonstration is most easily made if the manufacturer actually initiates such a labeling change through the CBE procedure," but *Wyeth* and *Albrecht* do not "preclude other means of making the required showing."[204] Here, the FDA made clear through an agency action having the force of law that it would not have allowed the change when it approved language that the data revealed "no significant effects of [Zofran] on the maternal animals or the development of the offspring."[205] "We think it is clear that when the FDA formally approves a statement that data reveals no effects, it necessarily rejects the contention that the data does reveal effects."[206] Finally, the First Circuit agreed with the lower court that it was immaterial whether the information was supplied by plaintiffs or the manufacturer: "we find the relevant issue to be whether the FDA was informed in a relevant context, not who exactly first informed it."[207]

Other courts have also observed there is no formalist approach to how the FDA must be informed of the risks at issue or how the FDA communicates it would not have approved the applicable warnings. They have noted that the Supreme Court "refused to opine" on such precise methods.[208] Several courts have affirmed that the manufacturer does not need to be the entity that informs the FDA of the risks; citizen petitions raising the risks are sufficient.[209] This makes sense. The citizen petition process is a formal one and provides the "official

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[203] *Id.* at 339.

[204] *Id.* at 342.

[205] *Id.*

[206] *Id.*

[207] *Perham*, 57 F.4th at 342.

[208] Pfaff v. Merck & Co., No. 12-MD-02331 (BMC), 2022 WL 4121406, *8 (E.D.N.Y. Sept. 9, 2022).

[209] *Id.* at *7 (noting the FDA "explicitly declined to require such a warning in its letter response to the September 2017 citizen petition."); *In re* Incretin-Based Therapies Prod. Liab. Litig., 524 F. Supp. 3d 1007 (S.D. Cal. 2021); Cerveny v. Aventis, Inc., 855 F.3d 1091 (10th Cir. 2017).

administrative record for an FDA decision" *Albrecht* finds to be a proper basis for preemption.[210] Also, courts have found for preemption based on a variety of FDA actions, including the release of an FDA risk assessment, rejection of a citizen petition raising the risks, and inaction with respect to requiring the warnings in light of "extensive and ongoing evaluation of the issue."[211] In these situations, where the FDA has been apprised of "known issues" and is actively considering the risks at issue, the FDA's inaction at the moment can represent "clear evidence" it would not have approved the warning at issue.[212] Also, courts have held that all such communications are backwards looking; they cover allegations the labeling should have been changed at any time before that date. For example, in one case, the court explained that the FDA's rejection of a citizen petition in 2017 "make[s] clear that, in retrospect, it would not have approved" the requisite warning in 2011, which is the

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[210] Merck Sharp & Dohme Corp. v. Albrecht, 139 S. Ct. 1668, 1680 (2019).

[211] *In re Incretin-Based Therapies*, 524 F. Supp. 3d at 1033 ("[P]ursuant to 21 U.S.C. § 355(o)(4)(), the FDA has the authority to mandate a label change if it learns of new safety information that should be included in the labeling of a drug" and therefore "the FDA's silence on [an] issue" may be "highly relevant to its preemption analysis"); Lyons v. Boehringer Ingelheim Pharms., Inc., 491 F. Supp. 3d 1350, 1360 (N.D. Ga. 2020) (explaining where the FDA had the information in question and had "taken no action to update" the warning label "as would be the FDA's responsibility of it was concerned about patient safety" under section 355(o)(4), the inaction can "reflect a rejection of the substance of Plaintiff's proposed warning"); Smith v. GE Healthcare Inc., No. 3:19-CV-00492, 2020 WL 1880787 (W.D. La. Mar. 31, 2020) ("The language of the label change, specifically stating facts contrary to the warnings sought by Smith, is clear evidence that the FDA would not have approved a label change which warned of such adverse effects.").

[212] Ridings v. Maurice, 444 F. Supp. 3d 973, 998 (W.D. Mo. 2020); *see also Albrecht*, 139 S. Ct. at 1684 (Alito, J., concurring) (noting that "if the FDA declines to require a label change despite having received an considered information regarding a new risk, the logical conclusion is that the FDA determined that a label change was unjustified.").

operative time frame raised by the plaintiffs: "No clearer evidence could be forthcoming that the FDA would not have approved the change in 2011 of anytime thereafter."[213]

Finally, several courts have explained the important health care rationale for not imposing a labeling change in private litigation that is not consistent with public health: the FDA's standard for requiring a warning label is "different from that imposed by state tort law" and "the manner in which state-law tort principles drive the labeling of consumer products as a general matter."[214]

> The FDA is concerned not only with avoiding insufficient warnings (that is, failing to warn against risks), but also avoiding over-warning (that is, warning against risks that are unduly speculative, hypothetical, or not adequately supported by science). Thus, while a consumer product such as a chainsaw might bear dozens and dozens of warnings, with little regard for the remoteness of obviousness of the risk, the FDA takes a more measured approach that is intended to provide accurate information to medical professionals and patients without unduly discouraging the use of the product. . . . Again, this is not a situation where a state may elect to provide greater protection to its residents than the federal government would provide; the FDA does not simply provide a minimum level of warning that may be exceeded by manufacturers in order to satisfy state law.[215]

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[213] *Pfaff*, 2022 WL 4121406 at *8.

[214] *In re* Zofran (Ondansetron) Prods. Liab. Litig., 541 F. Supp. 3d 164, 168, 171-72 (D. Mass. 2021).

[215] *Id.* at 168, 206; *see also* Robinson v. McNeil Consumer Healthcare, 615 F.3d 861, 869 (7th Cir. 2010) ("[T]he resulting information overload [from describing every remote risk] would make label warnings worthless to consumers."); Thomas v. Hoffman-LaRoche, Inc., 949 F.2d 806, 816 n.40 (5th Cir. 1992) (explaining that, if manufacturers were required to clutter their warnings with "every possible risk," then"physicians [would] begin to ignore or discount the warnings."); Dowhal v. Smithkline Beecham Consumer Healthcare, 88 P.3d 1, 14 (Cal. 2004) ("[A] truthful warning of an

Consequently, if the FDA has communicated that the label change at issue in the case would have been rejected, the manufacturer should not be encouraged to submit a CBE amendment anyway "merely to preserve its preemption defense."[216] The CBE process is to be used only when there is "reasonable evidence of a causal association"—not "regardless of risk magnitude or scientific justification."[217] The FDA "does not approve CBE amendments simply out of an abundance of caution, as Plaintiffs seem to suggest. The Agency regulates drug labels for precisely the opposite reason: so as not to 'cause meaningful risk information to lose its significance.'"[218]

The alternative regime would be to encourage manufacturers to paper the FDA with proposed labeling changes regardless of what the science says and whether the FDA has already been provided with the information.[219] FDA is bound to review all submissions, so such requirements would result in the FDA being inundated with labeling submissions and diverting valuable resources to defending decisions it has already made.[220] By contrast, the rules set forth above encourages

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uncertain or remote danger may mislead the consumer into misjudging the dangers stemming from use of the product, and consequently making a medically unwise decision.").

[216] *In re* Fosamax (Alendronate Sodium) Prods. Liab. Litig., 593 F. Supp. 3d 96, 144 (D.N.J. 2022).

[217] *Id.* at 144-45.

[218] *Id.* at 145 (citing Supplemental Applications Proposing Labelling Changes for Approved Drugs, Biologics, and Medical Devices, 73 Fed. Reg. 2848, 2851 (Jan. 16, 2008) (to be codified at 21 C.F.R. pts. 314, 601, 814)).

[219] *See, e.g.*, Seufert v. Merck Sharp & Dohme Corp., 187 F. Supp. 3d 1163, 1175 (S.D. Cal. 2016) ("A rule to the contrary would encourage prophylactic labeling changes by manufactures, which in turn, could inundate the FDA with labeling submission.").

[220] *See* Lofton v. McNeil Consumer & Specialty Pharm., 672 F.3d 372, 380 (5th Cir. 2012) (explaining that if manufacturers are going to be compelled "to flood the FDA with information" to protect itself from liability, the FDA will "lose[] control over its ability, based on scientific expertise, to

manufacturers to be thorough and proactive in sharing information with the FDA.

IV. CONCLUSION

After the Supreme Court provided additional guidance on the "clear evidence" standard in *Albrecht* and reasoned that conflict preemption is a question for the judge and not a jury, the lower courts have created a body of post-*Albrecht* case law that is helpful to contextualize instances where state law failure-to-warn claims are preempted. First, the burden is on the plaintiff to show the manufacturer had "newly acquired information" establishing a causal association between the drug and the injury that would justify using the CBE process. Once that burden has been met, the burden shifts to the manufacturer to show "clear evidence" the FDA was "fully informed" of this information and communicated that it would not have approved the proposed labeling change.

This review involves a judge's in-depth assessment of the substance and science, not a formalistic adherence to process or a battling of expert testimonies to lay juries. Judges can assess whether the FDA was fully informed, whether by the manufacturer, a citizen petition or other source. And, they can look at the various ways that FDA can communicate, as there is no single means through which the FDA must convey that it would not have approved the label change. By following these guideposts, district judges have been issuing thoughtful and thorough analyses of what the manufacturers and FDA knew, when they knew it, what they did with that knowledge, and, ultimately, what the FDA decided was the proper public health decision with regard to the drug's labeling. There is no doubt that a preemption remains a demanding defense, but it is also attainable.

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prescribe—and intelligently limit—the scope of disclosures necessary for its work.").