Legal Backgrounder

Vol. 34 No. 13 September 13, 2019

Washington Legal Foundation
Advocate for Freedom and Justice®
2009 Massachusetts Avenue, NW
Washington, DC 20036
202.588.0302 wlf.org

Drug Label "Highlights": An Overlooked Avenue to Preemption in Failure-to-Warn Litigation

by James M. Beck

In 2006 the Food and Drug Administration overhauled drug labeling and created a new section called "highlights." *See* 21 C.F.R. § 201.57(a) (specifying highlights section requirements). Such highlights must include "[a] concise summary of any boxed warning." §201.57(a)(4). With respect to all other warnings, contraindications, and adverse reactions, the highlights regulation provides:

> (9) Contraindications. A concise statement of **each of the product's contraindications**, as required under paragraph (c)(5) of this section, with any appropriate subheadings.
>
> (10) Warnings and precautions. A concise summary of the **most clinically significant information** required under paragraph (c)(6) of this section, with any appropriate subheadings, including information that would affect decisions about whether to prescribe a drug, **recommendations for patient monitoring** that are critical to safe use of the drug, and measures that can be taken to prevent or mitigate harm.
>
> (11) Adverse reactions.
>
> > (i) A list of the most frequently occurring adverse reactions, as described in paragraph (c)(7) of this section, along with the criteria used to determine inclusion (e.g., **incidence rate**). Adverse reactions important for other reasons . . . must not be repeated under this heading in Highlights if they are included elsewhere in Highlights. . . .

21 C.F.R. § 201.57(a)(9-11) (emphasis added).

> The FDA's final rule adopting the regulation described the Highlights section:
>
> [T]he final rule requires that the labeling for new and more recently approved products include introductory information entitled "Highlights of Prescribing Information" (Highlights) (§§201.56(d)(1) and 201.57(a)).
>
> The final rule requires the same headings for Highlights as proposed, except that, in response to comments, FDA moved "Most Common Adverse Reactions" from "Warnings and Precautions" (proposed §201.57(a)(10)) to a new heading entitled "Adverse Reactions" (§§201.56(d)(1) and 201.57(a)(11)). Like the proposed rule, the final rule requires that Highlights, except for the boxed warning, be limited in length to one-half of the page (§ 201.57(d)(8)) (see comment 104).
>
> The agency is also revising its regulations on supplements and other changes to an approved application in §§314.70 and 601.12 (21 CFR 314.70 and 601.12) **to require applicants to obtain prior approval of any labeling changes to Highlights**, except for identified minor changes (see comment 5).

Requirements on Content & Format of Labeling for Human Prescription Drug and Biological Products, 71 Fed. Reg.

James M. Beck is a Senior Life Sciences Policy Analyst with Reed Smith LLP in the firm's Philadelphia, PA office and founder of, and a regular contributor to, the award-winning *Drug and Device Law* blog.

3299, 3925 (FDA Jan. 24, 2006) (emphasis added).

The creation of this Highlights section directly affects preemption in prescription-drug product liability litigation. The U.S. Supreme Court in its October Term 2018 reaffirmed that limits to the preemption of labeling claims for prescription drugs are grounded in the availability of the FDA's changes being effected ("CBE") regulation, which defeats implied impossibility preemption by allowing certain unilateral label modifications:

> [A]n FDA regulation called the 'changes being effected' or 'CBE' regulation permits drug manufacturers to change a label without prior FDA approval if the change is designed to 'add or strengthen a . . . warning' where there is 'newly acquired information' about the 'evidence of a causal association' between the drug and a risk of harm. 21 C.F.R. §314.70(c)(6)(iii)(A).

Merck Sharp & Dohme Corp. v. Albrecht, 139 S. Ct. 1668, 1673 (2019). The Court also stated:

> [F]ederal law – the FDA's CBE regulation – permits drug manufacturers to change a label to 'reflect newly acquired information' if the changes 'add or strengthen a . . . warning' for which there is 'evidence of a causal association,' without prior approval from the FDA. 21 C.F.R. §314.70(c)(6)(iii)(A). Of course, the FDA . . . can reject label changes even after the manufacturer has made them. See §§ 314.70(c)(6), (7). . . . But in the interim, the CBE regulation permits changes, so a drug manufacturer will not ordinarily be able to show that there is an actual conflict between state and federal law such that it was impossible to comply with both.

Id. at 1679.

This CBE regulation the Court relied on in *Albrecht*—21 C.F.R. § 314.70—is precisely the same regulation that the FDA stated it was "revising" in 2006 "to require applicants to obtain prior approval of any labeling changes to Highlights." 71 Fed. Reg. at 3925 (listing "§314.70"). The CBE regulation thus has excepted all aspects of the Highlights section from its scope since 2006:

> (6) The agency may designate a category of changes for the purpose of providing that, in the case of a change in such category, the holder of an approved NDA may commence distribution of the drug product involved upon receipt by the agency of a supplement for the change. These changes include. . . .
>
> > (iii) Changes in the labeling to reflect newly acquired information, **except for changes to the information required in §201.57(a) of this chapter (which must be made under paragraph (b)(2)(v)(C) of this section)**, to accomplish any of the following:
> >
> > > (A) 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 under §201.57(c) of this chapter;

21 C.F.R. § 314.70(c)(6)(iii)(A) (emphasis added). This is the *Albrecht* FDA CBE regulation—down to the last subsection.

The FDA imposed this limitation on changes to Highlights information deliberately—through notice and comment rulemaking. *See Albrecht*, 139 S. Ct. 1680 (endorsing the preemptive power of "notice-and-comment rulemaking setting forth labeling standards"). This amendment was not some nefarious scheme to benefit manufacturers. To the contrary, as the FDA pointed out, "[m]anufacturers, with some exceptions, were opposed, or strongly opposed, to the inclusion of Highlights." 71 Fed. Reg. at 3930.

In response to "comment 5," the FDA stated, in 2006:

> [B]ecause Highlights is a summary of the most important information for prescribing decisions and some comments expressed concerns about the difficulty involved in summarizing the complex and often lengthy information in the FPI [full prescribing information], **the agency believes that it is essential for FDA to review and approve most proposed changes to the information in Highlights**. Accordingly, the agency is revising its regulations on supplements and other changes to an approved application. Under §§314.70(b)(2)(v)(C) and (c)(6)(iii) . . ., **applicants are required**

> **to obtain prior approval of any labeling changes to Highlights**, except for editorial or similar minor changes. . . .

71 Fed. Reg. at 3922 (emphasis added). *See id*. at 3922 ("a sponsor may not use a CBE supplement to make most changes to Highlights.").

The Federal Register cross-reference for modifications of highlights, 21 C.F.R. § 314.70(b)(2)(v)(C), is to "Changes requiring supplement submission and approval prior to distribution of the product made using the change (major changes)." *See also* FDA, Guidance for Industry: Labeling for Human Prescription Drug and Biological Products – Implementing the PLR Content & Format Requirements (Feb. 2013) (containing detailed information about how changes to "highlights" should be made). Thus, any modification of the language of Highlights is a "major change"—and tort actions demanding major changes are preempted. A federal appeals court embraced that principle just last year:

> Major changes require approval from the FDA prior to implementation, while moderate and minor changes do not. Controlling case law is clear − and plaintiffs here concede − that if the change they contend state law requires qualifies as 'major,' then federal law preempts plaintiffs' cause of action because defendants cannot lawfully make such a change without prior FDA approval. Our inquiry thus appears, at first glance, straightforward: Does the change urged by plaintiffs qualify as 'major'? If so, our work is done.

Gustavsen v. Alcon Laboratories, Inc., 903 F.3d 1, 10 (1st Cir. 2018) (citations omitted). *See also Yates v. Ortho-McNeil Pharmaceuticals, Inc.*, 808 F.3d 281, 298 (6th Cir. 2015) ("[Plaintiff's] post-approval design defect claim is clearly preempted by federal law. FDA regulations provide that once a drug . . ., is approved, the manufacturer is prohibited from making any major changes"); *Batoh v. McNeil-PPC, Inc.*, 167 F. Supp.3d 296, 320-322 (D. Conn. 2016) ("chang[ing] the active ingredient" would have been a "major change" requiring prior FDA approval).

Preemption cases specifically involving demands to modify Highlights have been uncommon, but have uniformly resulted in preemption. In *In re Zofran (Ondansetron) Products Liability Litigation*, 368 F. Supp. 3d 94, 127 (D. Mass. 2019), plaintiffs conceded preemption of any warning claim involving highlights. The issue was fully litigated in *Blackburn v. Shire US, Inc.*, 2017 WL 1833524, at *5-6 (N.D. Ala. May 8, 2017):

> [W]hen sufficient newly acquired information exists in order to support a label change under the CBE process, as has been plausibly pled here, the claim is not preempted. However, the same cannot be said with respect to Plaintiff's assertion that a change to the Highlights section would be permitted here. Where a private party seeks a label change which requires FDA approval, such as a change to the Highlights section, impossibility preemption exists. . . . The 'impossibility' inquiry turns on a private party's ability to act independently. It is of no consequence that the FDA may have allowed a change to the Highlights section of [the drug]. Because Defendants could not have independently changed the Highlights section of [the drug] in order to conform to state law, any argument that begins with the theory that Defendants could (or should) have changed the Highlights section of [the drug's] label ends in preemption.

Id. at *5-6 (citations omitted).

The same result was reached in *Patton v. Forest Laboratories, LLC*, 2018 WL 5270476 (C.D. Cal. May 10, 2018):

> [Defendant] also argues that Plaintiffs' failure-to-warn claim against it is preempted because: (1) [it] could not have 'unilaterally or independently change[d] the Highlights section; all changes to that section require FDA's pre-approval'. . . .
>
> In their Opposition, Plaintiffs do not address [defendant's] arguments concerning the permissible scope of label changes made by a NDA holder under the CBE process. Instead, Plaintiffs argue that their failure-to-warn claim is not preempted because 'Plaintiffs' contentions are that the Defendants did not comply with their obligations under Federal law regarding the labeling of [the drug]. . . .'

ISBN 1056 3059

> While it is obvious that the FDA, in approving the relevant [drug's] labeling, disagreed with Plaintiffs' contention that the labeling violates 'federal law' at the time it approved that labeling, even if the FDA were wrong, only the government (i.e., not Plaintiffs) may bring a lawsuit to enforce the FDCA and the FDA's regulations. Accordingly, Plaintiffs' failure-to-warn claim, as presently constituted, is preempted.

Id. at *16-17 (citations omitted). *See id*. at *4 ("NDA holders may not make any changes to the Highlights section of a drug's labeling without prior FDA approval"). *See also Patton v. Forest Laboratories, Inc.*, , 2018 WL 5269239, at *11 (C.D. Cal. Sept. 19, 2018) (plaintiffs conceded preemption of claims affecting highlights).

"Highlights summarizes the information from the FPI that is most important for prescribing the drug safely and effectively." 71 Fed. Reg. at 3922. "[I]t is critical to ensure accuracy and consistency in the information included in Highlights because it contains a summary of the most important information for prescribing the drug safely and effectively." *Id*. Thus, it would be impossible to maintain "Highlights [as] a concise extract of the most important information," *id*., if plaintiffs could demand different or additional warnings in the full labeling that would diverge from what is contained in unmodified, FDA-approved highlights. Thus, plaintiffs should not be able to evade preemption by ignoring disparities with highlights and demanding only changes to the rest of a drug's labeling. This need for consistency is analogous to the "sameness" requirement that drives preemption in generic drug cases—for highlights to serve their intended function, they must convey the same information (in abbreviated form) as is found in the rest of a drug's label.

Preemption exists "when a party cannot satisfy its state duties without the Federal Government's special permission and assistance, which is dependent on the exercise of judgment by a federal agency." *PLIVA, Inc. v. Mensing*, 564 U.S. 604, 623-34 (2011). Thus, the preemptive effect of this "independence principle" extends to any product liability claim demanding a change to a black box warning, contraindication, warning, adverse event (or anything else) that would require a corresponding modification to the drug's highlights section. As demonstrated above, the FDA's current regulatory regime concerning highlights meets *Albrecht*'s requirement 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." 139 S. Ct. at 1679.

Simply put, "to state a claim for failure-to-warn that is not preempted by the FDCA, a plaintiff must plead a labeling deficiency that Defendants could have corrected using the CBE regulation." *Gibbons v. Bristol-Myers Squibb Co.*, 919 F.3d 699, 708 (2d Cir. 2019) (quoting *Celexa*, 779 F.3d at 41). That regulation explicitly excludes any label change to the substance of the highlights section. Potentially, this involves considerable preemption, much more than suggested in *Wyeth v. Levine*, 555 U.S. 555 (2009)—which involved an older drug used in 2000, long before Highlights existed. Such older drugs are not subject to the Highlights requirement at all. 21 C.F.R. § 201.56(b) (new "labeling content and format requirements" apply only to post-2006 drugs). But the amended CBE provision says what it says, and the Supreme Court has put that sort of objection to rest:

> We acknowledge the unfortunate hand that federal drug regulation has dealt [these plaintiffs], and others similarly situated. But it is not this Court's task to decide whether the statutory scheme established by Congress is unusual or even bizarre. . . . But different federal statutes and regulations may, as here, lead to different pre-emption results. We will not distort the Supremacy Clause in order to create similar pre-emption across a dissimilar statutory scheme. As always, Congress and the FDA retain the authority to change the law and regulations if they so desire.

Mensing, 564 U.S. at 625-26 (citation, quotation, and footnote marks omitted).

Preemption of explicit plaintiff demands for changes to the Highlights section of drug labeling is the easy argument to win, and indeed to date it has never lost. However, now that *Albrecht* has clarified the standards for preemption, the broader argument should also be pursued, extending preemption to any informational claims that demand substantive changes that would necessarily require also modifying the language of the Highlights section. Defendants and their counsel should closely examine all allegations of "inadequate" warnings to determine whether such claims would create inconsistencies with Highlights information, and adjust their preemption strategy accordingly.

  ISBN 1056 3059