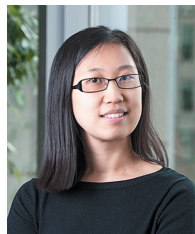


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FDA Proposes to Permit Generic Drug Manufacturers to Initiate Labeling Changes



BY DANIEL KRACOV, DANIEL PARISER, ANNA K. THOMPSON AND NARDA LUGO ALARCÓN PELHAM

Current Food and Drug Administration (FDA) regulations permit a new drug application (NDA) holder to submit a supplemental application to immediately implement certain labeling changes based on newly acquired information. Such changes are referred to as “changes being effected supplements” or “CBE-0 supplements.”¹ FDA reviews the CBE-0 supplement and may accept, reject, or request modifications to the labeling changes. In contrast, FDA has taken the position that an abbreviated new drug application (ANDA)

holder must, with very limited exceptions, have the “same” label as the reference listed drug (RLD).

In a November 13, 2013 *Federal Register* notice² FDA has proposed to amend its CBE-0 regulations to create “parity” among application holders with respect to certain safety-related labeling changes. ANDA holders, upon submission to FDA of a CBE-0 supplement, would be permitted to distribute revised generic drug labeling that differs in certain respects, and on a temporary basis, from the labeling of the RLD. If finalized, this proposal would have a major impact on the product liability landscape for drug manufacturers, engendering impor-

¹ 21 C.F.R. § 314.70(c) (2013). The current regulations provide that application holders may submit CBE-0 supplements for the following types of changes to drug labeling:

- 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);

Daniel Kracov is a partner with Arnold & Porter LLP in Washington. He also is a member of the advisory board for Bloomberg BNA's Pharmaceutical Law & Industry Report. Daniel Pariser is a partner with Arnold & Porter LLP in Washington. Anna K. Thompson and Narda Lugo Alarcón Pelham are associates with the firm.

- To add or strengthen a statement about drug abuse, dependence, psychological effect, or overdose;

- To add or strengthen an instruction about dosage and administration that is intended to increase the safe use of the drug product;

- To delete false, misleading, or unsupported indications for use or claims for effectiveness; or

- Any labeling change normally requiring a supplement submission and approval prior to distribution of the drug product that FDA specifically requests be submitted under this provision.

² Supplemental Applications Proposing Labeling Changes for Approved Drugs and Biological Products, 78 Fed. Reg. 67,985 (proposed Nov. 13, 2013) (to be codified at 21 C.F.R. pts. 314 & 601), available at <http://www.gpo.gov/fdsys/pkg/FR-2013-11-13/pdf/2013-26799.pdf> (11 PLIR 1369, 11/15/13).

tant shifts in the dynamics around drug labeling changes, and significantly increase the pharmacovigilance responsibilities of generic companies. **Comments on the proposal are due by January 13, 2014.**

Supplement Submissions by Generics for Safety-Related Labeling “Changes Being Effected”

As noted, the proposed rule would allow ANDA holders to submit a CBE-0 supplement—permitting immediate changes to labeling pending FDA review—for generic drug labeling, despite differences from the labeling of the RLD.³ Additionally, an ANDA holder which submits a CBE-0 supplement that meets the criteria in proposed 21 C.F.R. § 314.70(c)(6)(iii) could distribute “Dear Health Care Provider” letters regarding the labeling change.⁴ Some important elements of the proposal include:

- **Posting of Labeling Changes.** Under the proposal, FDA would promptly post on its website information regarding labeling changes proposed in a CBE-0 supplement to an NDA, ANDA, or BLA in order to “enhance transparency and facilitate ac-

³ *Id.* at 67,989–91. In situations where FDA has withdrawn approval of the NDA for the RLD, FDA may select a drug product approved through an ANDA to be the “reference standard.” The duty to maintain accurate labeling, however, will not differ based on whether ANDA holders are designated as the reference standard. The regulation clarifies FDA’s expectation of the contents of a CBE-0 supplement submitted under § 314.70(c)(6)(iii) by requiring that the CBE-0 supplement contain the following information:

- i. Identification of each application number to which the CBE-0 supplement pertains, where the NDA or ANDA holder submitting the application has multiple applications for a drug product or product class.
- ii. A description of the proposed labeling change in the CBE-0 supplement for posting on the FDA webpage. The description should include: (1) the affected section(s) of labeling, (2) the change, and (3) the source of the data.
- iii. Available data to support the labeling change proposed. Where the supplement is submitted at the request of FDA, the applicant should describe the change requested and reference communications with the agency.
- iv. A copy of the final printed labeling in structured product labeling (SPL) format, containing the changes being effected, along with a copy of the current labeling annotated with the proposed change(s).
- v. If the CBE-0 supplement is submitted by an ANDA holder, where approval of the NDA for the RLD has not been withdrawn, the ANDA holder must include a statement confirming notice, describing the change(s), has been sent to the NDA holder for the RLD.

⁴ *Id.* at 67,990. FDA proposes to expressly require that applicants submit a final printed labeling in SPL format at the time of their submission of the CBE-0 supplement, for access on the web page. Proposed §§ 314.70(c)(8) and 601.12(f)(2)(iii) place the burden on the applicant of verifying that correct information regarding labeling changes proposed in its CBE-0 supplement appear on the website.

cess by health care providers and the public to labeling containing newly acquired information about important drug safety issues so that such information may be used to inform treatment decisions.”⁵ The CBE-0 supplements would remain posted on FDA’s web page until FDA has completed its review and issued an action letter. If the CBE-0 supplement is approved, the final approved labeling will be made available on the proposed FDA website through a link to FDA’s online labeling repository at <http://labels.fda.gov/>.

- **Communications with NDA holder.** The proposed rule requires an ANDA holder to send notice of any labeling change proposed in the CBE-0 supplement to the NDA holder for the RLD concurrently with submission of the CBE-0 supplement to FDA, unless approval of the NDA has been withdrawn. The notice would include a copy of the information supporting the change. The NDA holder or any ANDA holder may submit a labeling supplement or correspondence to its NDA or ANDA regarding changes proposed in a CBE-0 supplement. If the NDA holder does not submit a supplement seeking approval for a related or conforming labeling change, FDA may send a supplement request letter to notify the NDA holder of new safety information. FDA may also send a letter, prompting submission of the CBE-0 supplement, where safety information would require a change to other drugs containing the same active ingredient.
- **Rejection of CBE-0 submissions.** The proposed rule also incorporates a mechanism for addressing situations where FDA rejects proposed CBE-0 submissions.⁶ Upon FDA’s determination that the CBE-0 supplement does not meet the criteria in the regulations, and upon FDA issuing a “complete response letter” to that effect, the supplement will be converted to a prior approval supplement and the manufacturer must stop distribution of the products with the revised labeling and take steps available to make the drug product available only with the previous version of the label.

Product Liability and Regulatory Ramifications

FDA’s proposed rule could have a significant effect on preemption of claims against generic manufacturers. In the last five years, the Supreme Court has addressed three times whether the Federal Food, Drug, and Cosmetic Act (FDCA) preempts state law claims involving prescription drugs. In 2009, the Court held that the FDCA did not generally preempt failure-to-warn claims involving brand-name prescription drugs because even after FDA approves the drug, branded manufacturers can unilaterally change the drug’s labeling through the CBE procedure.⁷ But two years later, the Court reached the opposite result in the context of generic drugs.

In *PLIVA Inc. v. Mensing*, the Court held that failure-to-warn claims against generic drug manufacturers were preempted.⁸ Because current federal regulations require generic labeling to be the same as that of the

⁵ *Id.*

⁶ *Id.* at 67,993.

⁷ *Wyeth v. Levine*, 555 U.S. 555 (2009) (7 PLIR 249, 3/6/09).

⁸ *PLIVA Inc. v. Mensing*, 131 S. Ct. 2567 (2011) (9 PLIR 805, 7/1/11).

brand-name drug, the generic manufacturers' ongoing duty of sameness prevents them "from independently changing their generic drugs' safety labels."⁹ Imposing state tort liability for failure-to-warn would conflict with this federal duty, the Court held, thereby preempting failure-to-warn claims in most circumstances.¹⁰ This year, the Court extended the preemption doctrine to "state-law design-defect claims [against generic manufacturers] that turn on the adequacy of a drug's warnings" and found that those claims were also preempted under federal law.¹¹ If generic companies could change labeling through a CBE-0 process, though, plaintiffs would likely argue that there is no conflict between complying with state tort law and federal regulations. Accordingly, plaintiffs would argue that, *Mensing* and *Bartlett* no longer preempt tort claims against generics.

Unsurprisingly, then, generic manufacturers have already suggested that they would challenge FDA's proposed rule as contrary to Hatch-Waxman's statutory "sameness" requirements.¹² No doubt these issues will play out in the courts for some time to come, should FDA adopt the proposed rule.

The adoption of FDA's proposed rule could also affect tort liability of branded companies, not just generics. The broad preemption of claims against generic companies had in recent years led to an effort by the plaintiffs' bar to try to hold branded companies liable for injuries caused from ingestion of the comparable generic product. The vast majority of courts have declined to hold a manufacturer liable for injuries that were not caused by its drug.¹³ But a handful of courts adopted the "innovator liability" theory to provide a cause of action against branded companies for plaintiffs taking generic drugs.¹⁴

Permitting generic companies to change labeling through the CBE process would undermine one of plaintiffs' core arguments behind "innovator liability": the notion that because generic companies simply must conform to branded labeling, it is appropriate to hold the branded drug company responsible for the generic's labeling deficiencies. For instance, earlier this year, in *Wyeth, Inc. v. Weeks*, the Alabama Supreme Court concluded that because of federal labeling regulations on sameness, "it is not fundamentally unfair to hold the brand-name manufacturer liable for warnings on a

product it did not produce . . . when those alleged misrepresentations were drafted by the brand-name manufacturer and merely repeated by the generic manufacturer."¹⁵ In addition, if *Bartlett* and *Mensing* did not bar claims against generic manufacturers, plaintiffs would once again be able to more broadly assert tort claims against the manufacturer of a generic product prescribed to a plaintiff. The wider availability of ordinary tort liability against generic companies could lessen the impetus behind plaintiffs' lawyers push for the novel "innovator liability" theory.

On the other hand, the prospect of generic companies unilaterally proposing labeling changes that might be applied to a branded product's labeling creates an opportunity for mischief. Plaintiffs no doubt would seek to take advantage of any difference in timing, position or proposals between generic and branded companies on labeling issues in product liability suits. For example, if an ANDA holder were to submit a CBE-0 supplement, plaintiffs might argue that the branded company should have recognized the issue and proposed a change much earlier, and claim that the branded company is liable for failure to warn as a result. In short, the proposed rule has the potential to significantly impact the product liability landscape, and is worth close attention from those defending product liability suits in both sectors of the industry.

The proposed rule would also have an impact on the regulatory risks and burdens on both brand and generic companies. To date, the framing of the label has largely been a matter of interaction between the brand company and FDA. To the extent a labeling change is warranted, the brand company may control the initial framing of the labeling change—subject to FDA review and negotiations. Under this proposal, however, branded companies will need to address—and at times rapidly rebut—labeling changes that are initiated by others. Given that NDA holders typically have much greater pharmacovigilance capabilities and resources to analyze issues such as causation, it is likely that we will see many ANDA holder-initiated CBE-0 labeling changes subject to significant change or reversal upon engagement by the NDA holder and agency. Moreover, while temporary labeling changes are posted by FDA, companies will need to consider the implications of such changes for labeling in other jurisdictions, as well as in the context of promotional and medical affairs activities.

With respect to generics, while such companies have had an obligation to report adverse events, the need to analyze adverse event data and submit CBE-0 labeling changes will require a level of pharmacovigilance and regulatory capabilities that are not currently well-established in many generic companies. A failure to take on those responsibilities could result in significant liability.

FDA has proposed that any final rule based on this proposal would become effective 30 days after the date of its publication in the *Federal Register*. However, as noted, any finalization of this proposal will likely result in a generic industry challenge to FDA's authority to implement a generic CBE-0 framework in light of statu-

⁹ *Id.* at 2577.

¹⁰ *Id.* at 2570.

¹¹ *Mutual Pharm. Co. v. Bartlett*, 133 S. Ct. 2466, 2470 (2013) (11 PLIR 799, 6/28/13).

¹² See, e.g., Stmt. from Ralph G. Neas, Pres. & CEO, Generic Pharmaceutical Ass'n (Nov. 8, 2013), available at <http://www.gphaonline.org/gpha-media/press/statement-by-ralph-g-neas-president-and-ceo-generic-pharmaceutical-association-regarding-the-fda-proposed-update-to-generic-labeling-regulations>.

¹³ See, e.g., *Foster v. American Home Products Corp.*, 29 F.3d 165 (4th Cir. 1994); see also, e.g., *Bell v. Pfizer, Inc.*, 716 F.3d 1087 (8th Cir. 2013); *Guarino v. Wyeth*, 719 F.3d 1245 (11th Cir. 2013); *Demahy v. Schwarz Pharma, Inc.*, 702 F.3d 177 (5th Cir. 2012); *Smith v. Wyeth, Inc.*, 657 F.3d 420 (6th Cir. 2011); *Phares v. Actavis-Elizabeth LLC*, 892 F. Supp. 2d 835 (S.D. Tex. 2012); *Hogue v. Pfizer, Inc.*, 893 F. Supp. 2d 914 (S.D. Ohio 2012); *Schrock v. Wyeth, Inc.*, 601 F. Supp. 2d 1262 (W.D. Okla. 2009), *aff'd* 727 F.3d 1273 (10th Cir. 2013).

¹⁴ See, e.g., *Conte v. Wyeth, Inc.*, 168 Cal. App. 4th 89 (2008); see also *Kellogg v. Wyeth*, 762 F. Supp. 2d 694 (D. Vt. 2010); *Wyeth, Inc. v. Weeks*, — So. 3d —, 2013 WL 135753 (Ala. Jan. 11, 2013) (11 PLIR 72, 1/18/13).

¹⁵ *Weeks*, 2013 WL 135753, at *19. The Alabama Supreme Court granted rehearing in the *Weeks* case and oral argument was held September 4, 2013.

tory language relating to the generics and RLDs having the “same” labeling in most circumstances.¹⁶

¹⁶ 21 U.S.C. § 355(j)(2)(A)(v).