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Amendments To Labeling: Implications For Preemption Defense

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In what is sure to be seen as more ammunition for the battle over the preemption defense, the Food and Drug Administration (FDA) proposes rulemaking to codify its longstanding view that changes to labeling for approved products (*i.e.* drugs, biological products, and medical devices) may be made before agency review only as a narrow exception to the requirement of FDA approval and under limited circumstances. In its proposed rule announced last week, a supplemental application to change labeling may be used to add or strengthen a contraindication, warning, precaution, or adverse reaction in advance of the agency's review of such change, but only based on newly acquired and novel safety information and only if there is sufficient evidence of a causal association with the drug, biologic, or device. The agency wishes to formalize this "narrow exception" position. *See* 73 Fed. Reg. 2848 (Jan. 16, 2008).

In very limited circumstances, under current regulations, a sponsor may implement changes to labeling of an approved product before FDA approves the change. For approved drugs, such changes may be implemented upon the agency's receipt of a supplemental new drug application (sNDA) specifying the change. 21 C.F.R. § 314.70(c)(6)(iii). The supplements are referred to as "changes being effected supplements" or "CBE supplements." Under the corresponding regulation for biological products, 21 C.F.R. § 601.12(f)(2), products with certain labeling changes may be distributed before FDA approval. Similarly for devices, 21 C.F.R. § 814.39(d) provides that certain labeling changes may be placed into effect upon submission of a PMA supplement, but before the sponsor's receipt of a written FDA order approving the supplement.

FDA views the CBE supplement as a mechanism designed to provide information to FDA so the agency can decide when safety information should be included in labeling. FDA views itself as having authority to accept, reject, or request modification to the proposed changes as the agency deems appropriate and to bring an enforcement action if the added information makes the labeling false or misleading. 21 U.S.C. § 352(a).

In the proposed regulation, supplemental labeling changes will be permitted only to reflect "newly acquired" safety information for which the evidence of a causal association "satisfies the standard under 201.57(c) of this chapter." Section 314.70(c)(6)(iii)(E). Analogous language is used for a premarket approval of medical devices.

"Newly acquired information" is defined to mean "data, analyses, or other information not previously submitted to the agency, which may include (but are not limited to) data derived from new clinical studies, reports of adverse events of a different type or greater severity or frequency that have been previously included in submissions to FDA, or new analyses of previously submitted data (e.g. meta analyses)." Section 314.3(b). In its preamble, FDA explains that it considers information "newly acquired" if it consists of data, analyses, or other information not previously submitted to the agency, or submitted within a reasonable time period prior to the CBE supplement, that provides novel information about the product, such as a risk that is different in type or severity than previously known risks about

the product. Information that is merely cumulative of data previously submitted, however, or reports of adverse events that are consistent in type, severity, and frequency with information previously provided, may not constitute newly acquired information appropriate for a CBE supplement.

Comment

FDA has recognized that, just as there are risks when labeling fails to express sufficient caution, there are risks when labeling overemphasizes risk. Congress charged FDA not merely with reducing the risk of adverse effects of drugs, devices, and biological products, but with optimizing their use. FDA approval of labeling reflects the agency's expert judgment that the text of the label strikes the proper balance between safety and efficacy. If every state can second-guess the agency and impose new or different labeling requirements, conflicting standards would arise, creating large practical problems for companies and impeding pursuit of the agency's public health goals.

FDA's proposal adds welcome clarity to the applicable rules. Equally or more important, its language is helpful in advancing the argument that states are not at liberty to impose new or different labeling requirements on life sciences companies.

In the background discussion of its proposal, FDA has provided language likely to be quoted in litigation giving rise to preemption disputes. It wrote that "[a]llowing sponsors to unilaterally amend the labeling for approved products without limitation—even if done to add new warnings—would undermine the FDA approval process required by Congress [P]ermitting a sponsor to unilaterally rewrite the labeling . . . would disrupt FDA's careful balancing of how the risks and benefits of the product should be communicated." 73 Fed. Reg. 2849.

When defendants raise preemption as a defense to plaintiffs' failure to warn claims, they may argue that a state labeling requirement different from the labeling approved by FDA conflicts with federal requirements. Moreover, once labeling is approved, "additional disclosures of risk information can expose a manufacturer to liability under the act if the additional statement is unsubstantiated or otherwise false or misleading." 71 Fed. Reg. 3922 at 3935 (Jan. 24, 2006). FDA's proposed rulemaking draws bright lines around what claims it considers preempted:

To the extent that state law would require a sponsor to add information to the labeling for an approved drug or biologic without advance FDA approval based on information or data as to risks that are similar in type or severity to those previously submitted to the FDA, or based on information or data that does not provide sufficient evidence of a causal association with the products, such a state requirement would conflict with federal law. In such a situation, it would be impossible to market a product in compliance with both federal and state law, and the state law would "stand[] as an obstacle to the accomplishment and execution of the full purposes and objectives of Congress," *Hines*, 312 U.S. at 67. Moreover, such a state law requirement relating to a medical device would constitute a requirement that is different from, or in addition to, a federal requirement applicable to the device, and which relates to the safety or effectiveness of the device. 21 U.S.C. 360k(a).

73 Fed. Reg. at 2853.

FDA's rulemaking should be helpful in countering plaintiffs' argument that manufacturers are at liberty to strengthen or add new warnings at any time.

FDA's codified position on CBE supplements sharpens the battle lines over the preemption defense.

Cases currently pending before the U.S. Supreme Court, including *Riegel v. Medtronic, Inc.*, No. 06-171, and *Warner-Lambert Co. v. Kent*, No. 06-1498, may shed further light on the scope of federal preemption afforded by FDA-approved labeling.

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