Proposed Rule Amending Regulations Governing Supplemental Applications Proposing Labeling Changes For Approved Drugs, Biologics, and Medical Devices

The FDA has proposed important new regulatory amendments to reaffirm existing law relating to when sponsors of new drugs, biologics, and medical devices may employ the “changes being effected” (“CBE”) supplement process to change the labels on their products without FDA pre-approval. The proposed amendments both elaborate on when such CBE supplements are appropriate and supply an important new weapon to the arsenals of defendants seeking dismissal of certain state law tort claims alleging defects in the labeling of medical products based on federal preemption.

The FDA’s CBE regulations allow sponsors of approved new drugs, biologics, and medical devices to make certain changes to the labeling of those products—including, in some circumstances, to strengthen safety language—without prior FDA approval. See 21 C.F.R. 314.70; 21 C.F.R. 601.12; 21 C.F.R. 814.39. For quite some time now, FDA consistently has held the position that the CBE supplement process is only intended to dispense with the general requirement of agency preclearance of a change to a product label when the information that is the basis for the enhanced warning is “newly discovered.” See, e.g., 47 Fed. Reg. 46622, 46623, 46635 (Oct. 19, 1982); Draft Guidance: Modifications to Devices Subject to Premarket Approval (PMA)—The PMA Supplement Decision-Making Process (March 9, 2007) (http://www.fda.gov/cdrh/ode/guidance/1584.pdf). Moreover, it also has long been clear that sponsors may strengthen safety language on their labels only when sufficient scientific evidence supports the change; otherwise, they are subject to potential legal liability if FDA—which possesses ultimate authority to approve or reject the change—determines that the change was not justified. See, e.g., 21 U.S.C. 352(a); 71 Fed. Reg. 3922, 3934 (FDA Jan. 24, 2006) (“[T]he determination whether labeling revisions are necessary is, in the end, squarely and solely FDA’s * * *.”).

FDA now has proposed to amend the CBE regulations to reaffirm that the CBE supplement process is to serve as a “narrow exception” to the baseline rule requiring FDA pre-approval of any labeling change, and is not a mechanism for sponsors “unilaterally” to amend drug labeling “without limitation.” 73 Fed. Reg. 2848, 2849 (FDA Jan. 16, 2008). Specifically, the amendments (i) “reaffirm [FDA’s] longstanding position that a [CBE supplement] is appropriate to amend the labeling for an approved product only to reflect newly acquired information” and (ii) clarify that such a supplemental application may be used to add or strengthen a contraindication, warning, precaution, or adverse reaction only if there is sufficient evidence of a causal association with the drug, biologic, or device.” Id. at 2848 (emphasis added).

In the proposed amendments, FDA invites comment on (i) when information is “newly acquired” and (ii) the appropriate standards for determining whether evidence of a causal association is sufficient. See 73 Fed. Reg. at 2850–2851. (Comments are due by March 17, 2008. Id. at 2848.). The Agency also provides
some detailed preliminary guidance on these questions. Information is “newly acquired” if it was “not previously submitted to the agency” (or not “submitted within a reasonable time period prior to the CBE supplement”) and “provides novel information about the product.” Id. at 2850. Specifically, a supplemental CBE may be warranted where the “new” information consists of (i) the results of a post-market study demonstrating that an approved product “has a more severe risk of a significant adverse reaction than previously known,” (ii) “reports of adverse events of a different type or greater severity or frequency than previously included in submissions to FDA,” or (iii) “significant new analyses of previously submitted data * * * that provide novel information about the product.” Id. By contrast, no supplemental CBE is warranted where the “new” information is “cumulative of” or “consistent with” information previously provided to FDA. Id. The proposed amendments also reaffirm that a sponsor of a drug or biologic product may use the CBE process to strengthen safety language only if the sponsor possesses evidence that satisfies 21 C.F.R. § 201.57, which requires “reasonable” evidence of a causal association between a product and a hazard or adverse reaction (see 73 Fed. Reg. at 2850); likewise, the proposed amendments reaffirm that the restrictions relating to evidentiary sufficiency that apply to CBE supplements by sponsors of medical devices are similar (see id. at 2851).

The proposed amendments are important both because they reaffirm and elaborate on existing standards for when a supplemental CBE is (and is not) appropriate and because they have the potential, in certain circumstances, to undermine plaintiffs’ arguments against federal preemption of certain state law tort claims alleging that medical product labeling is defective. Preemption is warranted in the case of new drugs and biologics where the state tort claim “conflicts” with the federal regulatory scheme; under the different regime governing medical devices, preemption also is warranted where the state law requirement “is different from, or in addition to,” a federal requirement applicable to the device. See 21 U.S.C 360k(a); Medtronic, Inc. v Lohr, 518 U.S. 470 (1996). In both contexts, plaintiffs traditionally have asserted broad arguments against federal preemption based on the existence of the CBE supplement process. For example, in the context of state law tort suits alleging that a drug or biologic sponsor failed to include an adequate warning on its product label, plaintiffs often oppose preemption by arguing that the defendant sponsor unilaterally could have added the allegedly required warning to the product label through the CBE supplement process. Some courts have rejected preemption at least in part in reliance on this argument, even where the alleged information that is the basis for the enhanced warning is not “newly discovered.” See, e.g., McNellis v. Pfizer, Inc., 2006 WL 2819046, at *7 (D.N.J. Sep. 29, 2006).

Anti-preemption arguments based on the CBE regulation no longer will be plausible in cases in which FDA already has reviewed essentially the same risk information as that advanced by plaintiffs as supplying the basis for the allegedly required strengthened warning. See 73 Fed. Reg. at 2853 (“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 product, such a state requirement would conflict with federal law.”); id. (such a state requirement applied to a medical device would be preempted as “a requirement that is different from, or in addition to, a federal requirement applicable to the device”). The anti-preemption argument based on the CBE regulation—assuming that it ever was viable, which we do not believe—now will be potentially helpful to plaintiffs only in those circumstances in which a manufacturer comes into possession of (i) information suggesting that the product is associated with a risk that is new or
significantly increased, as well as (ii) sufficient supporting scientific evidence of a causal relationship between the new or heightened risk and the product. The agency’s emphasis that the proposed amendments reflect existing practices means that, if enacted, the amended regulations will be useful in helping courts to understand how the CBE supplemental process is intended to function, even in those cases in which the old, unamended regulations apply.

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