DechertOnPoint

January 2008 / Issue 36

A legal update from Dechert's Mass Torts and Product Liability Group

Something Old is New Again: FDA Proposes Codifying "Longstanding View" of CBE Supplements

FDA has just proposed amendments to the regulations governing a drug, biologic, or medical device manufacturers' ability to implement labeling changes in advance of agency review and approval. *See* Supplemental Applications Proposing Labeling Changes for Approved Drugs, Biologics, and Medical Devices ("CBE Amendment"), 73 Fed. Reg. 2848 (Jan. 16, 2008) (to be codified at 21 CFR Parts 314, 601, and 814). The purpose of these amendments, proposed on January 15, 2008, is not to alter the requirements for CBE supplements but instead to codify the Agency's longstanding position and practice regarding them. This proposed codification and the Agency's accompanying summary may hold significant value for manufacturers throughout the litigation process.

Changes to a product label before review and approval by FDA are known as "changes being effected," commonly referred to as "CBE supplements." Under these procedures, FDA permits manufacturers to implement labeling changes simultaneously with the submission of the change to FDA for review and approval. FDA still holds the power to reject or modify the label change. As FDA explicitly states in the proposed amendment, it has viewed CBE supplements since their inception as a "narrow exception" to the general requirement that FDA approve all label changes prior to dissemination. CBE Amendment at 2849. This view of CBE is the only role consistent with FDA's near-total authority over labeling. Unfortunately for manufacturers, FDA has never explicitly codified this "narrow exception" concept, instead highlighting it in the preamble to the original proposed and final rules.

Plaintiffs' lawyers have frequently relied on the lack of explicit limiting language to convince some courts that manufacturers are permitted to amend a product label to strengthen or add warnings at any time based on any information. This argument is critical at more than one stage of the litigation process. Before trial, it can undermine defendants' attempts to argue that plaintiffs' state law failure-to-warn claims are preempted by a conflicting FDA regulatory scheme. *See, e.g., Levine v. Wyeth*, 2006 WL 3041078 at ¶ 13 (Vt. Oct. 27, 2006) (finding no conflict preemption because CBE procedure allows and arguably encourages manufacturers to strengthen warnings that are deficient despite FDA approval). If manufacturers are capable of implementing stronger or additional warnings at any time, then state law claims based on a failure to make such a change do not conflict with FDA's authority to regulate product labels. If, however, the CBE procedures do not permit a change, a state law requirement to do so directly conflicts with FDA authority and would thus be preempted.

FDA's summary makes clear its belief that a state law requiring a labeling supplement that the CBE procedure does not permit should be 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 product, such a state requirement would conflict with federal law." CBE Amendment at 2852.

Plaintiffs' lawyers have also successfully used the artificially broad CBE argument at trial. Many manufacturers rely heavily on FDA approval and the broader FDA regulatory story as a significant theme in their trial presentation. If a jury understands that FDA has complete authority over product labeling, and the manufacturer timely submitted all relevant data to FDA, it would be unjust, defendants argue, for that jury to hold the manufacturer responsible for FDA's labeling decisions. If plaintiffs can improperly persuade juries that defendant manufacturers could have implemented stronger or additional warnings without going through FDA, defendants lose a critical piece of defense strategy.

While some judges have acknowledged that the CBE procedure is a narrow exception to broader FDA regulatory authority, others have broadly characterized a manufacturer's authority while denying defendants' claims to the contrary. *See Levine*, 2006 WL 3041078 at ¶13; *Laisure-Radke v. Par Pharmaceutical, Inc.*, 2006 WL 901657 at *4 (W.D. Wash. Mar. 29, 2006); *Caraker v. Sandoz Pharmaceuticals Corp.*, 172 F. Supp.2d 1018, 1033-34 (S.D. Ill. 2001).

The proposed amendments clarify in two significant ways how the FDA considers—and has always considered—CBE supplements to be a narrow exception to the broader regulatory scheme. First, a CBE supplement may add ***only*** "newly acquired information." The proposal defines "newly acquired information" as "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 than previously included in submissions to FDA, or new analyses of previously submitted data (*e.g.,* meta-analyses)." CBE Amendment at 2850. Data or information that is merely cumulative of that previously submitted to FDA, including adverse events that are "consistent in type, severity, and frequency" of those previously submitted, cannot be the basis of a CBE supplement. *Id.*

Second, the proposed amendment states that CBE supplements may be used to amend contraindications, warnings, precautions or adverse reactions if the newly acquired information provides "evidence of a causal association [that] satisfies the standard for inclusion in the labeling under 201.57(c)." By pointing to this section of the CFR, FDA is requiring that the scientific evidence needed to support changing any of these labeling sections via a CBE supplement must, "at a minimum," be the same type of evidence needed to satisfy the standard that governs inclusion in those sections in the original label. *Id.* at 2851. Importantly, with regard to changing the warnings and precautions section via a CBE supplement, this means that the newly acquired information must provide "reasonable evidence of a causal association with the drug."

Finally, FDA makes a number of significant statements explaining the bases for its proposed amendments. FDA highlights that the CBE supplement procedure must be interpreted and enforced in the context of FDA's mandate and accompanying regulatory scheme. FDA states that it is "the expert public health agency charged by Congress with ensuring that . . . labeling for approved products appropriately informs users of the risks and benefits of the product," and "[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." *Id.* at 2849 (emphasis added). Most significantly, FDA undercuts plaintiffs' lawyers' view that the CBE procedure is a blank slate for new warnings by clarifying that a CBE supplement is "a mechanism primarily designed to provide information to FDA so that the agency can decide when safety information should be included in the labeling for a product." *Id.* at 2849. In an acknowledgment of the "real world" process of CBE supplement label changes, FDA notes that it "encourages sponsors to consult with FDA" before implementing new language via the CBE process, and "sponsors typically do so." *Id.* Finally, FDA provides additional support for a key consideration that can be especially important (and especially difficult) to explain to juries—overwarning. The FDA's summary states that "[e]xaggeration of risk, or inclusion of speculative or hypothetical risks, could discourage appropriate use of a beneficial drug, biologic, or medical device or decrease the usefulness and accessibility of important information by diluting or obscuring it." *Id.* at 2851.

It is important to remember that FDA "does not consider this amendment to be a substantive change." *Id.* Parties to existing litigation in which CBE label changes are a relevant issue can look to this document as support for FDA's "longstanding" view of the CBE process as a narrow exception to FDA's larger and pervasive regulatory authority over product labeling.

The proposed amendment to the language of the CBE regulations to explicitly include the narrowing language regarding new information and causal relationship provides nothing new to FDA's view of the CBE procedure. Defendant manufacturers, however, should find this new regulatory language, along with the language supporting the amendment, a potent new weapon in the fight

against plaintiffs' lawyers' arguments both in the preemption context and at trial.

The proposed amendments, currently available at http://www.fda.gov/OHRMS/DOCKETS/98fr/E8-702.pdf, allow for the submission of written or electronic comments by March 17, 2008.

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