New Jersey Law Journal

VOL. CXC– NO.12 – INDEX 1018 DECEMBER 17, 2007 ESTABLISHED 1878

Product Liability & Toxic Torts

The New Labeling Law

FDA's authority to regulate label changes and what it means to the pharmaceutical industry

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On September 27, President Bush signed into law the Food & Drug Administration Amendments Act of 2007 (FDAAA), Public Law 110-85. It has been widely reported that the impetus for much of this statute was Merck's withdrawal of Vioxx from the market. This characterization does not seem entirely fair, given that a significant component of the FDAAA was the renewal and expansion of the User Fee Program under the 1992 Prescription User Fee Act and the Medical Device User Fee and Modernization Act. That being said, there is little doubt that important sections of the statute pertain to the safety issues that were front and center in the Vioxx litigation, particularly post-marketing studies and product labeling. Indeed, Title IX of the FDAAA is devoted solely to enhancing the Food & Drug Administration's oversight of drugs already on the market. Among other things, it gives FDA the authority to require post-market studies and clinical trials, to review direct-to-consumer advertising, and to mandate a risk evaluation and mitigation strategy when it becomes necessary to ensure that the benefits of a drug outweigh its risks.

Of particular interest to any lawyer whose practice involves prescription drugs are the provisions of Title IX, which enhance FDA's ability to implement label changes based on "new safety information." 21 U.S.C. § 355(o)(4). Given the current political and litigation climate, it would be reasonable to expect that FDA would invoke these provisions rather liberally. This article describes the new labeling law and discusses its significance to the pharmaceutical industry.

Section 901(a) of the FDAAA — to be codified as 21 U.S.C § 355(o)(4) — authorizes the FDA to require label changes based on "new safety information." The FDAAA defines "new safety information" as information regarding: (1) a serious risk or an unexpected risk associated with use of a drug to which the agency has become aware since the drug was approved, or since the risk evaluation and mitigation strategy was required or last assessed; or (2) the efficacy of the approved risk evaluation and mitigation strategy. 21 U.S.C. § 355-1(b)(3). This is a mouthful. New safety information can derive from a wide range of sources, including a post-marketing study or clinical trial, an adverse event report, the peer reviewed literature, or "other scientific data." Since the FDA can now require a post-marketing study based on information concerning a chemically or pharmacologically-related drug (21 U.S.C. § 355(o)(3)(A)), and new safety information can be based on the results of such a study, it may follow that the agency can require a label change based on the information regarding a class of drugs rather than the drug itself.

When the FDA becomes aware of new safety information it believes should be included in a drug label, it must provide appropriate notification to the manufacturer — the entity that holds the NDA. 21 U.S.C. § 355(o)(4)(A), et seq. Within 30 days of receiving such notification, the manufacturer must submit to the FDA a supplement with a revised label to incorporate the new safety information. While the statute provides for the supplement to include changes to "box warnings, contraindications, warnings, precautions or adverse reactions," there is no requirement that the agency tell the manufacturer where in

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the package insert the new information should be placed or what it should say. These decisions are reasonably left to the discretion of the manufacturer. In lieu of a supplement, the manufacturer can submit a statement to the agency detailing the reasons why it believes the requested label change is not appropriate. Such a statement must be received by FDA within 30 days that notice of a label change is given.

The FDAAA directs the FDA to review the supplement and/or statement and initiate discussions with the manufacturer if the agency disagrees with the position taken in the submissions. Congress clearly intended for the discussions to be of limited duration, as the statute provides that they should not, as a general matter, be extended for more than 30 days absent a determination by the FDA that an "extension of such discussion period is warranted."

Within 15 days after the discussions are concluded, the FDA may issue an order directing the manufacturer to make a specific label change. Upon receipt of such an order, the manufacturer essentially has two choices: (1) comply and submit a supplement within 15 days; or (2) appeal the decision within five days. If the manufacturer fails to either appeal or submit the requested supplement, it is considered to be violation of the statute and has potential exposure for selling a "misbranded" drug.

The civil penalties for such violations are not inconsequential. Section 902(b) of the FDAAA provides for civil penalties of not more than $250,000 per violation, not to exceed $1 million for all violations addressed in a single proceeding. 21 U.S.C. § 333, as amended by FDAAA § 902(b). If the violation continues despite written notice, the manufacturer can be subject to a penalty of $250,000 for the first 30-day period, doubling every 30 days thereafter, subject to a $10 million cap in any single proceeding. In assessing the amount of the penalty, the agency can consider the manufacturer's effort to address and remedy the violation.

These provisions are significant in several ways. First, they reflect the intent of Congress that the FDA be more proactive in its initiation of safety-related label changes. Prior to the FDAAA, a manufacturer could seek approval for a label change through a prior approval supplement. Alternatively, a manufacturer could proceed without FDA approval to "add or strengthen a contraindication, warning, precautionary adverse reaction…" by notifying the FDA of the change through a "Changes Being Effected" submission. 21 C.F.R. § 314.70(c)(6)(iii). To be sure, nothing previously prohibited the FDA from initiating safety-related label changes, and there are many examples where FDA used the prior approval supplement to accomplish this. Yet, the FDAAA directs the FDA to act in situations it believes warrant safety-related label changes.

Second, the regulations did not provide a deadline for the FDA to approve a prior approval supplement or CBE, and some lawmakers complained that label negotiations between the agency and industry took too long, particularly in the case of Vioxx. See Todd Zwillich, "U.S. Lawmakers Tackle Safety Reforms at the FDA," *The Lancet,* June 16-22, 2007, at 1989. Congress has now made it quite clear that it expects label discussions to be focused and resolved in a defined period of time. Indeed, the FDA can accelerate the timeline prescribed in the statute if the agency concludes that the labeling changes are necessary to protect the public health. 21 U.S.C. § 355(o)(4)(H).

Third, the statute appears to vest the reviewing divisions within the Center for Drug Evaluation and Research (the division with the authority to approve the drug) with primary responsibility for identifying and initiating safety-related label changes. The statute requires that the decision be made by an individual at division director level or above. No mention is made of the role of the Office of Surveillance and Epidemiology, known formerly as the Office of Drug Safety. It will be interesting to see the role, if any, this office plays in implementing the statute.

Finally, one cannot help but wonder whether this new framework will impact the viability of the pre-emption defense. A written record of discussions between the agency and the manufacturer may provide a record to show that the FDA considered and rejected an alternative warning that plaintiffs claim should have been implemented. Such evidence would support a pre-emption defense. See e.g., *Colacicco v. Apotex, Inc*., 432 F. Supp. 2d. 514, 527-28 (E.D. Pa. 2006) (court accepted pre-emption defense because FDA rejected warning endorsed by plaintiff).

There has been some noise, however, that the Rule of Construction — a seven-line paragraph at the end of the label change section — was intended to undermine the pre-emption defense, because it preserves the responsibility of manufacturers to maintain their labels in accordance with current label requirements, particularly through CBEs for which FDA approval is not required. See 153 Cong. Rec. S. 11831, at 2-3, 8 (Senator Edward Kennedy (D-Mass.) and Senator Patrick Leahy (D-Vt.) argued that this legislation does not intend to alter existing state law duties of the drug manufacturers). The Rule of Construction states:

> This paragraph shall not be construed to affect the responsibility of the responsible person or the holder of the approved application under Section 505(j) to maintain its label in accordance with existing requirements, including subpart B of Part 201 and Sections 314.70 and 601.12 of Title XXI, Code of Federal Regulations (or any successor regulations). 21 U.S.C. § 355(o)(4)(I).

While a full analysis of pre-emption is beyond the scope of this article, it seems highly unlikely that Congress intended that this paragraph do anything other than preserve the obligations of manufacturers to continue to comply with current label requirements. For a more complete and entertaining analysis of the pre-emption issue see "Drug and Device Law: The 2007 FDCA Amendments and Preemption," (Oct. 18, 2007), at http://druganddevicelaw.blogspot.com/2007/10/2007-fdca-amendments-and-preemption.

Enhancing post-marketing drug safety is conceptually a good idea. How these provisions will work in practice and their impact on product liability and mass tort litigation is less clear and will likely play out in the months and years to come. In the meantime, it is useful for counsel to be aware of and anticipate their application to safety issues that often arise in the post-market arena. ■