



FDA Proposes Revised CBE Rules and Reiterates Preemptive Authority

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Over the past few years, the U.S. Food and Drug Administration (FDA) has issued a number of new guidances and rules about safety communications for prescription medical products, including a more intense focus on identifying and communicating post-marketing risks. In 2007, the agency received enhanced authority to do so under the 2007 Food and Drug Administration Amendments Act (FDAAA).

More recently, on Jan. 15, 2008, the FDA proposed revised rules that take a harmonized approach to “changes being effected supplements,” or “CBE supplements,” which modify the labeling of safety risks at post-approval stages in advance of agency review of the labeling change.¹

The procedures for CBE supplements have long been in effect to add or strengthen a contraindication, warning, precaution or adverse reaction,² although there have not been clear regulatory standards for doing so. The proposed rules fill in the standards in several key respects: they harmonize the labeling standards across product life-cycle stages by emphasizing the same criteria at the post-approval stage as are found in pre-approval standards; they

emphasize that there must be sufficient evidence of a causal association between the product and an adverse event before a label may be supplemented under the CBE rules; and they focus on implementing a supplement only where justified by newly acquired evidence.

At the same time, in setting forth criteria for CBE supplements, the agency reiterated its current preemption position—that FDA has the ultimate authority to regulate safety labeling, and that its labeling rules preempt any competing state laws. The agency’s view of preemption has become a hot topic since FDA issued an overview position in January 2006,³ leading to a spate of federal decisions regarding the implied preemption defense in prescription drug product liability cases, and culminating in the pending review of the issue by the U.S. Supreme Court.⁴ FDA’s newest statement about preemption, as set forth in the proposed regulations, may have added impact in light of the pending cases.

CBE Supplements

Before a sponsor makes almost any post-approval labeling change, it must submit a supplemental application to FDA and receive approval for the

change. At the same time, the regulatory scheme allows a CBE supplement as an exception, so that sponsors may make a labeling change before receiving FDA approval to do so (although FDA may affirm or reject the change after review of it).⁵ In announcing the proposed regulations, the agency articulated what type of data would justify a CBE supplement:

[A] sponsor may utilize the limited CBE provisions only to reflect *newly acquired* information. FDA intends to consider information ‘newly acquired’ if it consists of data, analyses, or other information not previously submitted to the agency, or submitted within a reasonable time 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.⁶



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Cumulative data are not considered newly acquired, although “significant new analyses” of previously submitted data, including meta-analyses, meet the criteria.

Focus on Causal Association

At the same time, under the proposed regulations, to justify a supplemental change there must be “sufficient evidence of a causal association with the drug biologic or medical device.”⁷⁷ The focus on causal association takes its lead from the core labeling rules, which generally rely on evidence of causation before allowing a safety risk to be labeled, although the language from rule to rule certainly varies. As examples, the regulations with respect to recently approved prescription drugs speak of “warning about a clinically significant hazard as soon as there is reasonable evidence of a causal association with a drug” although a causal association need not be “definitely established.”⁷⁸ The rule for labeling adverse reactions requires only that the reactions be “reasonably associated with use of a drug” or “some basis to believe there is a causal relationship between the drug and the occurrence of the adverse event.”⁷⁹ The rule about contraindications states yet another standard, for sponsors to list “[k]nown hazards and not theoretical possibilities,” and not “relative of hypothetical hazards.”⁸⁰ The current rules for biologics follow a similar approach,⁸¹ as do the guidances applicable to medical devices. For device warnings, there should be “reasonable evidence of an association of a

serious hazard with the use of the device” without proof of a causal relationship, and adverse reactions should be “reasonably associated with use of a device.”⁸²

The proposed regulations harmonize standards among a broad range of prescription products, including drugs, biologics and medical devices, honing in on the causal connection raised by newly acquired evidence, regardless of the type of medical product.

Preemption Reiterated

The focus on harmonizing rules across prescription products shows, as well, in FDA’s statement about preemption, a doctrine that the agency would apply to all prescription products. Citing Executive Order 13132, FDA reiterated that the proposed rules fall under the doctrine of conflict preemption, i.e., the rules preempt state law where it “stands as an obstacle to the accomplishment and execution of the full purposes and objectives of Congress.”⁸³

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. 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.’⁸⁴

These statements highlight FDA’s primacy in reviewing and approving a label based on a scientifically rigorous array of data and the agency’s continuing role as the single entity that has the legal authority to vet the connection between scientific data and product labels for prescription products. In FDA’s view, the regulatory scheme gives it exclusive authority over the labeling of drugs, biologics and medical devices, even when there is not an expressly applicable preemption provision.⁸⁵

Agency pronouncements about labeling and preemption affect matters beyond the regulatory arena, especially because Congress has not passed legislation for the labeling of drugs with an express preemption clause.⁸⁶ High stakes product liability litigation typically involves failure-to-warn claims, often focusing on whether a company did or did not adequately warn about safety information that it acquired after approval. The litigation fights can involve similar issues as those raised in these proposals. One is whether information was newly acquired and should have been the subject of a CBE supplement even before FDA approval of a labeling change, or whether information was cumulative and, therefore, covered by the existing label. Another often disputed issue is whether the data show a meaningful causal association between product use and a newly revealed adverse event, or whether the observed association has no meaningful causal connection.

In litigation, it is judges or juries, not the FDA, that review such issues under state law regimes. The pending federal cases on preemption may, of course, significantly change the landscape for prod-

uct litigation, and the agency's forceful expression of its view that it is the only legitimate entity for reviewing the adequacy of the labeling for regulated prescription products may be a key deciding factor. But independently of whether the courts enforce the implied preemption doctrine, the proposed rules could have a temporizing impact on product litigation by increasing the standards for when a CBE supplement should be filed, and in particular, by emphasizing the need for obtaining reasonable evidence of a causal association before undertaking a CBE supplement.

Plaintiff's Bar Pushback

Not surprisingly, early reactions to the proposed regulations indicated at least some pushback, especially from the plaintiff's bar. The leading national organization for the plaintiff's bar complained specifically about FDA's emphasis on finding a causal association between a drug and a newly identified risk, claiming that the proposed rules conflict with FDAAA, to the extent it requires drug companies to update prescription drug labels to warn consumers of drug hazards at the earliest sign of a problem.¹⁷ A group of federal legislators wrote to FDA that the proposals are "apparently designed to bolster the argument by companies defending against lawsuits that the regulations precluded them from adding contraindications, warnings, precautions and adverse reactions in the absence of FDA approval."¹⁸ Their analysis is that the proposed regulations, because of the need for evidence of a causal association, would "drastically *limit* the situations in which a manufacturer is permitted to make add or strengthen a contraindication, warning, precaution, or adverse reaction without waiting for FDA to approve such a change."¹⁹

Conclusion

At the end of the day, if the proposed regulations become final, they will offer some better guidance, not just to sponsors but also potentially to judges and juries about when postmarket information requires supplemental labeling—and by reference, a standard that could be useful for gauging the duty to warn in tort litigation. Δ

- 1 See 73 Fed. Reg. 2848, *et seq* (Supplemental Applications Proposing Labeling Changes for Approved Drugs, Biologics and Medical Devices).
- 2 See, e.g., 21 CFR 314.70(c)(6)(iii)(A).
- 3 "Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products," which took effect June 30, 2006, including "Comments on Product Liability Implications of the Proposed Rule." 71 Fed. Reg. 3921, 3933-36 (January 24, 2006).
- 4 See Warner-Lambert Co., LLC v. Kent, 76 USLW 3020 (September 25, 2007) (No. 06-1498); and *Wyeth v. Levine*, 76 USLW 3500 (January 18, 2008) (No. 06-1249). One analysis calls *Levine* the "600 pound gorilla," given the huge impact it will have on whether "federal law displac[e] all product liability claims brought against all manufacturers of prescription drugs." See James Beck and Mark Hermann, <http://druganddevicelaw.blogspot.com/2007/12/supreme-courts-preemption-trilogy.html>. The Court also accepted a preemption case decided under

- the express preemption clause of the medical device amendments, *Riegel v. Medtronic*, 75 USLW 3017 (June 25, 2007) (No. 06-179). The government's position in each of these cases is that FDA regulations provide both a floor and ceiling for product labeling, and that conflicting state law—e.g., in the form of a jury verdict finding an approved label to be an inadequate warning of risks—cannot decide otherwise.
- 5 21 U.S.C. 352(a).
- 6 73 Fed. Reg. at 2850.
- 7 *Id.*
- 8 21 CFR 201.57(c)(6).
- 9 21 CFR 201.57(c)(7).
- 10 21 CFR 201.57(c)(5); 71 FR 3922 at 3927.
- 11 21 CFR 201.80.
- 12 See, e.g., *Device Labeling Guidance* (1991).
- 13 73 Fed. Reg. at 2852-53, quoting *English v. General Electric Co.*, 496 U.S. 72, 79 (1990).
- 14 *Citing Hines v. Davidowitz*, 312 U.S. 52, 67 (1941).
- 15 In the case of medical devices, of course, there is an express preemption clause. 21 U.S.C. 360k(a).
- 16 Compare *Medical Device Amendments*, 21 U.S.C. 360k(a); and *Dietary Supplement and Nonprescription Drug Consumer Protection Act*, 21 USC 379aa-1(h)(1)(2007): "IN GENERAL.—No State or local government shall establish or continue in effect any law, regulation, order, or other requirement, related to a mandatory system for adverse event reports for dietary supplements, that is different from, in addition to, or otherwise not identical to, this section."
- 17 See <http://www.atla.org/pressroom/PressReleases/2008/jan16.aspx>
- 18 See http://kenedy.senate.gov/newsroom/press_release.
- 19 *Id.*

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