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Drug Safety

Unscrambling Post-Approval Drug Safety Monitoring



BY BERT W. REIN

Among the thorny issues confronting newly-confirmed FDA Commissioner Gottlieb is the unresolved rulemaking proposal to permit generic drug manufacturers to amend safety warnings in their labels without prior FDA approval. At present, only pioneer branded manufacturers holding New Drug Applications may make such amendments to respond to newly-discovered evidence of a reasonable association between use of the drug and a safety hazard. Generic manufacturers holding Abbreviated New Drug Applications must conform their labels strictly to the pioneer label for the drug they are imitating.

Pressure for the proposed change largely comes from plaintiffs' product liability counsel and public interest groups who are concerned that the current regulatory regime permits generic manufacturers to avoid failure to warn product liability suits by invoking federal preemption so long as their labels are, as required by FDA, the same as the predicate pioneer labels. Since 90 percent by volume of drugs consumed in the United States are generic, proponents of the proposal argue that it is necessary to close a gap in compensatory relief for in-

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jured patients and enhance post-approval surveillance of adverse events.

There are, however, significant reasons not to adopt the proposed rule. First, its legal validity is questionable since the Food, Drug and Cosmetic Act expressly requires generic labels to be the "same" as pioneer labels. Second, in a multi-seller market, enormous confusion could result if manufacturers of identical drugs had differing warnings on their labels. Thus, any introduction of a change by one generic manufacturer would require a mechanism to force all other manufacturers, including the pioneer, to conform whether or not they agreed. Third, and perhaps most important, generic manufacturers are not staffed to monitor safety and rarely are notified of adverse events because identifying which generic manufacturer's product was dispensed by substitution to a patient whose prescription is generally for the pioneer product is difficult. Thus, without some requirement that generic manufacturers substantially, expensively and duplicatively expand their safety-monitoring capability, opening label change to them, whatever its effect on tort compensation, is unlikely to enhance drug safety.

These conflicting considerations and the powerful interests behind each side of the rulemaking proposal have led, not surprisingly, to delay and inaction. But inaction is not exclusively attributable to controversy. The more fundamental problem is the absence of any clear Congressional or Agency determination about where the responsibility for ensuring post-approval drug safety should rest. The status quo, somewhat haphaz-

ardly, divides that responsibility between the FDA, pioneer drug manufacturers and courts and juries sitting in product liability cases.

The 1962 Federal Food Drug and Cosmetic Act that establishes FDA's drug authority provided no effective mechanism for managing post-approval drug safety. FDA was given the power to terminate an NDA after going through elaborate, time consuming procedures, but that all-or-nothing power did not protect the public during the pendency of the process and, if invoked, could foreclose access to an effective drug whose safety issues could be resolved by adding new warnings or methods of use. Not surprisingly, FDA has not chosen to rely on this authority.

More recently, FDA has been authorized to condition new drug approvals, but not existing approvals, on the adoption of Risk Evaluation and Mitigation Strategies (REMs) that more closely supervise the use of effective drugs once approved. FDA also now has statutory authority to mandate safety-related label changes, again subject to extended and complex procedures and again largely dormant. The net result of these limited legal authorities, together with budget restraints and coupled with the prioritization of bringing new drugs to market, is that FDA's post-approval supervision is largely ineffective.

Partly in recognition of this limitation, FDA staff has taken a generally favorable view of label-based tort litigation. By giving pioneer NDA holders authority to initiate safety-related label changes under its Changes Being Effected ("CBE") regulation, FDA has permitted tort plaintiffs to overcome federal preemption defenses by claiming that "new" information should have caused a label change that would have persuaded the injured plaintiff's doctor not to prescribe the injurious drug. While successful tort suits may compensate some injured plaintiffs, product liability litigation is a slow and expensive process burdening the courts and unlikely to reduce injury while the cases are fought. In addition, resolving complex scientific issues on whether a plaintiff's injury can be traced to a drug through jury evaluation of testimony from conflicting advocate experts is far from optimum. Most importantly, tort litigation does not seem over its 50 plus year history, to have stimulated substantial numbers of CBE filings given the difficulty of acquiring injury information and the natural tendency of pioneer manufacturers to avoid disparagement of their products—the very reason that Congress gave pre-marketing approval authority to the FDA rather than rely on ex post facto tort litigation to protect the public health.

Moreover, because the CBE rule is entirely a creature of regulation with no firm statutory foundation, FDA cannot entirely disassociate itself from the CBE process. CBE changes must be submitted to FDA review 30 days before becoming effective and FDA can reject them. In addition, FDA must affirmatively approve CBE changes before they become permanent. This residuum of power was recognized by the Supreme Court in *Wyeth v. Levine*, 555 U.S. 555 (2009) as creating a narrow exception to the general rule that CBE shifts post-approval safety responsibility from the FDA to pioneer manufacturers. The Court held that when a pioneer provides clear evidence that FDA would have rejected the CBE change that a tort plaintiff contends the pioneer should have made, the change becomes impossible and federal preemption applies.

Trying to answer the question how FDA would have responded to a hypothetical CBE filing at a past date is far from simple. The Third Circuit in *In re Fosamax*, No. 14-1900 (3d Cir. 2017), recently raised the bar for those claiming preemption holding that it required demonstrating to a jury by "clear and convincing" evidence that no change relating to the hazard at issue would have survived FDA review. Later, the Tenth Circuit in *Cerveney v. Aventis (Clomid)*, No. 16-4050 (10th Cir.), neither adopted nor rejected the Third Circuit standard but did at least clarify that where FDA rejected a proposed change because it could find no link between the drug and the claimed hazard, FDA rejection of CBE change and preemption were clearly established.

While the applicability of the *Levine* preemption exception to individual cases makes for interesting litigation, it does nothing to clarify the base question of who is responsible for post-approval surveillance. FDA takes no role in this litigation letting others engage in creative speculation whether or not it would have used its residual authority to block CBE changes. And whatever the outcome of a specific historic case litigation, it has no effect on current labeling or safeguarding the public health.

Recognizing the messy state of post-approval surveillance should lead Commissioner Gottlieb to turn attention from the generic CBE proposal to a more fundamental consideration of post-approval safety. If FDA's Congressional mandate is to be the independent authority that determines if and how a drug may be safely and effectively administered to patients, it makes no sense for FDA to delegate this responsibility to manufacturers post-approval while holding them at arms-length pre-approval. FDA has, however, sought to sidestep this responsibility and shift blame to the Congress by complaining that it lacks the necessary resources to monitor and regulate the labeling and use of the thousands of approved drugs now on the market. But even assuming, as appears correct, that Congress is not prepared to appropriate the funds necessary for a large FDA staff expansion, alternatives are available.

On the pre-approval side, FDA is having applicants pay user fees to expand its resources with no impact on appropriations. Those fees are a reasonably easy "sell" to the affected community because there is an obvious benefit to an expedited approval process permitting a manufacturer an accelerated return on its research, development and testing costs. The "sell" is harder post-approval where safety-related safety changes are likely to be revenue negative. But Congress has the power to mandate payment of such fees for each approved manufacturer of a drug as a condition on continuing approval, and to earmark those funds for the retention of independent, consulting, monitors who could gather and review all new safety-related information and, as appropriate, propose additional warnings, improved instructions for use and even the commencement of withdrawal proceedings to FDA for final decision. The net inconsiderable quid pro quo for manufacturers and patients as a whole would be an end to CBE and a clear affirmation of FDA responsibility for the full life cycle safety regulation of prescription drugs with federal preemption of the vast majority of drug product liability claims. The resulting elimination of the billions of dollars of deadweight loss (the vast majority of which go to lawyers and experts rather than injured plaintiffs) now

inflicted by the complex litigation of these claims, would be a significant contribution to the public health.