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Generics and Biosimilars Catch the FDA's Eye

The Food and Drug Administration's regulation of drugs in 2014 reflected the agency's constant effort to balance a range of interests and pressures to ensure the safety and effectiveness of drugs marketed in the United States. Here are some of the drug regulation issues that garnered attention last year and will remain relevant in 2015 even as the FDA transitions to new leadership. Commissioner Margaret Hamburg announced on Feb. 5 that she will step down at the end of March. Dr. Stephen Ostroff, FDA's chief scientist, will serve as acting commissioner until a replacement is confirmed.

Biosimilars. The Biologics Price Competition and Innovation Act, enacted in 2010 as part of the Affordable Care Act, created an approval process for biosimilars — that is, highly similar copies of approved biologic products. In 2014, the FDA issued new draft guidance documents on biosimilars for the first time in more than two years. In July, the FDA accepted its first biosimilar application, for Sandoz Inc.'s version of Amgen Inc.'s Neupogen, and on Jan. 7 an FDA panel recommended that the agency approve Sandoz's biosimilar.

The new draft guidances address scientific standards for establishing biosimilarity and the FDA's current thinking on the act's marketing exclusivity provisions. (FDA cautions that guidance documents and draft guidance documents do not create enforceable rights or requirements and do not bind FDA.)

However, the FDA has not yet issued its long-awaited guidance on naming conventions for biosimilars. The generic industry and others want the FDA to assign a biosimilar the same nonproprietary name as the product on which it is based, contending that such an approach is necessary to avoid confusion among health care providers and to facilitate substitution and its attendant cost savings.

On the other side, certain brand-name manufacturers argue that because biological products inevitably differ, every biological product needs a unique name to protect patient safety.

This year also saw continued debate about how to apply the Biologics Price Competition and Innovation Act's patent-challenge procedures. Although two district courts have found that a biosimilar maker must follow the act's procedures to challenge the reference product's patents, the first appellate decision, issued in December, affirmed the dismissal of the biosimilar maker's patent challenge without reaching the act's procedures. In October, the FDA received a citizen petition addressing the same issues.

FDA's increased overseas activity. About 40 percent of the finished drugs taken by Americans and 80 percent of the active ingredients in those drugs are made outside the United States. Thus, the FDA's ability to effectively regulate the U.S. market requires the agency to increase its presence in countries where all or part of FDA-approved products are made.

In 2014, Commissioner Hamburg traveled to India and China to meet with regulatory authorities and industry leaders, emphasizing the need for greater collaboration and for aggressive responses to safety lapses and counterfeiting threats. The FDA also continued to increase the number of inspections of foreign facilities that make drugs or drug

components imported to the U.S.

Generic drug labeling. In late 2013, the FDA issued a proposed rule in response to the U.S. Supreme Court's 2011 decision in *Pliva v. Mensing* and its 2009 decision in Wyeth v. Levine. Together, those decisions stand for the proposition that the Food, Drug and Cosmetic Act preempts state failure-to-warn suits against generic manufacturers, but not against brand-name manufacturers.

The basis for the distinction is that federal law allows branded drug makers to independently change the product label to reflect updated safety information, but generic companies cannot do so because of the statutory requirement that generic labeling be the "same as" the branded version. As proposed, the rule would allow generic companies to change the label without prior FDA approval.

The generic industry opposes the proposed rule, claiming departing from the same-labeling requirement would violate the Food, Drug and Cosmetic Act, and would sow confusion and threaten the public benefits of the same-labeling requirement.

The comment period for the proposal originally ended in March 2014; however, in early February 2015 FDA indicated its intent to re-open the comment period, hold a public meeting about the proposed rule, and do a new economic analysis for the final rule.

Risk Evaluation and Mitigation Strategies. In 2014, the FDA continued to approve risk evaluation and mitigation strategies — postapproval mechanisms such as communications to health care providers in addition to product labeling and restrictions on distribution — to help ensure that certain drugs maintain a positive risk-benefit profile.

As the FDA has recognized, however, sponsors of reference listed drugs have used risk evaluation and mitigation strategies as a basis to refuse to sell such drugs to generic companies seeking to conduct preapproval bioequivalence testing.

In December, the FDA issued a draft guidance to clarify how a generic company can obtain an FDA letter confirming that its bioequivalence protocol meets the risk evaluation and mitigation strategies requirements so as not to prevent a generic applicant from obtaining drug product needed for its testing. It remains to be seen whether the draft guidance will affect the use of risk evaluation and mitigation strategies as a competitive sword.

Social media communications. In June, the FDA issued companion draft guidance documents addressing drug-related communications on social media. In the first, the FDA attempted to explain how a firm using Twitter (or other character-limited platforms) might successfully shoehorn both benefit and adequate risk information into a tweet that the agency does not consider misleading. In the second, the FDA advised how a company can correct misinformation about its product posted by a third party on the Internet, such as in blogs and chatrooms.

Compounding. The FDA traditionally has had limited jurisdiction over drug compounding — the small-scale manufacture of drugs by pharmacists or physicians tailored for particular patients. Compounded drugs that meet certain criteria in the Food, Drug and Cosmetics Act do not require the FDA's premarketing approval, need not meet current good manufacturing practices standards and do not have to bear FDA-approved labeling.

After an outbreak of fungal meningitis was traced to a compounder in late 2012, Congress enacted the Drug Quality and Security Act of 2013. The act expanded the FDA's oversight, providing for registered outsourcing facilities that compound in compliance with current good manufacturing practices standards. In 2014, the FDA issued several guidance documents in connection with its implementation of the Drug Quality and Security Act's compounding provisions.

Hatch-Waxman Amendments. Finally, 2014 marked the 30th anniversary of the Hatch-Waxman Amendments. The law was an example of effective bipartisan legislating. It provided a pathway for abbreviated approval that effectively created the modern generic-drug industry, and increased rewards for new drug innovation. In so doing, Hatch-Waxman balanced legal, scientific, policy, and economic forces at play in FDA's regulation of prescription drugs.

The FDA in 2014 continued its consideration of critical issues pertaining to drug regulations — those that will prove important in 2015 as well.

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