Compliance Issues

In General

Regulatory compliance issues may pose a hurdle to approval of an original ANDA or 505(b)(2) NDA and to approval of supplements to an approved ANDA or 505(b)(2) NDA seeking permission to change the formulation or manufacturing process or make other product improvements. These issues may also threaten the continued manufacture and distribution of an approved drug product. These issues generally first come to light during FDA inspections. The FDA may conduct inspections as part of its statutory obligation to inspect all drug manufacturers once every 2 years,* the Agency's investigation of complaints or other reports about product failures, or preapproval inspections.

If an FDA investigator observes what he or she views as significant problems, particularly in the area of current good manufacturing practices (cGMPs), the investigator is likely to leave a Form FDA-483 listing "Inspectional Observations" at the close of the inspection. Depending on the seriousness of the perceived deviations, the FDA may send the inspected firm a Warning Letter, which is a cease-and-desist letter.

If a drug manufacturer fails to resolve alleged violations that are addressed in the Warning Letter, and particularly if the alleged violations continue over a series of inspections, federal court legal action may result. By going to federal court, where FDA is represented by the US Department of Justice, the government can seek to seize and "condemn" violative products, enjoin a firm and it employees from continued violations of the law, or impose criminal sanctions against a firm and its management.†

The approvability of an ANDA or 505(b)(2) NDA or supplemental ANDA or 505(b)(2) NDA may be affected not only by the compliance status of the sponsor's own facilities but also by the regulatory status of active pharmaceutical ingredient suppliers, clinical research organizations, testing laboratories, and other firms referenced in the ANDA or 505(b)(2) NDA that have a role in the development and production of the generic drug product. This situation is complicated by the fact that, under typical commercial arrangements, the ANDA or 505(b)(2) NDA sponsor has no direct access to its suppliers' internal procedures and similar documents, which are typically made available to FDA in the form of a drug master file that the ANDA or 505(b)(2) NDA sponsor has the right to reference but not actually review. Similarly, correspondence between the FDA and a supplier may not be available to the ANDA or 505(b)(2) NDA sponsor. Thus, the ANDA or 505(b)(2) NDA sponsor may be at the mercy of others, without having any ability to resolve the compliance issues, or even find out about them. An ANDA or 505(b)(2) NDA sponsor should seek to address this area in contracts with its suppliers.

Recalls

Problems uncovered during FDA inspections, as well as problems discovered by a manufacturer itself or by others, can lead to product recalls. In general, the FDA

* 21 USC § 360(h).

† 21 USC § 334, § 332, and § 333, respectively.