LOEB & LOEB LLP

FDA Regulatory and Compliance Monthly Recap

FEBRUARY 2017

KEY FINDINGS

FDA's enforcement stats paint opposing pictures for pharmaceuticals, medical devices

The agency's annual enforcement report signals mixed enforcement trends for pharmaceutical companies and medical device makers. While the pharmaceutical sector appears to be increasingly in the crosshairs of warning letters, recalls have fallen. On the flip side, medical device makers are seeing a notable decline in warning letters but an uptick in recalls.

The FDA's annual enforcement statistics show that in FY2016, the Center for Devices and Radiological Health (CDRH) issued only 85 warning letters – a notable decline from the 168 it issued in 2015. In parallel, the Center for Drug Evaluation and Research (CDER) issued notably more letters in 2016 (151) compared with 2015 (76). Enforcement levels at the Center for Biologics Evaluation and Research (CBER) remained flat, with only four letters issued in 2016. Overall, the agency experienced a substantial decline in warning letters in 2016, dropping from a peak of 17,232 in 2015 to 14,590 in 2016. With the exception of the Center for Tobacco Products, which is responsible for the majority of letters, CDER lagged only behind the Center for Food Safety and Applied Nutrition (CFSAN) in the number of warning letters.

The agency experienced an overall decline in recalls, though levels remained above lows observed in 2013 and 2014. As is typically the case, the CDRH continued to lead the pack in terms of recall events – issuing slightly more in FY2016 (1,183) than in 2015 (1,175). The CDER experienced a decline in recalls from 303 in 2015 to 277, as did the CBER, which saw recalls decline from 651 to 575.

Notably fewer recalls by the CDRH were classified as Class I in 2016 (111) than 2015 (287). However, this drop was accompanied by a jump in the number of Class II (2,671 v. 2,484) and Class III (116 v. 69) recalls. Recalls by the CDER were primarily deemed Class II (1,272), though there was an uptick in the number of Class III recalls (170 vs. 120).

Recalls by the CBER were mostly categorized as Class II (513) and Class III (267), with only one deemed Class I. Indeed, CBER lagged only behind the CFSAN in terms of Class III recalls.

Despite the decline in warning letters and recalls, the FDA actually experienced a slight increase in the number of seizures – up from one CDER seizure in 2015 to a total of four, one of which was by the CDRH and one of which was by CDER. Irrespective of the slight climb, however, seizure levels remained low compared with the high observed in 2011 (15). In terms of injunctions, there was a slight decline (17 vs. 21), primarily due to a drop in CDRH injunctions (from four in 2015 to none in 2016).

Industry groups say final rule on intended use establishes unfounded legal standard, call for indefinite stay

Citing violations of the APA and what they call the establishment of a "new and unjustified legal standard," a coalition of industry groups is requesting the FDA indefinitely stay the rule. In a petition to the FDA, the groups raise concerns about the FDA's backpedaling on claims it would rein in its oft-contentious definition of intended uses.

The Medical Information Working Group, PhRMA and BIO jointly filed a petition calling on the FDA to stay its final rule on intended use over concerns about alterations the rule would make to the legal concept of intended use. The groups criticize the FDA for not sufficiently communicating with the public before finalizing revisions to the intended use definition for drugs and medical devices as well as establishing a new "totality of evidence" standard.

Since these substantial changes were not communicated to the public before the final rule was published on Jan. 9, the groups argue they were deprived of fair notice and a chance to voice their opinion – a violation of the Administrative Procedure Act. The APA requires the FDA to make its views known to the public in a way that permits criticism or formulation of alternatives. Though proposed and final rules don't need to be totally identical, the petitioners claim they may only differ if the final version is a "logical outgrowth" of the proposed version. In this case, they say, the changes to the proposed rule are substantial, and the FDA failed to provide sufficient notice "of a fundamental change to the regulatory scheme for drugs and devices."

The petition also calls into question the FDA's updated definition of intended use, saying it contradicts the statutory definitions in the Federal Food, Drug, and Cosmetic Act and the mandate that drug and device labeling bear adequate directions for use. Citing committee reports from 1934 and 1935, the groups argue the FDCA made clear that intended use would be based on representations by the manufacturer, meaning a manufacturer could determine how the article would be used. The petition further cites court cases to demonstrate that courts have upheld this definition of intended use and treated the legislative history as authoritative. The petition refers to a D.C. circuit court ruling that a claims-based understanding of intended use had been recognized "as a matter of statutory interpretation."

The petition also addresses the FDA's definition of intended use established in 1952, with particular reference to the requirement that if a drug manufacturer is aware a drug or device may be used for conditions other than the one for which it is offered, it must provide adequate labeling for such uses (the last sentence in the rule). This requirement, they say, has long been an issue and has been questioned by the courts. The petition cited a court ruling rejecting the FDA's expanded definition of intended use. In that case, Association of American Physicians and Surgeons, Inc. v. FDA, the court determined the FDA can only regulate claimed uses of drugs rather than "all foreseeable or actual uses."

Although the FDA proposed in 2015 to remove the last sentence of the intended use definition, the petitioners say it "dramatically shifted gears" in the final rule. Instead of deleting the final sentence, the FDA replaced it with a new sentence establishing an open-ended "totality of evidence" standard, stating that if the evidence indicates a manufacturer objectively intends for a drug to have off-label uses, it must provide adequate labeling that accords with such intended uses.

The FDA argues the addition of the standard is merely a clarification of law to indicate that knowledge of an actual use didn't automatically trigger adequate labeling obligations. The petition alleges, however, that the final rule adopts a new standard not supported in existing law, and that represents a significant change with constitutional and public health consequences. The petitioners cite case law to support their position that the totality of evidence approach has no standing in law. In particular, the petition cites the United States v. Article of 216 Cartoned Bottle ("Sudden Change") case in which the court said, "[T]he intended use of a product may be determined from its label, accompanying labeling, promotional material, advertising and any other relevant source."

The petition also cites recent lawsuits by drug and device makers alleging the FDA's intended use regulations have a chilling effect on speech to minimize the risk and ameliorate the quality of care related to off-label uses. These cases, the petition states, highlight the First Amendment challenges raised by the traditional claims-based interpretation of intended use. The new standard "all but guarantees significant constitutional harms will result," the petitioners write. They say it would not only risk the restriction of truthful and non-misleading promotional speech but also raise Fifth Amendment challenges because no one will know in advance what evidence may be considered sufficient to deem an actual use an intended use.

President Trump signs 'two out, one in' executive order with implications for FDA

The executive order requires at least two regulations be slashed to offset the costs associated with new regulations. For the current fiscal year, the order applies to significant regulatory actions, and the allotted cost for new regulations is set at zero.

To close out the first month of 2017, President Trump signed an executive order requiring at least two prior regulations be repealed for every new regulation issued by a federal department or agency. Citing the need to be financially responsible in the expenditure of funds and to carefully manage the cost of planned regulations, the order states the cost of new regulations must be fully offset by the elimination of existing costs associated with two previous regulations.

Beginning in FY2018, the order requires that regulatory plans submitted by federal agencies to the Office of Management and Budget (OMB) identify, for each regulation that increases incremental cost, the offsetting regulations and provide an estimation of the total costs or savings associated with the new or repealed regulations. During the budget process, the OMB will provide agencies with a total amount of incremental costs permitted. For FY2017, the order sets the total incremental cost of new regulations at zero. No regulations surpassing the cost allowance will be allowed, unless required by law or approved by the OMB director. Regulations approved during the budget process will be included in the Unified Regulatory Agenda. No regulation may be issued that's not included in the agenda, unless approved by the OMB director.

The order defines regulation or rule as "an agency statement of general or particular applicability and future effect designed to implement, interpret, or prescribe law or policy or to describe the procedure or practice requirements of an agency." It notes, however, that it does not include regulations related to the military, national security or foreign affairs; regulations related to agency organization, management or personnel; or

any other category of regulations exempted by the OMB director.

Following publication of the order, the OMB issued guidance to help federal agencies ascertain how the order applies to their issuance of guidance or rules. The guidance indicates that order requirements apply only to significant regulatory actions in FY2017, defined by Executive Order 12866 as any action likely to result in a rule that may:

- Have an annual impact of $100 million or more on the economy or negatively impact the economy in a material way.
- Establish a serious inconsistency or interfere with an action taken or planned by another agency.
- Materially modify the budgetary impact of entitlements, grants, user fees or loan programs.
- Bring to light new legal or policy issues arising from legal mandates, the president's priorities or the principles of the order.

As an example, significant regulatory actions taken by the FDA in the past year include final and proposed rules related to:

- Postmarket safety reporting for combination products.
- Revisions to medical device and biologic labeling regulations.
- The implementation of provisions in the Medicare Prescription Drug, Improvement and Modernization Act of 2003 related to the approval of 505(b)(2) applications.
- ANDAs and revisions to the list of drugs withdrawn or removed from market due to safety or efficacy concerns.

Agencies planning to issue one or more significant regulatory actions are directed to identify deregulatory actions to eliminate to fully offset the incremental costs as of Sept. 30, 2017. Per the guidance, any existing regulatory action that imposes cost and that would produce verifiable savings if eliminated may qualify as a deregulatory action. Regulations voided by a court will generally not count, though there may be instances in which the savings may be counted. The guidance indicates that new significant guidance or interpretive documents will be addressed on a case-by-case basis and directs agencies to ensure documents are the appropriate method for the policy goal.

FDA issues warning letter to Fresenius subsidiary over misleading promotional material

For the second time, the FDA warned Fenwal about misleading promotional material for InterSol that omits risk information. The agency raises concerns about the repeated nature of the violations and is requesting the company implement procedures to prevent such violations in the future.

The Center for Biologics Evaluation and Research's Office of Compliance and Biologics Quality issued a warning letter to Fresenius Kabi subsidiary Fenwal over misleading promotional material for InterSol (Platelet Additive Solution 3). The warning letter raises concerns about omitted risk information and continued violative promotion of the product because similar violations were observed in 2012.

InterSol has no direct therapeutic effect and is not meant to be infused into a patient. The warning letter takes issue with a presentation designed to introduce blood facility staff to the product, as it fails to disclose facts related to consequences that may result from the product's use, including warnings and precautions and information pertaining to the risk due to direct infusion. Leaving out such information from promotional material renders the product misbranded.

The CBER calls on Fenwal to immediately stop disseminating the violative promotional materials, provide a written response listing all promotional materials used for the product that contain such violations, and outline plans to discontinue their use. Given the previous violations, the CBER also requests Fenwal provide a written response detailing which policies and procedures it plans to adopt to ensure its promotional activities comply with laws and regulations, as well as an explanation of how the policies are expected to succeed.

For more information on any of these FDA regulatory and compliance updates, please contact Scott S. Liebman at sliebman@loeb.com.

Loeb & Loeb LLP's FDA Regulatory and Compliance Practice

Loeb & Loeb's FDA Regulatory and Compliance Practice comprises an interdisciplinary team of regulatory, corporate, capital markets, patent and litigation attorneys who advise clients on the full spectrum of legal and business issues related to the distribution and commercialization, including marketing and promotion, of FDA-regulated products. Focusing on the health and life sciences industries, including pharmaceuticals, biologics, medical devices, wellness products, dietary supplements and organics, the practice counsels clients on regulatory issues, compliance-related matters and risk management strategies; advises on laws and regulations related to product advertising and labeling; counsels on FDA exclusivity policies and related Hatch-Waxman issues; and provides representation in licensing transactions and regulatory enforcement actions.