LOEB & LOEB LLP

FDA Regulatory and Compliance Monthly Recap

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KEY FINDINGS

Medical device enforcement report points to heightened oversight, uptick in foreign inspections

The report signals an uptick in device inspections, driven by increasing attention to foreign firms and a risk-based approach to oversight. The CDRH describes its shift from an aggressive approach to warning letters to a more interactive approach focusing more on untitled letters, leading to an uptick in corrective activities.

The Center for Devices and Radiological Health (CDRH) published its Medical Device Enforcement and Quality Report for 2017, which outlines the office's oversight of the more than 21,000 registered medical device manufacturers in 106 countries. According the report, the FDA's oversight of these facilities has increased markedly over the past 10 years. In 2017, the agency carried out a total of 2,952 inspections of medical device makers – 46% more than were conducted a decade earlier.

The uptick in oversight was driven by a 243% increase in the number of foreign inspections during the past 10 years. As part of their international oversight, the FDA and international regulatory partners established a Medical Device Single Audit Program (MDSAP) to permit a single regulatory audit of a medical device maker's quality management system enabling it to adhere to requirements in multiple jurisdictions. According to the report, the FDA classified almost 600 audits under the MDSAP from 2013 to 2017.

The report points to a shift in the FDA's approach to inspections and enforcement, noting that its risk-based approach focusing on "high-risk" firms or products has yielded a 59% increase in the number of inspections resulting in official action. The agency said that starting in 2008, it took a more "aggressive" approach to issuing warning letters, reaching a high of 189 letters in 2012. However, the FDA has transitioned to a more interactive approach to enforcement, under which it reviews responses to Form 483s, provides feedback on proposed

corrective action and monitors progress. Warning letters have instead focused on firms with severe violations or that fail to implement correction plans. This interactive approach, according to the report, has resulted in a decline in the number of warning letters – in favor of untitled letters – and has resulted in 82% of firms correcting violations on follow-up.

Generally, medical device recalls are carried out voluntarily by device makers, per requirements under 21 CFR Part 906 that medical device companies report to the FDA if they correct or remove a device in order to reduce a risk posed by the device and to remedy a potential legal violation. The FDA has focused on identifying reporting deficiencies under Part 806 during its inspections. Per the report, this emphasis has yielded an increased number of reported voluntary recalls. Companies cited for Part 806 inspectional observations recorded 20% more voluntary recalls in the year after inspection compared with the year prior and were eight times more likely than the industry average to report a recall following the inspection. Separately, the FDA has focused on compliance with 21 CFR Part 803 adverse event reporting. Its emphasis on identifying device makers with adverse event reporting deficiencies led to an increase in medical device reports received, with firms cited in 2017 for such violations reporting more than three times more medical device reports compared with 2016.

The report also takes note of the FDA's recent efforts to bolster device quality, such as the Case for Quality project launched in 2011 and the Medical Device Innovation Consortium's development of a collaborative forum to discuss quality. In 2018, the CDRH initiated a voluntary quality maturity appraisal pilot, under which third-party groups certified by the Capability Maturity Model Integration Institute assess the maturity of a quality system. So far, 94% of participants have reported that appraisals were beneficial and 86% have said they had a positive impact on product quality. In 2019, the FDA is planning to explore whether to develop a formal appraisal program to supplement its traditional oversight activities.

OPDP warning raises concerns with lack of risk disclosure in Vanda's promotion of Fanapt, Hetlioz

The warning letter cites issues with online representations describing the benefits of treatments for psychiatric disorders without disclosing risk information. The letter calls on Vanda to disseminate truthful, nonmisleading and complete corrective messages.

In its second warning letter of the year, the Office of Prescription Drug Promotion (OPDP) took issue with the paucity of risk information disclosed on Vanda Pharmaceuticals' webpage for Fanapt (iloperidone), an antipsychotic indicated for the treatment of schizophrenia, and Hetlioz (tasimelteon), a treatment for Non-24-Hour Sleep-Wake Disorder (Non-24). The letter comes amid a slight uptick in enforcement activity by the OPDP, which has issued seven enforcement letters so far in 2018 (two warning letters, five untitled), after issuing only five in 2017 (three warning, two untitled).

The warning letter raises concerns about the webpage promoting the uses and benefits of the drugs without disclosing any risk information whatsoever. Although the webpage includes a statement directing viewers to the prescribing information, including boxed warnings, the OPDP determined the statement doesn't mitigate the omission of risk information. Leaving out the risk information represents a failure to provide material information about the potential impacts of using the drugs, the office said.

Given the serious and potentially life-threatening side effects associated with the drugs, particularly the boxed warnings associated with Fanapt, the lack of risk information on the webpage raises concerns from a public health perspective. As such, the letter directs Vanda to provide a list of all promotional materials that contain similar representations and to disseminate "truthful, nonmisleading, and complete corrective messages" clearly identifying the promotional

material at issue and providing information to correct the violative communications. The warning letter notes that corrective messages shouldn't include promotional claims or representations.

FDA issues proposed rule to bring informed consent regulations in line with Common Rule

The proposed rule would bring the FDA's regulations in harmony with the Common Rule by allowing institutional review boards to waive or alter informed consent requirements for minimal-risk trials so long as four criteria are met and documented. The rule would adopt four of the criteria established by the Common Rule for informed consent waivers in minimal-risk trials, but not a fifth due to come into effect next year.

The FDA issued a proposed rule to provide an exception from informed consent requirements for clinical trials that pose only minimal risk to human subjects, so long as sufficient safeguards are in place. The rule would allow an institutional review board (IRB) to waive or alter informed consent requirements in certain FDA-regulated, minimal-risk clinical trials. The proposed rule, which would add §50.22 to Part 50 (21 CFR Part 50), would establish four criteria for IRBs to approve a waiver or alteration of informed consent requirements, consistent with the Federal Policy for the Protection of Human Subjects, also known as the Common Rule.

The rule aligns with statutory changes under the 21st Century Cures Act, which provided the FDA with the authority to allow an exception to informed consent for minimal-risk trials with protections in place for participants. As it stands, the FDA's regulations provide an exception from informed consent requirements only in life-threatening situations or for emergency research. The Common Rule, however, has included a waiver of informed consent for minimal-risk trials since 1991. The FDA did not adopt the Common Rule's waiver because the Federal Food, Drug, and Cosmetic Act (FDCA) required that informed consent be obtained for all participants "except in very limited circumstances."

With the new authority granted under the Cures Act, the proposed rule would adopt the Common Rule exception by establishing that a waiver or alteration to informed consent may be approved by an IRB if:

1. **The clinical study poses no more than minimal risk to participants:** The likelihood and magnitude of harm or discomfort expected by the research is not greater than that encountered in daily life or during routine physical or psychological examinations.

2. **The waiver or alteration of informed consent will not adversely impact the rights or welfare of participants:** To meet this criterion, IRBs are not required to find that obtaining consent would be harmful or be contrary to the best interests of participants. However, they may take into consideration the impact on subjects' well-being and whether the subject population would likely object to the waiver or alteration.

3. **The study couldn't practicably be conducted without the waiver or alteration of informed consent:** According to the FDA, "practicably" means that recruitment of consenting participants doesn't bias the science or render it less rigorous, and the research isn't unduly delayed by restricting it to consenting subjects.

4. **When appropriate, participants are provided with additional relevant information after participation:** This may include, for instance, providing information previously withheld about the trial in order to prevent bias.

Per the rule, the IRB must find and document that these criteria have been met. The Common Rule adopted a fifth element in January 2017, based on whether a trial "involves using identifiable private information or identifiable biospecimens" and whether the trial could "practicably be carried out without using such information or biospecimens in an identifiable format." The FDA opted not to adopt this fifth criterion, which is slated to go into effect on January 21, 2019.

The FDA said it expects the rule to be beneficial because it brings FDA regulations in line with the Common Rule while allowing for more healthcare advances from minimal-risk trials. In line with the proposed rule, the FDA previously issued guidance describing its intent not to object to an IRB waiving or altering informed consent requirements for minimal-risk studies. The FDA is seeking input on which types of trials sponsors expect would meet the criteria for a waiver or alteration to informed consent.

FDA proposes new framework surrounding drug-associated software

As the digital shift permeates the drug industry, the FDA is calling for input on a proposed framework for regulation apps used in conjunction with prescription drugs. The proposed framework would treat the output of software backed by a drugmaker as labeling. The FDA anticipates that most software outputs will constitute promotional labeling, though there are instances in which it may fall under FDA-required labeling.

The FDA is proposing a new framework for the regulation of software applications for use with prescription drug products. In a request for comments, the FDA outlined a proposed framework for overseeing the dissemination of software, by or on behalf of drugmakers, to coincide with the use of one or more prescription drugs. The framework comes amid increasing recognition of the role digital health may play in patient care and the emergence of an array of mobile applications for health-related issues such as tracking drug ingestion. It also comes in response to requests by drug sponsors developing or obtaining rights to prescription drug-use-related software for clarification from the FDA about the regulatory status of such software.

Per the request for comments, the proposed framework is designed to encourage innovation while also ensuring drugmakers' communications adhere to prescription drug labeling requirements. The framework doesn't apply to software for use with prescription drugs not distributed by or on behalf of a drug sponsor. It applies only to software disseminated by or on behalf of a prescription drug sponsor, such as software branded with a drug name for use in medication adherence tracking or software that helps a drug sponsor communicate with a device in a drug-led, drug-device combination. The framework centers on the output of software and the material – such as displays, sounds or audio – presented to end users, which may include patients, caregivers or healthcare practitioners. The FDA is proposing a risk-based approach to its oversight, under which the FDA doesn't anticipate the output of prescription drug-use-related software will require review before dissemination in most instances.

The FDA notes that in certain instances, prescription drug-use-related software may meet the definition of a device, as determined by the CDRH. The proposed framework doesn't change the regulatory framework for devices. Irrespective of whether a software function is categorized as a device, the output distributed by or on behalf of a drugmaker for use with a drug would be treated as drug labeling under the proposed framework since it "accompanies" a specific drug. Output that doesn't accompany a specific drug will not be regulated as labeling, unless its categorization changes – for instance, if a drugmaker licenses software developed by a third party and begins disseminating it alongside a drug. The request for comments cites the Supreme Court's interpretation of the FDCA to argue that materials that supplement or explain an article fall under the definition of labeling.

Per the FDA, the software output will primarily fall under the category of promotional labeling, which is not reviewed by the agency before being distributed but is submitted to the OPDP or Advertising and Promotional Labeling Branch (APLB) at the time of initial distribution. Under the proposed framework, prescription drug-use-related software output would be subject to the same regulations as other promotional material and would therefore need to be submitted to OPDP or APLB upon initial dissemination (under a Form FDA 2253). The FDA will then use a risk-based approach

to review promotional pieces submitted. Examples of output that would be considered promotional labeling include information about prescribed drugs also found in FDA-required labeling, simple tools to track health information related to the condition for which the drug was intended, or dosing instructions consistent with FDA-required labeling.

There are two instances in which the FDA expects prescription drug-use-related software output may instead fall under FDA-required labeling:

1. The drug sponsor demonstrates there is substantial evidence of an effect on a clinically meaningful outcome as a result of using the software; or

2. The software provides a function or information critical to one or more intended uses of a drug-led, drug-device combination of which the software is a device constituent part or an element thereof.

At this stage, the proposed framework remains under discussion and is not the subject of draft guidance. The agency expects to issue draft guidance on the proposed framework once it has received input from stakeholders.