



# FDA Regulatory and Compliance Monthly Recap



SEPTEMBER 2016

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### FDA issues final rule modifying regulations for drug establishment registration, listing requirements

*The final rule, which comes nearly 10 years after changes were initially proposed, updates the regulations to require electronic submission and also makes modifications to national drug codes. The final version leaves out certain elements of the proposed rule that were met with particular opposition.*

The FDA issued a [final rule](#) updating its regulations governing who needs to register drug establishments and list human drug products, including biologics and certain animal drugs. The changes are designed to ensure that regulations align with Section 510 of the Federal Food, Drug, and Cosmetic Act; the 1962 Kefauver Harris Amendments, which require drug manufacturers to register their facility with the agency annually; and 1973 amendments requiring that each registered establishment submit a list of drugs it produces.

The 202-page final rule not only requires that manufacturers make their submissions electronically, unless an exception is granted, but also clarifies that the onus to register rests with the persons who manufacture, repack, relabel or salvage drug products. Those acting as private label distributors do not need to register or list drugs, but are permitted to submit drug listing information as agents acting on behalf of those manufacturing the drugs. Individuals or establishments engaged only in recording cells or tissues as part of a biological product at a registered establishment are generally exempt from registration and listing. The rule also makes clear that information regarding drug registration and listing should be made available for public disclosure, with certain exceptions.

Specific elements of the final rule include:

- Modifications that accommodate alternatively formatted national drug codes, or NDCs, in bar codes.

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- Amendments that permit an FDA Center Director to approve an additional bar code standard or format.
- Amendments stating the agency may refuse to approve a new drug application if the drug will be developed in whole or in part at an unregistered facility that is not exempt from registration.
- Technical modifications.
- Requirements for electronic submissions.

The agency notes that the final rule does not incorporate aspects of a proposed rule that were met with heavy criticism, including a requirement that the FDA, rather than industry, develop NDCs for listed drugs, as well as a requirement that the NDC appear in a form legible by humans on the label of each listed drug. The rule allows for 10- or 11-digit NDCs, expanding the labeler code from five to six numeric characters.

In terms of costs, the FDA anticipates one-time costs of \$59.7 million and recurring costs of \$500,000, representing total annualized costs of \$9 million using a 7 percent discount rate of 10 years, and \$7.5 million when using a 3 percent discount rate. The agency expects the most substantial costs to be the result of registrants understanding the rule and adjusting their standard operating procedures as needed. The rule provides registrants with 90 days following the Aug. 31, 2016, posting to comply with the rule, which applies to both newly submitted information and updates to information previously submitted. Two years following the effective date, the agency plans to remove registration and listing information previously submitted on paper and not updated with electronic submissions from its database.

## Untitled letter takes issue with promotional material for investigational drug at cancer conference

*A Jazz Pharmaceuticals subsidiary received a warning letter from the FDA over promotional material suggesting an investigational cancer drug is effective and safe for the intended uses for which it is being investigated. In just the third untitled letter of the year, the Office of Prescription Drug Promotion took issue with specific claims made in the exhibit display, as well as with a lack of clear identification of the drug as investigational.*

The FDA issued an [untitled letter](#) to Celator Pharmaceuticals, a subsidiary of Jazz Pharmaceuticals, after inspectors found material exhibited at the American Society for Clinical Oncology annual meeting for an investigational drug suggested in a promotional context that the product is safe and effective. The agency's Office of Prescription Drug Promotion took issue with material describing the use of an investigational liposome injection, CPX-351, in treating cancer in general and specifically in newly diagnosed patients with high-risk acute myeloid leukemia.

The OPDP deemed the investigational product misbranded under Section 501(f)(1) of the Federal Food, Drug, and Cosmetic Act, as the touted uses require a prescription as well as the supervision of a physician. As such, adequate directions for use cannot be written such that a layman may use the product safely for its intended purposes. The office also determined that the investigational drug fails to comply with the regulation of Section 505(i), which provides an exemption from the adequate directions for use requirement. Section 505(i) states that sponsors, investigators or persons acting on their behalf may not suggest in a promotional context that an investigational new drug is safe or effective for the uses it is being developed for. This section is designed to limit promotional claims and preclude

commercialization before approval, while allowing for the dissemination of scientific research.

Specific claims with which the OPDP took issue include statements suggesting research has shown that the product “delivers optimal anti-cancer activity” and that a Phase 3 trial has “demonstrated improved survival” when used by newly diagnosed, high-risk AML patients. OPDP officials noted that the promotional material included only the proprietary name Vyxeos, without identification of the investigational drug product. They further observed that the cited references include preclinical studies and an analysis in cell lines, neither of which support claims of efficacy in human patients. Celator also failed to include in its ASCO display information identifying the drug as an investigational product that has not been approved for commercial disruption.

### **FDA’s OPDP takes issue with promotional claims made about unapproved opioid**

*The office sent an untitled letter to Durect and Pain Therapeutics for online claims promoting an unapproved opioid as safe and effective and as having abuse-deterrent properties. The letter raised concerns about the lack of clear statements establishing the drug as unapproved. The FDA, citing labeling and abuse-deterrent concerns, subsequently rejected an NDA for the product for the third time.*

The FDA’s Office of Prescription Drug Promotion sent an [untitled letter](#) to Durect Corporation and Pain Therapeutics after a review of their websites found they are promoting the investigational new drug Remoxy Extended-Release Capsules, or Remoxy ER, as safe and effective for the uses for which it is being investigated. The oxycodone product is not the subject of an approved marketing authorization. Pain Therapeutics submitted a new drug application in March 2016.

Although investigational new drugs that comply with Section 505(i) of the Federal Food, Drug,

and Cosmetic Act may be exempt from premarket approval requirements for adequate directions for use, the act also indicates that sponsors or investigators must not present in promotional content that the product is safe or effective, or otherwise promote it.

The OPDP identified several instances in which presentations on the websites suggest the product is safe or effective for the uses for which it is being investigated. On the landing page of the Durect website, information about the product appears on a rotating basis with information about other products, with a link titled “Learn More.” However, the statements about the product on this page are present as established facts, suggesting the product is safe and effective with characteristics such as “long-lasting” and “tamper-resistant.” The presentation identifies the product only by its proposed trade name and fails to indicate that the product is an investigational new drug that has not yet received approval.

The product webpage is broken down by separate headers, but only one can be expanded to review content at a time. Under “Potential Benefits,” the OPDP identified claims such as “effective long-term pain control” and “designed to deter abuse.” The most prominent claims suggest the product is safe or effective for the purposes in which it is being assessed, or promoted the drug as having specific properties. The webpage is misleading in that it also fails to clearly identify the product as investigational. Although the “Current Status” heading states that an NDA has been submitted, the agency determined that this “indirect statement” about the drug not being approved yet is visible only to those who click the heading, and noted that the statement cannot be viewed at the same time as the material promoting the drug. The OPDP found these presentations to be inadequate in conveying the product’s unapproved status and in mitigating impressions that the drug is safe or effective.

The OPDP identified similar issues on Pain Therapeutics' websites, with claims promoting the drug and indicating it has properties such as "resists injection or snorting."

The OPDP said these conclusory statements suggest an effort to shape public perception of the drug in the lead-up to its launch, before the FDA's assessment of the product. These statements not only raise public health concerns, but may also remain probative evidence after a product is in distribution. The untitled letter raises particular concerns about these "irresponsible" claims during the height of a national opioid abuse epidemic. The agency notes that for all the extended-release opioids the FDA has approved to date, labeling that describes abuse-deterrent properties includes information not presented on the Remoxy ER website, clarifying that even with these properties, opioids still expose users to risks of addiction, misuse and abuse.

After the untitled letter was issued, the FDA sent a complete response letter [rejecting](#) the NDA for the product over concerns about abuse-deterrent properties and proposed labeling. The rejection is the third failed NDA for the product.

### **FDA issues draft guidance on recognition in 510(k) Third Party Review Program**

*The draft guidance incorporates elements from an international regulatory assessment program and outlines the factors the FDA will consider in determining whether to recognize a third-party organization for participation in the program.*

The FDA published [draft guidance](#) describing the recognition, re-recognition, denial and withdrawal process under the 510(k) Third Party Review Program, previously known as the Accredited Persons program. Under Section 523 of the Federal Food, Drug, and Cosmetic Act, the FDA is sanctioned to accredit third parties to review premarket notification

submissions and recommend the preliminary classification of certain devices.

The draft guidance incorporates elements from the International Medical Device Regulators Forum's Medical Device Single Audit Program, a regulatory assessment program outlining the critical building blocks of an auditing program, which are based on a common set of criteria for the recognition and monitoring of regulatory auditing entities. The FDA guidance states that the agency will use IMDRF criteria for the recognition, re-recognition, withdrawal or denial of recognition under the TP Review Program.

Under the TP Review Program, third-party organizations carry out the equivalent of an FDA premarket review of a 510(k) submission and then forward their reviews and recommendations to the FDA for a decision on substantial equivalence, due within 30 days. The program is unavailable for class III devices, any class II devices designed to be permanently implanted or life sustaining/supporting, and devices that require clinical data. It also excludes 510(k)s that require multicenter review. To participate, review organizations need to be recognized by the FDA. In determining recognition, the FDA takes into account:

- **Operational considerations.** Applications and communications must be in English, and a U.S. representative must be designated if the organization is foreign.
- **Management of impartiality.** Organizations should be impartial and free from commercial, financial or other pressures that may result in a conflict of interest or the appearance thereof.
- **Personnel involved in reviewing.** Organizations and their staff should have clear knowledge and experience in the FD&C Act, the Public Health Service Act and regulations in the Code of Federal Regulations related to the implementation of these statutes.

- **Use of external technical experts.** If an organization uses external experts, they should meet the same standards outlined for organization staff.
- **Outsourcing.** Use of any external organization is deemed outsourcing and should meet the same standards as those established for review organizations themselves.
- **Confidential information.** Organizations must treat information received, as well as recommendations, as proprietary and should not publicly disclose a 510(k) submission for a device that is not currently on the market and where the intent to market has not been made public.
- **Complaints.** Organizations should follow IMDRF procedures in forwarding complaints to the FDA about 510(k) submitters that could suggest an issue related to a device's safety or efficacy.
- **Recordkeeping.** To merit recognition, TP Review Program organizations need to keep records that support their initial and continuing qualifications.

The draft guidance outlines how TP Review Program organizations should review and analyze the data submitted in a 510(k) to make a recommendation on substantial equivalence, and describes the steps in a 510(k) review. It also provides recommendations on the content and format for submitting an application for initial recognition to participate in the TP Review Program.

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

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