Top 10 Recent FDA & DEA Developments — And What's Next in 2024

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The FDA-regulated community witnessed many notable events during 2023 — including a federal appeals court's upholding of the criminal convictions of two medical device company officials on charges related to alleged off-label marketing, the FDA's issuing of a proposed rule to fully regulate laboratory developed tests (LDTs) as devices following decades of controversy about the agency's authority over the tests, important FDA guidance dealing with device cybersecurity, new final FDA guidance on informed consent in clinical trials, and a long-awaited final rule on the use of the major statement in direct-to-consumer (DTC) TV and radio advertisements.

Developments during 2023 related to FDA and Drug Enforcement Administration (DEA) regulatory and enforcement activities will continue to reverberate throughout 2024 and beyond. Below is our list of the 10 most important FDA and DEA developments of 2023 — and our view of what's to come in the near future.

Court Upholds Convictions for Off-Label Promotion of Device, Rejecting First Amendment Arguments

First Circuit: Defendants' Promotional Speech Could Constitute Evidence of the Device's Intended Use

A federal appeals court upheld the convictions of two medical device company executives on adulteration and misbranding charges stemming from their alleged off-label promotion of a device (*United States v. Facteau*, 89 F.4th 1 (1st Cir. 2023)).

In its 83-page opinion, the U.S. Court of Appeals for the First Circuit rejected the defendants' argument that their misdemeanor convictions under 21 U.S.C. §333(a)(1) violated the First Amendment, holding that the executives' promotional speech constituted evidence of the device's intended use.

Background. William Facteau served as the CEO of Acclarent Inc., and Patrick Fabian served as the company's vice president of sales. Acclarent developed the Relieva Stratus Microflow Spacer, a medical device intended for the treatment of chronic sinusitis.

To obtain FDA authorization to market the device, the company decided to first gain premarket notification (510(k)) clearance for the device for use as a post-surgical spacer that could maintain an opening to the ethmoid sinus and that was capable of releasing saline into the sinuses.

The company determined that it would later seek a second 510(k) clearance for the use of the device to deliver Kenalog, a topical steroid used to reduce sinus inflammation, to the ethmoid sinuses.

In August 2006, the company submitted its first 510(k) for the use of the Stratus device as a spacer. The following month, the FDA cleared the Stratus device for the use indicated in the 510(k).

In April 2007, Acclarent wrote to the FDA seeking to change the device's labeling to add an indication for use of the product "to irrigate the sinus space for diagnostic and therapeutic procedures" and to inject either saline or some "other therapeutic agent."

In May 2007, the FDA denied the company's request, saying that the proposed use of the device with a therapeutic agent might render the device a drug-device combination product. In any event, the agency told Acclarent, the proposed indication would constitute a significant change to the device, meaning that the company would need to submit a new 510(k) and receive FDA clearance "prior to marketing [Stratus]" with the proposed changes to its indicated use.

By November 2007, the company determined that a successful 510(k) for use of the Stratus device to deliver a drug would need to be supported by clinical studies. However, the study that Acclarent was conducting at the time had to be halted in December 2007 when the FDA determined that the study posed a significant risk to its subjects. The FDA approved a new study in August 2008, but that study was halted in July 2009 following reports of adverse events.

Acclarent never completed an FDA-approved study to support the use of the Stratus device with Kenalog, and the company never filed a 510(k) for that intended use. Nevertheless, the company proceeded with a plan to begin promoting the Stratus device for that use in the second half of 2008.

District court proceedings. In April 2015, a grand jury of the U.S. District Court for the District of Massachusetts returned an 18-count indictment against Facteau and Fabian that included 10 counts of marketing an adulterated and misbranded device that were directed to the alleged off-label promotion of the Stratus.

Following a 30-day trial in June and July 2016, a federal jury returned misdemeanor convictions of Facteau and Fabian on the 10 counts.

The following month, the defendants moved for judgments of acquittal, arguing that:

- their convictions were based on truthful, non-misleading speech and therefore violated their rights under the First Amendment;

- the regulatory scheme under which they were convicted was unconstitutionally vague;

- the jury was improperly instructed on the evidence that might be considered in determining a device's intended use;

- the two defendants lacked fair notice of the case against them and therefore were denied due process, because the government proceeded on a supposedly novel prosecutorial theory and relied on internal company communications as evidence of intended use; and

- the government had provided insufficient evidence of statements promoting off-label use made by the two executives or by Acclarent employees with respect to 10 shipments of the Stratus device upon which their convictions had been based.

In September 2020, the district court rejected these and other claims and denied the defendants' motion (*United States v. Facteau*, No. 15-cr-10076-ADB, 2020 U.S. Dist. LEXIS 167169, 2020 WL 5517573 (D. Mass. Sept. 14, 2020)). Later the court imposed a $1 million fine on Facteau and a $500,000 fine on Fabian. The defendants appealed to the First Circuit.

Two First Amendment arguments. Facteau argued on appeal that the district court improperly rejected the two defendants' proposed jury instruction that would have barred the jury from considering any truthful, non-misleading promotional speech as evidence of the intended use of the Stratus device.

He argued that:

- using promotion speech as evidence of a device's intended use in effect criminalizes that speech — despite a growing body of law in the Second Circuit holding that truthful, non-misleading speech promoting off-label use is protected; and

- because the FDA had through guidance adopted a policy that shields certain nonpromotional speech from evidentiary use, allowing speech outside of this safe harbor to serve as evidence imposes an impermissible content-based burden on "disfavored" speech, especially off-label promotion.

Jury instruction. The appeals court noted that, instead of providing the jury instruction about truthful, non-misleading speech that the defendants proposed, the district court had told the jury that, because "it is not illegal in and of itself for a device manufacturer to provide truthful, non-misleading statements about an off-label use," the jury could not find a defendant guilty "based solely on truthful, non-misleading statements promoting an FDA-cleared or approved device, even if the use being promoted is not a cleared or approved use."

Nevertheless, the district court had continued, the jurors could consider truthful, non-misleading speech promoting off-label use as "evidence" in determining "whether the government has proved each element" of the charged adulteration and misbranding offenses, "including the element of intent."

The appellants objected to the district court's "failure to instruct the jury that truthful speech cannot be considered as evidence of intended use."

Use of speech to prove intent. The First Circuit panel noted that the Supreme Court has held that as a general matter the First Amendment does not apply to the "evidentiary use of speech to establish the elements of a crime or to prove motive or intent" (*Wisconsin v. Mitchell*, 508 U.S. 476 (1993)).

Nevertheless, Facteau argued that the First Amendment does not permit a jury to consider off-label promotional speech as evidence of intended use.

He pointed to the Second Circuit's decision in *United States v. Caronia*, 703 F.3d 149 (2d Cir. 2012), and its progeny in *Amarin Pharma, Inc. v. FDA*, 119 F. Supp. 3d 196 (S.D.N.Y. 2015).

Applying Caronia. *Caronia,* the First Circuit panel noted, had for the first time limited the use of off-label promotional speech in the context of misbranding prosecutions — with the Second Circuit holding that the defendant's conviction in that case violated the First Amendment because the prosecution "repeatedly argued that he engaged in criminal conduct by promoting and marketing the off-label use of … an FDA-approved drug," leaving "the jury to understand that [the defendant's] speech itself was the proscribed conduct."

However, the First Circuit panel distinguished *Caronia*, saying that the Second Circuit's decision was "meaningfully different" from the appeal before it.

"Unlike in *Caronia*," the court said, "the government's case here relied on a wide array of evidence, which included not only promotional speech about off-label uses but also internal communications regarding regulatory and marketing strategy and the product's physical design."

"It was not the case, as it was in *Caronia*," the First Circuit continued, "that the government set out to punish appellants for what they said about the product; rather, what appellants said about Stratus simply shed light on how they intended it to be used."

"The district court's instructions made as much clear," the court added, "specifying that 'it is not illegal in and of itself for a device manufacturer to provide truthful, non-misleading information

about an off-label use' and that the jury may not find a defendant guilty 'based solely on truthful, non-misleading statements promoting an FDA-cleared or approved device, even if the use being promoted is not a cleared or approved use.'"

The First Circuit also said that the government's "successful theories" for the misbranding and adulteration charges "did not turn on whether Acclarent's statements left Stratus without adequate directions for use, as was the case in *Caronia*. Though the government did present that theory of misbranding to the jury, the jury rejected that approach and instead found appellants guilty of misbranding because Stratus lacked the proper regulatory clearance — a theory of misbranding less intertwined with appellants' speech."

Moreover, the court noted, "unlike the defendant in *Caronia*, both Facteau and Fabian were high-level executives at Acclarent responsible not just for what was said about Stratus publicly but also for internal decisions on product design and regulatory strategy (in the case of Facteau), as well as sales strategy (in the case of both)."

"In short," the appeals court concluded, "*Caronia* does not render appellants' proposed instruction an accurate statement of law that properly captured the nuances of the First Amendment interests at stake in this case. Calculated to cut off any evidentiary use of off-label promotional speech, appellants' preferred instruction would have removed this case from the teachings of *Mitchell* and placed it within the domain of *Caronia* without the facts to justify such a move. We discern no error in the district court's refusal to take that step, nor in the instructions it ultimately handed down, which better respected the sensitive balance between protecting promotional speech without shielding such speech from evidentiary value."

Safe harbor policy. Facteau's other First Amendment argument focused on FDA guidance explaining when truthful, non-misleading speech regarding off-label uses will not be considered evidence of a product's intended use.

He pointed to two agency guidance documents as the source of the safe harbor policy:

- the 2011 draft guidance "Responding to Unsolicited Requests for Off-Label Information About Prescription Drugs and Medical Devices"; and

- the 2014 revised draft guidance "Distributing Scientific and Medical Publications on Unapproved Uses — Recommended Practices."

The argument relied in part on the Supreme Court's decision in *Sorrell v. IMS Health Inc.,* 564 U.S. 552 (2011), in which the Court held unconstitutional a Vermont law that required drug marketers to obtain a physician's consent before they could use data about the physician's prescribing practices to inform their marketing strategy but imposed no similar requirement on using the data for other purposes, such as for research or patient education.

"Facteau contends that the FDA's safe harbor operates in similar fashion by using the content of a medical product manufacturer's speech to determine whether that speech will bear the burden of potentially being used as evidence of intended use," the First Circuit panel noted.

His argument, the court said, was that "although it is generally permissible for a jury to consider promotional speech as evidence of intent, any evidence so presented to the jury because it is not protected by the safe harbor would be the product of a government policy that unequally foists the burden of potential evidentiary use upon certain speech based on its content. Thus, the court should have instructed the jury to exclude *all* evidence derived from appellants' promotional speech, as appellants requested."

The appellate panel, however, rejected Facteau's safe harbor argument, agreeing with the government that Facteau had forfeited this argument because it had not been raised in the district court.

"Although appellants made general First Amendment objections to the court's instruction that the jurors may consider promotional speech as evidence of intent, and at times couched their arguments in terms of content-and-viewpoint-based discrimination," the court said, "they never suggested that the FDA's safe harbor guidance constituted such discrimination. Indeed, Facteau's trial counsel insisted — over the government's objection — that the court adopt an instruction modeled on one of the guidance documents, hardly suggesting that appellants viewed the safe harbor as odious to protected speech."

In the end, the court held that, because Facteau's safe harbor argument failed to clear the threshold hurdle of demonstrating that the safe harbor policy "burdens" protected speech within the meaning of the First Amendment, the court need not analyze whether the safe harbor policy imposed such a burden by drawing content-based distinctions or whether those distinctions would satisfy heightened scrutiny.

"Facteau's argument fundamentally misconstrues the nature of the FDA safe harbor," the First Circuit panel added. "Far from burdening what device manufacturers may say, the safe harbor guidance *expands*, rather than contracts, the domain of speech that the government shields from being used as evidence. If, as a general matter, the evidentiary use of speech discussing off-label use does not raise First Amendment concerns, then presumably a policy that limits the consideration of such speech as evidence of intended use does not raise First Amendment concerns either."

"It is of course true that medical device sellers, aware that their speech may become evidence of intended use, will necessarily choose their words carefully when promoting their products," the court said. "But such efforts do not amount to a 'burden' on free expression when it is conduct — in this case, introducing misbranded or adulterated devices into commerce — and not speech that the law aims to control."

"We thus find no merit in Facteau's apparent contention that, because the FDA's safe harbor policy shields some speech from evidentiary use, the jury should have been instructed to disregard all promotional speech as evidence of intended use," the First Circuit concluded. "And, having rejected the *Caronia* argument as well, we conclude that Facteau's First Amendment arguments fail to support departing from *Mitchell*'s long-standing rule that using speech as evidence of intent does not implicate the First Amendment. Accordingly, neither the district court's rejection of appellant's proposed instruction nor its decision to instead instruct the jury that it could consider speech for evidentiary purposes was in error."

DOJ To Require Compliance-Related Criteria in Compensation Programs as Part of Criminal Resolutions

Criminal Division Will Offer Penalty Reductions to Firms That Seek To Claw Back Pay From Wrongdoers

The Department of Justice (DOJ) established a three-year pilot program intended to reward corporations that incentivize compliance as part of their compensation programs, including through the use of clawback policies.

According to the DOJ, one goal of the pilot program is to explore "how policies may seek to potentially shift the burden of corporate financial penalties away from shareholders — who in many cases do not have a role in misconduct — onto those more directly responsible."

Using compensation to encourage compliance. The pilot program was announced in March 2023 by Deputy Attorney General Lisa Monaco, who in September 2022 announced that the DOJ would examine how to encourage compliance through corporate compensation programs.

Monaco told an audience at a Miami meeting of the American Bar Association (ABA) National Institute on White Collar Crime that "every corporate resolution involving the Criminal Division will now include a requirement that the resolving company develop compliance-promoting criteria within its compensation and bonus program."

Moreover, she noted, the Criminal Division "will provide fine reductions to companies who seek to claw back compensation from corporate wrongdoers."

"At the outset of a criminal resolution," she said, "the resolving company will pay the applicable fine minus a reserved credit equaling the amount of compensation the company is attempting to claw back from culpable executives and employees."

"If the company succeeds and recoups compensation from a responsible employee," she continued, "the company gets to keep that clawback money — and also doesn't have to pay the amount it recovered."

Even where a company in good faith pursues a clawback but is unsuccessful, she said, the company is "still eligible to receive a fine reduction."

The program is intended "to encourage companies who do not already factor compliance into compensation to retool their programs and get ahead of the curve," Monaco said.

Fostering a culture of compliance. Elaborating on the pilot program the following day, Assistant Attorney General Kenneth A. Polite Jr. told the ABA audience, "Compensation structures that clearly and effectively impose financial penalties for misconduct can deter risky behavior and foster a culture of compliance."

"At the same time," he added, "positive incentives, such as promotions, rewards and bonuses for improving and developing a compliance program or demonstrating ethical leadership, can drive compliance."

The pilot program was launched with these principles in mind, he said.

Compliance enhancements. According to a detailed DOJ description of the pilot program, beginning March 15, 2023, when the pilot program went into effect, every corporate resolution entered into by the DOJ's Criminal Division requires that the company "implement criteria related to compliance with its compensation and bonus program."

During the term of the resolution, the company will be required to report to the Division annually about the implementation of the criteria.

The criteria may include:

- a ban on bonuses for employees who do not satisfy compliance performance requirements;

- discipline of employees who violate the law, as well as discipline of others (a) who had supervisory authority over the employees or business areas engaged in the misconduct and (b) who knew of or were blind to the misconduct; and

• incentives for employes who demonstrate “full commitment to compliance processes”.

Prosecutors “will use their discretion in fashioning the appropriate requirements based on the particular facts and circumstances of the case,” the department said, including applicable U.S. and foreign law. “In making this determination,” the department said, “prosecutors will be mindful of, and afford due consideration to, how the company has structured its existing compensation program.”

Fine reductions. In cases where a criminal resolution is called for, if a company “fully cooperates and timely and appropriately remediates” and demonstrates that before the time of the resolution it had implemented a program to recoup compensation from employee wrongdoers and their responsible supervisors that is consistent with the compliance-related compensation criteria, “an additional fine reduction may be warranted,” the DOJ said.

In such circumstances, in addition to any other applicable reduction, federal prosecutors will reduce the criminal fine in the amount of 100% of compensation that is recouped during the period of the resolution. Any applicable restitution, forfeiture, disgorgement or other agreed-upon payment by the company will not be affected.

Specifically, the company will be required to pay the otherwise applicable fine reduced by 100% of the amount of compensation that the company is attempting to claw back (the “possible clawback reduction”).

At the end of the resolution period, if the company has not recouped the full amount of compensation that it sought to claw back, the company will be required to pay the amount that it attempted to claw back minus 100% of the compensation actually recovered.

Even if a company’s good-faith attempt to recover the compensation is unsuccessful, Criminal Division prosecutors may in their discretion “accord a reduction of up to 25% of the amount of compensation the company attempted to claw back — such that the company must at the conclusion of the resolution term make an additional fine payment of the possible clawback reduction less the determined reduction percentage of the compensation sought.”

Such a reduction may be appropriate, the DOJ said, where, for instance, a company has incurred significant litigation costs for shareholders or can demonstrate that it is highly likely that it will successfully recoup the compensation shortly after the end of the resolution term.

FDA Proposed Rule Would Fully Regulate LDTs as Devices With Phaseout of Enforcement Discretion

On Sept. 29, 2023, the FDA released a long-anticipated proposed rule under which the agency’s regulations would specify that LDTs are to be regulated as medical devices. In addition, the FDA proposed a phaseout period for the enforcement discretion that the agency has exercised for years with respect to the tests.

The proposed rule — the latest step in the agency’s year-long effort to more vigorously regulate LDTs — was published in the *Federal Register* on Oct. 3, 2023 (88 Fed. Reg. 68006).

LDTs are in vitro diagnostic products (IVDs) that the FDA has described as intended for clinical use and that are designed, manufactured and used within a single clinical laboratory that meets certain laboratory requirements.

"Long-standing view." Specifically, the FDA proposed to update the definition of "in vitro diagnostic products" at 21 C.F.R. §809.3(a) to make explicit that IVDs are devices under the Federal Food, Drug, and Cosmetic Act (FD&C Act), including when the manufacturer of the IVD is a laboratory.

"The amendment would reflect FDA's long-standing view that LDTs are devices under the FD&C Act and would reflect the fact that the device definition in the FD&C Act does not differentiate between entities manufacturing the device," the agency said in the preamble to the proposed rule. "In other words, whether an IVD is a device does not depend on where or by whom the IVD is manufactured."

The agency also proposed to end its general enforcement discretion approach for LDTs in stages over a four-year phaseout period. "FDA intends to phase out its general enforcement discretion approach for LDTs so that IVDs manufactured by a laboratory would generally fall under the same enforcement approach as other IVDs," the agency said.

Agency rationale. In implementing the Medical Device Amendments of 1976 (MDA), the FDA said in the preamble, the agency "has generally exercised enforcement discretion such that it generally has not enforced applicable requirements with respect to most LDTs. Enforcement discretion for LDTs developed as a matter of general practice. However, the risks associated with LDTs are much greater today than they were at the time of enactment of the MDA."

"The agency has become increasingly concerned that some LDTs may not provide accurate test results or perform as well as FDA-authorized tests and others complying with FDA requirements," an agency announcement of the proposed rule asserted. "Recent information, including evidence from a variety of sources, including published studies in scientific literature, allegations of problematic tests reported to the FDA, the agency's own experience in reviewing IVDs offered as LDTs, news articles and class action lawsuits suggest that the situation is getting worse."

"In FDA's experience, including with COVID-19 tests and IVDs that are offered as LDTs after FDA's approval of a comparable companion diagnostic," the agency said in the preamble, "many test systems made by laboratories today are functionally the same as those made by other manufacturers of IVDs. They involve the same materials and technologies, are intended for the same or similar purposes, are developed by and for individuals with similar expertise, and are marketed to the same patients, sometimes on a national scale. For these reasons, tests made by laboratories are often used interchangeably by health care providers and patients with tests made by other manufacturers."

The agency said that some LDTs may have led to patients being over- or undertreated for heart disease, patients with cancer being exposed to inappropriate therapies or not getting effective therapies, and incorrect diagnoses of rare diseases, autism and Alzheimer's disease.

However, the agency insisted that it recognized that many IVDs manufactured by laboratories are currently being marketed as LDTs and that a sudden change could negatively affect the public, including patients and industry. "In particular, FDA understands that the health care community and patients have been using these IVDs, and that coming into compliance will take time for manufacturers," the agency said.

Device requirements affected. The FDA proposed to apply the enforcement discretion phaseout policy to IVDs offered as LDTs — i.e., IVDs that are manufactured and offered as LDTs by laboratories that are certified under the Clinical Laboratory Improvement Amendments (CLIA) and that meet the regulatory requirements under CLIA to perform high-complexity testing, even if those IVDs do not fall within the FDA's traditional understanding of an LDT because they are not designed, manufactured and used within a single laboratory.

The phaseout would gradually eliminate the agency's general enforcement discretion approach with respect to:

- premarket review requirements;
- quality system (QS) requirements;
- registration and listing requirements;
- medical device reporting (MDR) requirements (i.e., reporting adverse events);
- device correction and removal requirements; and
- "other requirements applicable to such tests."

Possible exemptions for some LDTs. Anticipating that some stakeholders will suggest that the agency continue to maintain its general enforcement discretion with respect to (1) premarket review and some or all QS requirements, (2) a subset of LDTs (for example, low- and moderate-risk LDTs), or (3) LDTs offered by laboratories with annual receipts below a certain threshold (for example, $150,000), the FDA specifically asked for commenters to suggest public health rationales for continuing any form or degree of enforcement discretion.

The agency also asked for comment on whether any enforcement discretion should be retained for LDTs manufactured by academic medical center laboratories, as well as whether programs such as the New York State Department of Health Clinical Laboratory Evaluation Program or programs within the Veterans Health Administration could be leveraged to continue the general enforcement discretion approach.

Proposed phaseout stages. The FDA structured its proposed phaseout policy to contain five key stages:

- ***Stage 1:*** End the general enforcement discretion approach with respect to MDR requirements and correction and removal reporting requirements one year after the FDA publishes a final phaseout policy, which the agency said it intends to issue in the preamble of the final rule.
- ***Stage 2:*** End the general enforcement discretion approach with respect to requirements other than MDR, correction and removal reporting, QS, and premarket review requirements two years after the FDA publishes a final phaseout policy.
- ***Stage 3:*** End the general enforcement discretion approach with respect to QS requirements three years after the agency publishes a final phaseout policy.
- ***Stage 4:*** End the general enforcement discretion approach with respect to premarket review requirements for high-risk IVDs three and a half years after the FDA publishes a final phaseout policy, but not before Oct. 1, 2027.
- ***Stage 5:*** End the general enforcement discretion approach with respect to premarket review requirements for moderate-risk and low-risk IVDs that require premarket submissions four years after the agency publishes a final phaseout policy, but not before April 1, 2028.

Each of the phases is discussed in detail in the preamble to the proposed rule.

The proposed phaseout policy does not in any way alter the fact that it is illegal to offer IVDs without complying with applicable requirements, the FDA asserted. Regardless of the phaseout time frame and continued enforcement discretion approach for certain IVDs, the agency said, the FDA "retains discretion to pursue enforcement action at any time against violative IVDs when appropriate."

The agency proposed that the effective date for the final rule would be 60 days after the final rule is published in the *Federal Register.*

In a September 2023 preliminary regulatory impact analysis of the LDT proposed rule, CDRH estimated that the final rule would result in tens of thousands of submissions for FDA review of IVDs currently offered as LDTs, including:

• 4,210 original PMAs, product development protocols, and panel-track PMA supplements;

• 32,160 510(k) submissions; and

• 4,202 de novo classification requests.

Finalized Cybersecurity Guidance Covers FDORA Mandates, Adds Quality System and TPLC Recommendations

In September 2023, the FDA issued an important update of its October 2014 guidance on cybersecurity assurances that medical device manufacturers should include in their premarket submissions to the agency. The new guidance, intended to address the heightened level of risk posed by the increased interconnectivity of devices, also covers cybersecurity considerations that device firms should address in their quality systems on an ongoing basis.

The new guidance includes recommendations for compliance with the enhanced cybersecurity requirements included in the Food and Drug Omnibus Reform Act of 2022 (FDORA) — specifically, the statute's premarket and postmarket requirements for devices that can be connected to the internet and that could be vulnerable to cybersecurity threats.

"As more medical devices are becoming interconnected, cybersecurity threats have become more numerous, more frequent, more severe, and more clinically impactful," the FDA said in a Sept. 27, 2023, *Federal Register* notice of the availability of the new final guidance (88 Fed. Reg. 66458).

"As a result," the agency continued, "ensuring medical device safety and effectiveness includes adequate medical device cybersecurity, as well as its security as part of the larger system."

The guidance, "Cybersecurity in Medical Devices: Quality System Considerations and Content of Premarket Submissions" (https://www.fda.gov/media/119933/download), supersedes the October 2014 guidance, "Content of Premarket Submissions for Management of Cybersecurity in Medical Devices."

FDORA requirements for cyber devices. Under FDORA, a person who submits a 510(k), premarket approval (PMA) application, product development protocol, de novo classification request, or humanitarian device exemption application for a product meeting the statutory definition of a cyber device must include in the submission information needed to ensure that the device meets FDORA's cybersecurity requirements (21 U.S.C. §360n-2(b)).

A cyber device is a device that includes software validated, installed or authorized by the sponsor as a device or in a device; has the ability to connect to the internet; and contains technological characteristics validated, installed or authorized by the sponsor that could be vulnerable to cybersecurity threats (21 U.S.C. §360n-2(c)).

Specifically, the sponsor of a cyber device must create a cybersecurity management plan — i.e., "a plan to monitor, identify, and address, as appropriate, in a reasonable time, postmarket cybersecurity vulnerabilities and exploits, including coordinated vulnerability disclosure and related procedures" (21 U.S.C. §360n-2(b)(1)).

The new guidance recommends that manufacturers submit their cybersecurity management plans as part of their premarket submissions "so that FDA can assess whether the manufacturer has sufficiently addressed how to maintain the safety and effectiveness of the device after marketing authorization is achieved."

According to the guidance, cybersecurity management plans should include the following information:

- an identification of the personnel responsible;
- the sources, methods, and frequency for monitoring and identifying vulnerabilities (e.g., researchers, the National Institute of Standards and Technology (NIST) National Vulnerability Database (NIST NVD), third-party software manufacturers);
- a plan to identify and address vulnerabilities identified in the Cybersecurity and Infrastructure Security Agency (CISA) Known Exploited Vulnerabilities Catalog;
- periodic security testing;
- a timeline to develop and release patches;
- update processes;
- the sponsor's patching capability (i.e., the rate at which updates can be delivered to devices);
- a description of the sponsor's coordinated vulnerability disclosure process; and
- a description of how the manufacturer intends to communicate forthcoming remediations, patches, and updates to customers.

Under FDORA, a sponsor of a cyber device must design, develop, and maintain processes and procedures to provide a reasonable assurance that the device and related systems are cybersecure, and make available postmarket updates and patches to the device and related systems to address, (1) on a reasonably justified regular cycle, known unacceptable vulnerabilities; and, (2) as soon as possible out of cycle, critical vulnerabilities that could cause uncontrolled risks (21 U.S.C. §360n-2(b)(2)).

Failure to comply with the FDORA cyber device requirements of 21 U.S.C. §360n-2(b)(2) is a prohibited act under 21 U.S.C. §331(q)(3).

Secure product development framework. In addition to outlining the FDA's recommendations for premarket submissions information addressing cybersecurity concerns, the agency said, the changes since the October 2014 guidance incorporated in the new guidance "are intended to further emphasize the importance of ensuing that devices are designed securely and are designed to be capable of mitigating emerging cybersecurity risks throughout the total product life cycle (TPLC)."

One way to satisfy quality system regulation requirements related to cybersecurity, the guidance suggests, is through a secure product development framework (SPDF), "a set of processes that help identify and reduce the number and severity of vulnerabilities in products."

According to the guidance, an SPDF "encompasses all aspects of a product's life cycle, including design, development, release, support, and decommission. Additionally, using SPDF processes during device design may prevent the need to reengineer the device when connectivity-based features are added after marketing and distribution, or when vulnerabilities resulting in uncontrolled risks are discovered. An SPDF can be integrated with existing processes for product and software development, risk management, and the quality system at large."

Revisions to draft guidance. A draft of the new final device cybersecurity guidance was issued in April 2022 (87 Fed. Reg. 20873).

The FDA said that in revising the draft guidance it aligned the document's recommendations with industry best practices, clarified the level of documentation recommended, clarified interoperability considerations, and clarified that "cybersecurity controls should not be intended to prohibit a user from accessing their device data."

FDA Now Recommends Risk-Based Monitoring for Clinical Trials

In April 2023, the FDA moved from saying that risk-based monitoring for clinical trials is "an important tool" to recommending that "sponsors use a risk-based approach to develop their monitoring plans and to revise their monitoring plans, if needed, as the clinical investigation proceeds."

The change is reflected in an agency final guidance, "A Risk-Based Approach to Monitoring of Clinical Investigations — Questions and Answers" (https://www.fda.gov/media/121479/download), which was released on April 12, 2023.

The final guidance expands on both the August 2013 guidance "Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring," which the new guidance complements but does not supersede, and the 2019 draft guidance by providing additional information to aid sponsors' implementation of risk-based monitoring.

The new guidance focuses on the FDA's recommendations for planning a monitoring approach, developing content for monitoring plans, and addressing and communicating results from monitoring. The questions and answers in the guidance are intended to help sponsors plan and use risk-based approaches to monitor clinical investigations, the agency said.

Revisions to the draft guidance included changes made in response to public comments that requested clarification of some of the FDA's recommendations for planning and implementing risk-based approaches to monitoring clinical investigations.

"This system to manage the quality of the investigation should help ensure data integrity while safeguarding the rights, safety and welfare of trial participants by, for example, focusing on the design of efficient clinical trial protocols, tools for identifying and tracking potential risks, and procedures for data collection and processing," the FDA said in announcing the final guidance.

"This system should include a risk-based approach to monitoring tailored to the potential risks for the specific clinical investigation," the FDA said. "Clinical investigation monitoring is a quality control tool for determining whether investigation activities are being carried out as planned, so that, among other things, deficiencies can be identified and corrected. The types and intensity of monitoring activities should be proportionate to the risks to participants' rights, safety, and welfare and to data integrity inherent in the investigation. Effective implementation of risk-based monitoring of clinical investigations, including the prioritization of monitoring and other oversight activities directed at processes and procedures critical for human subject protection and maintaining data integrity, should help maximize the quality of a clinical investigation."

FDA Releases Long-Awaited Final Informed Consent Guidance

After nearly a decade, the FDA issued final informed consent guidance. The August 2023 guidance — "Informed Consent Guidance for IRBs, Clinical Investigators, and Sponsors" (https://www.fda.gov/media/88915/download) — supersedes the FDA's "Guide to Informed Consent," issued in September 1998, and finalizes draft guidance released in July 2014.

The final guidance provides new information on sponsor personnel being present for some medical device studies, emancipated children, legally authorized representatives, obtaining informed consent through electronic methods, informing subjects of new information, and discussing risks and benefits. The final guidance also includes references and links to relevant guidance issued since 2014.

The FDA noted that a number of federal agencies have revised the Common Rule to include "significant changes to the provisions regarding informed consent." Issued while the FDA was working on its December 2023 final rule to harmonize its regulations with the revised Common Rule, the final guidance did not address "possible future changes to FDA's informed consent regulations that may be developed as part of these harmonization efforts," the agency said. The FDA added that it might amend the guidance "to reflect such changes or to address new questions related to informed consent."

The final guidance follows the outline of the draft guidance, except that the 10 items addressed under additional considerations in the draft guidance have been converted into frequently asked questions in the final.

The frequently asked questions are:

- What are some considerations for enrolling a child into a clinical investigation?
- Are there any additional protections required when enrolling children who are wards of the state?
- What are some considerations for enrolling non-English speaking subjects?
- What process should be followed when it is expected that subjects who do not understand English will be enrolled?

- What process should be followed when the enrollment of subjects who do not understand English is not expected?
- What should be considered when enrolling subjects with low literacy and numeracy?
- What should be considered when enrolling subjects with physical or sensory disabilities?
- What should be considered when enrolling adult subjects with impaired consent capacity?
- Can a subject participate in more than one clinical investigation simultaneously?
- How should data be handled when an enrolled subject decides to withdraw from a trial?
- What steps should be taken to inform subjects when a study is suspended or terminated?
- Should subjects be informed of aggregate study results at the completion of a trial?
- Is informed consent required to review patient records?

The final guidance adds three questions on topics that were not included in the draft guidance. They are:

- Who can serve as a legally authorized representative (LAR) and what is their role?
- How can informed consent be obtained through electronic methods?
- How should subjects be informed of new information that may affect their willingness to continue participation in the research?

FDA Issues Final Rule on Major Statement in DTC Drug Ads

Nearly a decade and a half after a proposed rule was published, on Nov. 20, 2023, the FDA issued a final rule amending its prescription drug advertising regulations concerning the major statement in a DTC TV or radio advertisement that states the name of the drug and its conditions of use.

The rulemaking implements a requirement of the FD&C Act added by the Food and Drug Administration Amendments Act of 2007 (FDAAA, Pub. L. No. 110-85). The notice of proposed rulemaking (NPRM) for the amended regulation was released in March 2010.

The NPRM proposed four standards and one potential additional standard for determining whether the major statement in DTC ads is presented in the statutorily required manner. The final rule, published in the *Federal Register* Nov. 21, 2023 (88 Fed. Reg. 80958), includes all five standards.

The standards are:

- Information is presented in consumer-friendly language with terminology that is readily understandable.
- Audio information, in terms of the volume, articulation and pacing used, is at least as understandable as the audio information presented in the rest of the advertisement.

- In TV advertisements, the information is presented concurrently using both audio and text (dual modality). To achieve dual modality, (1) the text displays either the verbatim key terms or phrases from the corresponding audio or the verbatim complete transcript of the corresponding audio, and (2) the text is displayed for a sufficient duration to allow it to be read easily. The duration is considered sufficient if the text display begins at the same time and ends at approximately the same time as the corresponding audio.

- In TV advertisements, for the text portion of the major statement, the size and style of the font, the contrast with the background, and the placement on the screen allow the information to be read easily.

- During the presentation of the major statement, the advertisement does not include audio or visual elements, alone or in combination, that are likely to interfere with comprehension of the major statement.

The final rule is effective May 20, 2024, and the compliance date for the final rule is Nov. 20, 2024. "The FDA believes that this approach will enable firms to bring DTC TV/radio ads subject to the final rule into compliance with the rule, regardless of where those ads may be in their lifecycle," the agency said.

Submissions to the FDA's Office of Prescription Drug Promotion (OPDP) requesting comments on draft DTC TV/radio ads made on or after the effective date for the final rule will be reviewed for compliance with the final rule. Before the rule's effective date, OPDP comments on submitted ads will not reflect the final rule unless the company specifically requests review of the ad for compliance with the final rule.

Companies should note in their submission cover letter that they are requesting OPDP comments for compliance with the final rule. They also should note whether the draft DTC TV/radio ad in the submission is new promotional material or a revised version that was previously submitted to OPDP on Form FDA 2253 along with the date of the original 2253 submission. OPDP recommended that companies include timestamps for storyboard and video frames.

In addition, if a company chooses to submit a request for comments, OPDP recommends that the company submit proposed DTC TV/radio ads in their entirety.

Rulemaking is "sound," FDA says. The FDA noted that more than a decade had passed between the last comment period to the publication of the final rule. "We recognize the passage of time between the closure of the last comment period on the proposed rule and the issuance of this final rule, which resulted in large part from competing demands for limited agency resources," the agency said. "Despite this passage of time, FDA concludes that this rulemaking is both procedurally and substantively sound," the notice said.

The FDA added that the "fundamental concepts" in the final rule "remain the same as those articulated in the proposed rule. Evolving technologies have allowed for DTC TV/radio ads to be presented on a broader range of devices and disseminated via a broader range of platforms since the issuance of the proposed rule."

However, the FDA noted that an informal review of ads that had recently been submitted to the agency found that companies "have not developed distinct ads for dissemination on these new devices and platforms and that DTC TV/radio ads remain essentially the same. Moreover, fundamental attributes of communication that impact the likelihood that audiences will notice, attend to, and comprehend information, which the standards in the proposed and final rules concentrate on, do not turn on the delivery technology."

In addition, the final rule implements the FDAAA requirement that DTC TV and radio ads for human prescription drugs that state the name of the drug and its conditions of use must have a major statement relating to side effects and contraindications presented in a clear, conspicuous, and neutral manner.

In line with other government standards, findings from scientific research and literature, and the proposed rule, "this final rule establishes standards for determining whether the major statement in these ads is presented in a clear, conspicuous, and neutral manner," the FDA said. However, the final rule does not address "neutral" separately from the overall concept of a "clear, conspicuous, and neutral manner" of presentation, nor does the FDA "associate that attribute exclusively with any single standard. Rather, we conclude that the final standards, independently and collectively, contribute to a clear, conspicuous, and neutral manner of presentation."

FDA Issues Revised Draft Guidance on Providing Scientific Information on Unapproved Uses

In October 2023, the FDA released a revised draft guidance regarding three types of communications by companies to health care providers (HCPs) of scientific information on unapproved uses (SIUU) of approved or cleared medical products.

The guidance, "Communications From Firms to Health Care Providers Regarding Scientific Information on Unapproved Uses of Approved/Cleared Medical Products Questions and Answers" (https://www.fda.gov/media/173172/download), superseded a 2014 draft guidance on distributing scientific and medical publications on unapproved new uses. The revised guidance expanded the scope of the 2014 guidance by covering animal drugs and company-generated presentations. It also stated that SIUU information must be "scientifically sound and clinically relevant." The guidance also adopted a question-and-answer format.

The four questions answered in the guidance are:

- What should companies consider when determining whether a source publication is appropriate to serve as the basis for an SIUU communication?
- What information should companies include as part of SIUU communications?
- What presentational considerations should companies take into account for SIUU communications?
- What additional recommendations apply to specific types of SIUU communications?

The guidance covers companies sharing:

- published scientific or medical journal articles (reprints);
- published clinical reference resources — clinical practice guidelines (CPGs), scientific or medical reference texts, and materials from independent clinical practice resources; and
- company-generated presentations of scientific information from an accompanying published reprint.

In the guidance, the FDA said that it had "sought to strike a careful balance between supporting HCP interest in scientific information about unapproved uses of approved/cleared medical products to inform clinical practice decisions for the care of an individual patient, and mitigating the potential that the government interests advanced by these statutory requirements will be undermined."

"This includes the government interest in incentivizing the development of and satisfaction of applicable premarket requirements for medical products, which reduces the need to rely on unapproved use(s), and in protecting patients from medical product uses that have not been shown to be safe and effective," the agency said.

The FDA said that it "believes it is critical that SIUU communications be truthful, non-misleading, factual, and unbiased and provide all information necessary for HCPs to interpret the strengths and weaknesses and validity and utility of the information in the SIUU communication."

"In addition," the agency said, "any study or analysis described in a source publication that serves as the basis for an SIUU communication should be scientifically sound. The study or analysis should also provide information that is relevant to HCPs engaged in making clinical practice decisions for the care of an individual patient."

However, if companies "choose to use persuasive marketing techniques in communications regarding unapproved uses, this suggests an improper intent to market the relevant products for unapproved uses."

If a company follows the guidance, the FDA said, the agency "does not intend to use such communication standing alone as evidence of a new intended use." However, the agency cautioned, the guidance "does not describe the only circumstances in which FDA does not intend to consider a firm's dissemination of information about an unapproved use of its approved/cleared medical product to be evidence of the firm's intent that the medical product be used for an unapproved use."

"Furthermore, in amending FDA's regulations regarding evidence of intended use in 2020–2021, FDA provided several examples of evidence that, standing alone, are not determinative of intended use," the agency said in the guidance. "In addition, it has long been FDA policy not to consider a firm's presentation of truthful and non-misleading scientific information about unapproved uses at the planned sessions and presentations at medical or scientific conferences to be evidence of intended use when the presentation is made in non-promotional settings and not accompanied by promotional communications."

"Nothing in this draft guidance is intended to convey new policy regarding a firm's existing obligations under the FDA authorities to update FDA-required labeling to accurately reflect what is known about the safety profile of the drug, to ensure that the FDA-required labeling is not false or misleading, or for other reasons," the agency said.

USDA Strengthens Enforcement of Organic Rules

The USDA Agricultural Marketing Service (AMS) amended its National Organic Program (NOP) regulations to strengthen oversight and enforcement of the production, handling and sale of organic agricultural products.

The amendments were issued to "protect integrity in the organic supply chain and build consumer and industry trust in the USDA organic label," AMS said in the preamble to the Jan. 19, 2023, rulemaking (88 Fed. Reg. 3548).

The Strengthening Organic Enforcement (SOE) final rule implemented mandates enacted in the 2018 Farm Bill (the Agriculture Improvement Act of 2018), responded to industry requests for amendments to the organic regulations, and addressed National Organic Standards

Board (NOSB) recommendations. The NOSB assists the USDA in the development of standards for substances to be used in organic production and advises on the implementation of the Organic Foods Production Act of 1990 (OFPA), 7 U.S.C. §6501–§6524.

"When implemented, this rulemaking will improve organic integrity across the organic supply chain, and benefit stakeholders throughout the organic industry," AMS said. "These amendments close gaps in the current regulations to build consistent certification practices to deter and detect organic fraud and improve transparency and product traceability. In addition, the amendments will assure consumers that organic products meet a robust, consistent standard and reinforce the value of the organic label."

The organic marketplace has grown in recent years, both in the number and types of product offerings and in the "increasingly complex organic supply chains," according to AMS. "The absence of direct enforcement over some entities in the organic supply chain, in combination with price premiums for organic products, has created the opportunity for organic fraud."

The OFPA is the statute from which the AMS derives authority to administer the NOP and issue regulations as set down in the recent rulemaking.

The SOE final rule strengthened enforcement of the USDA organic regulations through several actions mandated by 2018 Farm Bill, including the following:

- ***Crackdown on uncertified entities.*** The final rule reduced the types of uncertified entities in the organic supply chain that operate without USDA oversight — including importers, brokers and traders of organic products — to safeguard organic product integrity and improve traceability.

- ***Broader use of import certificates.*** The final rule requires the use of NOP import certificates for all organic products entering the U.S., which will improve the oversight and traceability of imported organic products.

- ***NOP authority.*** The final rule clarified the NOP's authority to oversee certification activities, including the authority to act against an agent or office of a certifying agent. Additionally, certifying agents must notify the NOP upon opening a new office, which allows the NOP to provide more effective and consistent oversight of certifying agents and their activities.

The rule may affect USDA-accredited certifying agents, organic inspectors, certified organic operations, operations considering organic certification, businesses that import or trade organic products, and retailers that sell organic products.

Additional changes to the regulations:

- Require nonretail containers used to ship or store organic products to properly label the products to ensure their accurate identity and traceability.

- Require certifying agents to conduct unannounced inspections of at least 5% of the operations they certify, complete mass-balance audits during annual onsite inspections, and verify traceability back to the previous certified operation in the supply chain during annual onsite inspections.

- Require certifying agents to issue standardized certificates of organic operation generated from the USDA's Organic Integrity Database (OID), in order to verify the validity of certificates of organic operation. Certifying agents must also keep accurate and current certified operation data in OID.

- Clarify how certified operations may submit changes to their organic system plan, with the goal of reducing paperwork burden for organic operations and certifying agents. Certifying agents must conduct on-site inspections at least once per calendar year.

- Establish specific qualification and training requirements for certifying agent personnel, including inspectors and certification reviewers. Personnel must meet minimum education and experience qualifications to ensure high-quality and consistent certification activities.

- Clarify conditions for establishing, evaluating and terminating equivalence determinations with foreign government organic programs, based on an evaluation of their organic foreign conformity systems. This was meant to ensure the compliance of organic products imported from countries that have organic trade arrangements or agreements with the U.S.

- Clarify that the NOP may initiate enforcement action against any violator of the OFPA, including uncertified operations and responsibly connected parties; clarify what actions may be appealed and by whom; and clarify NOP's appeal procedures.

- Specify certification requirements for producer group operations, to provide consistent, enforceable standards and ensure compliance with the USDA organic regulations. Producer groups must meet certain criteria to qualify for certification and must use an internal control system to monitor compliance.

- Clarify the method of calculating the percentage of organic ingredients in a multi-ingredient product to promote consistent interpretation and application of the regulation.

- Require certified operations to develop and implement improved recordkeeping and organic fraud prevention processes and procedures. Certifying agents must conduct supply chain traceability audits and develop and implement information-sharing processes.

The effective date of the rulemaking was March 20, 2023. Stakeholders had one year from the effective date of the rule — until March 19, 2024 — to comply with the changes.

The rulemaking was applauded by the Organic Trade Association (OTA), which called it a "major accomplishment." The regulation "will have significant and far-reaching impacts on the organic sector and will do much to deter and detect organic fraud and protect organic integrity throughout the supply chain," OTA said.

The SOE final rule is "the biggest update to the organic regulations" since passage of the OFPA in 1990, said USDA Under Secretary for Marketing and Regulatory Programs Jenny Lester Moffitt. She noted that it provides "a significant increase in oversight and enforcement authority to reinforce the trust of consumers, farmers and those transitioning to organic production."

DEA Finalizes Regulations Allowing Transfers of Electronic Prescriptions for Controlled Substances

A final rule issued by the DEA in July 2023 allows an electronic prescription for a controlled substance (EPCS) in Schedule II-V to be transferred between registered retail pharmacies for initial filling on a one-time basis upon request by the patient. The rule took effect on Aug. 28, 2023 (88 Fed. Reg. 48365, July 27, 2023).

An NPRM to allow electronic controlled substance prescription transfers was published in the *Federal Register* in November 2021 (86 Fed. Reg. 64881).

Requirements. The final rule provides that any authorized refills included on a prescription for a Schedule III, Schedule IV or Schedule V controlled substance are to be transferred with the original prescription.

Also under the final rule:

- the transfer must be communicated between two licensed pharmacists;
- the prescription must remain in electronic form; and
- the contents of the prescription required under 21 C.F.R. Part 1306 must remain unaltered during the transmission.

Moreover, the transfer of an EPCS for initial dispensing is allowed only if it is allowed under applicable state law or any other applicable laws.

Specific requirements. The final rule also specifies the following:

(1) Information to be recorded to document the transfer of the EPCS. The transferring pharmacist must add the following to the electronic prescription record:

- information that the prescription has been transferred;
- the name, address and DEA registration number of the pharmacy to which the prescription was transferred, as well as the name of the pharmacist receiving the prescription information; and
- the date of the transfer along with the name of the pharmacist transferring the prescription information.

The final rule also imposes duties on the pharmacist who receives the EPCS. The receiving pharmacist must:

- add the word “transfer” to the electronic prescription record at the receiving pharmacy;
- include in the prescription record the name, address and DEA registration number of the pharmacy from which the prescription was transferred, along with the name of the transferring pharmacist; and
- record the date of the transfer and the name of the receiving pharmacist.

(2) Use of prescription processing software. Instead of by manual data entry, the information required to be added to the prescription record may be captured by either pharmacy’s prescription processing software, which may automatically populate the corresponding data fields to document the transfer of the EPCS between the pharmacies.

The transferring or receiving pharmacist, as applicable, must ensure that the populated information is complete and accurate.

(3) Maintenance of electronic records. The electronic records documenting the transfer of the electronic prescription must be maintained by both the transferring pharmacy and the receiving pharmacy for two years from the date of the transfer.

(4) Refills. A pharmacy may transfer electronic prescription information for a Schedule III, Schedule IV or Schedule V controlled substance to another pharmacy for purposes of refill dispensing in compliance with 21 C.F.R. §1306.25. No prescription for a controlled substance in Schedule II may be refilled (21 U.S.C. §829(a); 21 C.F.R. §1306.12(a)).

Cost savings. In the preamble to the final rule, the DEA estimated the cost savings under the final rule at $29 million per year — an increase of $7 million over the estimated cost savings included in the NPRM.

The DEA promulgated the rule in part to alleviate the possible diversion of controlled substances when a pharmacy that receives an electronic prescription cannot fill it.

In such a case, the agency noted, if the patient is forced to contact his or her practitioner to request that a new prescription be sent to a different pharmacy, duplicate prescriptions could be filled if the first pharmacy does not cancel or void the original prescription. The scenario risks the possibility of the prescription being filled twice, the DEA said, as well as creating an additional burden for the patient.

"As more practitioners are issuing controlled substance prescriptions electronically," the DEA said in the preamble to the final rule, "there is an increasing need to address how a pharmacy should handle an electronic controlled substance prescription that it receives but cannot fill."

A DEA interim final rule issued in March 2010 (75 Fed. Reg. 16236) provided practitioners the option of issuing — and provided pharmacies the option of receiving, dispensing and archiving — EPCS for Schedule II-V controlled substances.

In August 2020, the Centers for Medicare and Medicaid Services reported that it had seen a steady increase in the volume of controlled substance prescriptions submitted electronically.

Since January 2021, electronic prescribing for most Schedule II-V controlled substances covered by Medicare Part D has been mandated under the Substance Use-Disorder Prevention that Promotes Opioid Recovery and Treatment for Patients and Communities Act (SUPPORT Act).

According to one study, the rate of electronic prescribing of controlled substances increased from 38 percent in 2019 to 58 percent in 2020 and to 73 percent in 2021.

The final rule amends 21 C.F.R. §1306.08 by adding five subparts to the regulatory section.

What's Next in 2024

Finalized Guidance on Remote Regulatory Assessments May Boost Their Use

In January 2024, the FDA took the unusual step of issuing a revised draft guidance on remote regulatory assessments, which the agency has increasingly used as an alternative to onsite inspections since their widespread use during the COVID-19 pandemic.

The revised draft guidance amended a July 2022 draft guidance document to reflect public comments on the agency's earlier recommendations as well as amendments to the FDA's authority enacted under FDORA — including:

- the expansion of the set of entities subject to manufactory requests for records and other information in advance of or in lieu of an inspection under Section 704(a)(4) of the FD&C Act to include medical device establishments and bioresearch sites; and

- the agency's authority to rely on such records or other information to satisfy requirements related to preapproval or risk-based inspections or to resolve deficiencies identified during such inspections.

The issuing of the revised draft guidance and the FDA's requests in its fiscal year 2025 budget proposal to have Congress further expand its authority to use RRAs — including a request to have its mandatory Section 704(a)(4) records request authority expanded to apply to food, tobacco product, and cosmetic establishments — may signal the agency's readiness to step up its use of RRAs.

FDA-regulated establishments can prepare for RRAs by reviewing the revised draft guidance and the finalized guidance once it is issued to understand both the agency's expectations in connection with the assessments and the establishments' rights with respect to RRAs.

Expect More Guidance on Decentralized Trials, Other Innovative Approaches

The FDA issued draft guidance in 2023 on using decentralized trials, which should spur the use of the clinical research approach by medical product sponsors.

In announcing the availability of the May 2023 draft guidance, "Decentralized Clinical Trials for Drugs, Biological Products, and Devices" (https://www.fda.gov/media/167696/download), Commissioner of Food and Drugs Dr. Robert M. Califf said that the agency "has long considered the benefits of decentralized clinical trials."

"As we seek to improve our evidence generation system," he added, "decentralized clinical trials may enhance convenience for trial participants, reduce the burden on caregivers, expand access to more diverse populations, improve trial efficiencies, and facilitate research on rare diseases and diseases affecting populations with limited mobility."

The FDA is also expected to issue or revise draft guidance on the use of seamless, concurrent, and other innovative clinical trial designs to support the expedited development and review of medical product applications.

Look for More Intensive Promotion-Related Enforcement — With a Possible Shift in Focus

After not issuing an enforcement letter in slightly more than a year, OPDP finished 2023 by issuing four Untitled Letters (one more than in all of 2022) and one Warning Letter (the same number as in 2022).

"OPDP has made no public statements and has delivered no messages about this surge in activity," noted Wayne L. Pines, the editor-in-chief of Thompson's *FDA Advertising and Promotion Manual.* "But whether OPDP intended to send a message or not, many in industry are taking away the message that OPDP is telling the world it is back in the regulation/enforcement business."

This may indicate that OPDP intends to intensify its issuance of enforcement letters in 2024.

In addition, OPDP may be changing the focus of its regulatory work. For several years, most OPDP enforcement letters have cited the minimization or lack of risk information in promotions. Interestingly, the last three enforcement letters of 2023 dealt with the interpretation of efficacy data. This may reflect a new focus on the part of OPDP reviewers.

In all three efficacy-focused letters, OPDP stated that disclaimers are inadequate to mitigate the alleged violations — again sending a clear message that the office does not view disclaimers favorably.

Moreover, with the increase in the impact of internet influencers, bot the FDA and the Federal Trade Commission (FTC) are taking an increased interest in the presentation of product endorsements. The two agencies likely will be watching for misrepresentations or unbalanced endorsements, with the FTC applying the standards that apply specifically to prescription medical products.

Look for Litigation Over FDA's Final Rule on LDTs

The issuing of a final rule phasing out the FDA's enforcement discretion policy for LDTs and making the tests subject to premarket review, quality system, MDR and other device-related requirements is almost certain to spark intensive challenges to the final rule in the courts.

The agency has long asserted that it has regulatory authority over in vitro diagnostic tests produced by laboratories. With the issuance of the final rule, arguments against the FDA's authority to regulate LDTs raised in January 2015 by former Solicitor General Paul D. Clement and Harvard Law School Professor Laurence H. Tribe, who served as counsel to the American Clinical Laboratory Association (ACLA) (https://www.acla.com/wp-content/uploads/2015/01/Tribe-Clement-White-Paper-1-6-15.pdf), are likely to resurface. Other challenges may arise from the specific provisions of the final rule.

Attempts to craft legislation determining the FDA's specific regulatory power over LDTs have continued to be futile. During a March 2024 hearing on the impact of the FDA's proposed rule, convened by the House Energy and Commerce Committee's Subcommittee on Health, members of Congress and most witnesses asserted that action by Congress would be the appropriate way to set up a mechanism for regulating LDTs, but lawmakers have failed several times in the past to agree on legislation proposed by congressional committees and various members of the House and Senate.

It remained to be seen whether the issuing of the FDA's final rule on LDTs will motivate members of Congress to attempt yet again to come up with a legislative resolution of the issue.

Front-of-Package Labeling Rulemaking, Other Food Labeling Changes Are Possible

Both FDA Commissioner Califf and Deputy Commissioner for Human Foods Jim Jones, who joined the FDA in September 2023 to help implement the agency's new unified Human Foods Program, have indicated that front-of-package labeling (FOPL) for food products is a priority for the FDA.

FOPL "is a key aspect of the FDA's nutrition work and an important priority," Califf said at a public meeting on FOPL held in November 2023. He added that the agency's work on front-of-package labeling has the potential to be "iconic."

Jones added that FOPL "has the potential to be a very useful tool for U.S. consumers. It will complement the Nutrition Facts label and work with our other labeling initiatives, including our updates to the definition of the 'healthy' claim and our research on a potential healthy symbol."

The FDA projected that an NPRM regarding FOPL would be issued in June 2024. However, Robin McKinnon, the FDA's senior advisor for nutrition policy, noted that "timelines are dependent on a number of factors. We are not in a position to be able to provide specific feedback on timelines, given how challenging they can be to predict."

Other upcoming changes in food labeling may originate in Congress. Recent legislative proposals have included guaranteeing online shoppers the same access to country-of-origin and seller location information that in-store shoppers have, requiring that the labeling of alternative protein sources that are beef and pork substitutes include the word "imitation," and establishing a USDA advisory panel to study the possibility of a climate-friendly certification and labeling program for food products.

Undercover Agents Will Continue To Play a Crucial Rule in Controlled Substance Enforcement

A common feature of some DEA enforcement actions has been the government's use of undercover agents in actions targeting physicians and pharmacies accused of illegally prescribing or dispensing controlled substances.

For example, a December 2023 DEA decision and order revoking the registration of a Florida pharmacy was based in part on evidence presented by special and undercover officers indicating that the pharmacy had filled at least 47 controlled prescriptions that had been "issued to individuals who, at the time, were deceased" (*APEXX Pharmacy, L.L.C.; Decision and Order*, 88 Fed. Reg. 86941 (Dec. 15, 2023)).

Similarly, during an investigation conducted by the DEA, the California Department of Health and Human Services Office of Inspector General, and the Division of Medical Fraud and Elder Abuse of the California Division of Justice, undercover agents visited the medical practice of a California-based physician 13 times between April and November 2021. During the visits, the physician wrote opioid prescriptions for the undercover agents. The undercover agents' testimony helped lead to the physician's guilty plea to a charge of distributing hydrocodone outside the scope of professional practice in violation of 21 U.S.C. §841. She was sentenced to serve a year and a day in prison (*United States v. Karimi,* No. 4:23-cr-00055-JST (N.D. Cal.)).

Look for the DEA and the DOJ to continue to use undercover agents during investigations of alleged noncompliance with Controlled Substance Act mandates.

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