Top 10 FDA & DEA Developments of 2022 — And Predictions for 2023

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During 2022, as COVID-19 illness became less deadly and less of a disruption in the lives of many Americans, the FDA to a substantial extent turned its attention to other matters, including regulatory issues that had necessarily been lower priorities while the agenda dealt with urgent public health needs during the first years of the pandemic.

The year 2022 brought important court decisions affecting the regulatory and enforcement realities facing the medical product and food industries, as well as significant initiatives from the government agencies that regulate them.

Developments during 2022 related to FDA and Drug Enforcement Administration (DEA) regulatory and enforcement activities are likely to reverberate throughout 2023. Below is our list of the 10 most important FDA and DEA developments of 2022 — and some predictions of what to expect during 2023.

Top 10 FDA & DEA Developments of 2022

1. Revised Device Quality System Regulation Would Incorporate ISO 13485 Requirements by Reference

The FDA Feb. 22 released its long-awaited proposed rule to align the agency's quality system (QS) regulation more closely with ISO 13485, the internationally recognized consensus standard for device quality management systems (QMSs).

The proposed rule, which was published in the Federal Register Feb. 23 (87 Fed. Reg. 10119), would amend the FDA's QS regulation, 21 C.F.R. Part 820, by incorporating by reference International Organization for Standardization (ISO) 13485:2016, Medical devices — Quality management systems — Requirements for regulatory purposes, Third Edition 2016-03-01.

The FDA proposed that a final rule based on the proposed rule would become effective one year after the final rule's publication in the *Federal Register.*

The proposed rulemaking is the first significant revision to Part 820 since 1996, when design controls requirements were added to the regulation.

Removing duplicate requirements. The adoption of ISO 13485 would help remove unnecessary duplicative regulatory requirements, the agency said, including the need for manufacturers in other countries and for U.S. manufacturers that export devices to comply with both Part 820 and ISO 13485, which is already the adopted QMS standard in Canada, Australia, the European Union and Japan.

The agency said that, if finalized, the rule would help harmonize its regulatory framework with that used by other regulatory authorities "to promote consistency in the regulation of devices and provide timelier introduction of safe, effective, high-quality devices for patients."

"While the current QS regulation provides sufficient and effective requirements for the establishment and maintenance of a [QMS]," the FDA said in a Feb. 22 announcement,

"regulatory expectations for a [QMS] have evolved since the regulation was implemented over 20 years ago. The FDA seeks to explicitly require current internationally recognized regulatory requirements for [QMSs] for devices subject to the FDA's jurisdiction."

The FDA also proposed requirements to align the new regulation with existing requirements under the Federal Food, Drug, and Cosmetic Act (FD&C Act) and its implementing regulations.

The agency estimated that the proposed rule would produce approximate annualized net cost savings of between $439 million and $533 million over 10 years.

ISO requirements "substantially similar." According to the FDA, the requirements of ISO 13485 "are, when taken in totality, substantially similar to the requirements of the current Part 820, providing a similar level of assurance in a firm's quality management system and ability to consistently manufacture devices that are safe and effective and otherwise in compliance with the FD&C Act."

ISO 13485 requirements "allow a manufacturer to demonstrate its ability to provide devices and related services that consistently meet customer requirements applicable to such devices and services," the FDA said. The standard's requirements cover device design and development, production, storage, distribution, installation and servicing, as well as the final decommissioning and disposal of devices.

The proposed rule would replace the current Part 820 but preserve the scope of the current regulation, retain and modify a number of the current regulations' definitions, and add FDA-specific requirements and provisions that clarify some concepts used in ISO 13485.

The new regulation would be referred to as the Quality Management System Regulation (QMSR).

In addition, the proposed rule would amend 21 C.F.R. Part 4 to clarify the device QMS requirements for combination products. The amendments would not impact the current good manufacturing practice (cGMP) requirements for combination products, the FDA said.

Future revisions. While the final rule would adopt by reference the current 2016 version of ISO 13485, the agency noted that any future revisions to the ISO standard would need to be evaluated to determine the impact of the changes and whether the finalized version of the proposed rule should be amended.

"Where ISO 13485 diverges from the current Part 820, these differences are generally consistent with the overall intent and purposes behind FDA's regulation of QMSs," the FDA said. "Almost all requirements in the current Part 820 correspond to requirements under ISO 13485."

The agency added, however, that it recognized that reliance on ISO 13485 "without clarification or modification could create inconsistencies with FDA's statutory and regulatory framework." Consequently, it said, the proposed rule includes "additional definitions, clarifying concepts, and additional requirements" that would also require compliance.

"Overall," the FDA said, "we are not proposing to modify the clauses in ISO 13485."

Key Provisions

Definitions. The current 21 C.F.R. §820.3, which defines terms used in Part 820, contains definitions that ISO 13485 does not, and vice versa. Also, some definitions in ISO 13485 do not align with the requirements of the FD&C Act and its implementing regulations.

The proposed rule replaces the term "management with executive responsibility" with the ISO 13485 term "top management," but the proposed rule retains the definition in the current Part 820. As previously, the FDA said, "the most senior employees of a manufacturer are responsible for establishing and making changes to the quality policy and ensuring the manufacturer follows the policy."

Significantly, the Part 820 term "device master record" (DMR) would be removed. "FDA believes the concept of DMR is adequately covered under the requirements for a medical device file under Clause 4.2.3 of ISO 13485," the agency said.

Because the term "customer" is important for interpreting the proposed rule, the FDA proposed adding a definition of the term to cover "persons or organizations, including users, that could or do receive a product or service that is intended for or required by this person or organization." A customer can be internal or external to the organization. The term, the agency said, "can encompass many types of individuals and organizations throughout the device manufacturing process, such as component manufacturers, contract manufacturers, and end users."

The FD&C Act definitions of "device" and "labeling" in 21 U.S.C. §321 would supersede the definitions in ISO 13485.

Similarly, the definitions of "manufacturer" and, with some changes, "product" in Part 820 would supersede the definitions in the ISO standard. The current definition of "manufacturer" would be retained, the agency said, "because it is more comprehensive than the definition in ISO 13485." The FDA is applying a similar logic in proposing a definition of "product" that includes a list of items considered to be "product" under Part 820 that is not included in ISO 13485. As specified in the ISO standard, however, the agency said, the term "product" can also mean "service."

Requirements 'substantially similar.' "While we recognize that adopting ISO 13485 could seem like a significant change," the FDA said, "the current Part 820 and ISO 13485 are substantially similar, and this effort promotes international harmonization. The substance of the ISO 13485 requirements and the activities and actions required for compliance are primarily the same as under the current Part 820."

Risk management. "Risk management" is explicitly addressed in Part 820 only in the risk analysis requirement within the section on design validation (21 C.F.R. §820.30(g)), but risk management is more broadly integrated into ISO 13485. "FDA, however, has expected that manufacturers, led by top management, integrate risk management activities throughout their QMS and across the total product life cycle," the agency said. The FDA said that this was the most noticeable difference between the current Part 820 and ISO 13485.

Although the integration of risk management principles throughout ISO 13485 "does not represent a shift in philosophy," the agency said, "the explicit integration of risk management throughout the clauses of ISO 13485 more explicitly establishes a requirement for risk management to occur throughout a QMS and should help industry develop more effective total product life cycle risk management systems."

Design and development. The ISO standard's Clause 7.3 would apply only to manufacturers of the Class I devices listed in the proposed 21 C.F.R. §820.10 in addition to all manufacturers of Class II and Class III devices. "This retains the scope of current [21 C.F.R.] §820.30(a)," the agency said.

Traceability of life-supporting or life-sustaining devices. Under the proposed rule, devices that support or sustain life, the failure of which to perform when properly used in accordance with instructions for use provided in the labeling can be reasonably expected to result in a significant injury, would be required to comply with ISO 13485 Clause 7.5.9.2's traceability requirements for implantable devices. Life-supporting or life-sustaining devices are currently subject to similar requirements under 21 C.F.R. §820.65, but under the ISO standard only implantable devices are subject to traceability requirements.

Proposed Clarifications of Concepts

Safety and performance. The ISO standard often refers to "safety and performance" as a standard to measure devices. The FDA proposed that readers should construe the phrase to mean the same as "safety and effectiveness" under 21 U.S.C. §360j(f).

Validation of processes. ISO 13485 uses the term "validation of processes" but does not define the term. The proposed rule would retain the definition of "process validation" under 21 C.F.R. §820.3(z)(1).

Proposed Supplemental Provisions

The FDA is proposing additional requirements beyond the requirements of ISO 13485 in two areas: (1) the control of records and (2) device labeling and packaging controls.

Control of records. The FDA proposed to include signature and date requirements for records subject to ISO 13485 Clause 4.2.5. "Records are not necessarily limited to hard-copy documents that are physically signed," the agency said. "Manufacturers can choose to develop electronic records and electronic methods for signing and dating such records, if that best suits their business practices. Our focus is on whether the substance of the requirements is met and not the physicality of the record or signature methodology."

The FDA also proposed requirements intended to ensure that the information required by 21 C.F.R. Part 803, Medical Device Reporting, is captured on certain records of complaints and servicing activities.

In addition, the agency proposed to require that firms document the unique device identification (UDI) for each device or batch of devices in accordance with 21 C.F.R. Part 830 in their records.

Also, the FDA proposed to retain the clarification in current 21 C.F.R. §820.180 about the confidentiality of records that the FDA receives. "This reminds firms that FDA protects such records in accordance with 21 C.F.R. Part 20," the agency said.

Labeling and packaging. Because the ISO standard does not provide requirements for device labeling and packaging beyond a broad requirement to implement defined operations for labeling

and packaging (Clause 7.5.1(e)), the FDA proposed a new Section 820.45, which would retain Part 820 requirements for labeling and packaging controls.

Among the requirements are manufacturer procedures "to ensure the integrity, inspection, storage, and operations for labeling and packaging, during the customary conditions of processing, storage, handling, distribution, and where appropriate, use of the device."

The new Section 820.45 also would require manufacturers to ensure that labeling and packaging have been examined for accuracy before release or storage. The release of labeling would have to be documented (ISO 13485 Clause 4.2.5), and the manufacturer would be required to establish operations to prevent errors, including "inspection of the labeling and packaging immediately before use to assure that all devices have correct labeling and packaging, as specified in the medical device file." Results of this labeling inspection would be required to be documented in accordance with ISO 13485 Clause 4.2.5.

Conforming amendments for combination products. 21 C.F.R. Part 4 provides a streamlined option to demonstrate compliance with the multiple, applicable sets of cGMP requirements for single-entity and co-packaged combination products. One option for such combination products that contain device components is to demonstrate compliance with one other applicable set of requirements along with specified provisions of Part 820.

The FDA's proposed rule would change Part 4's Part 820 references to the corresponding clauses in ISO 13485. "The QS requirements outlined in Part 4 are not fundamentally different than the corresponding requirements in ISO 13485," the agency said. The FDA invited comments on the proposed corresponding amendments and whether additional changes are needed to assure compliance with Part 4.

Future of QSIT. The proposed rule does not affect the FDA's authority to conduct inspections. However, the agency said that it intends to review its Quality System Inspection Technique (QSIT) and, where applicable, revise it to ensure that the FDA's inspection approach is consistent with the ISO 13485-focused final rule.

"Similar to the current QSIT inspection approach," the agency said, "these inspections would involve the collection of information to support observations noted during the inspection and those included on a Form FDA 483, as appropriate and necessary."

The FDA stressed that an agency inspection would not result in the issuance of certificates of conformance to ISO 13485, that it would not develop an ISO 13485 certification program, and that manufacturers with ISO 13485 certificates of performance would not be exempt from FDA inspections.

Comments submitted to the FDA on the proposed rule are available online at https://www.regulations.gov (Docket No. FDA-2021-N-0507).

Specific questions about the proposed rule may be submitted to the agency at Proposed-Device-QMSR-Rule@fda.hhs.gov.

2. FDA Recommends Race and Ethnicity Diversity Plan for Clinical Trials; Congress Enacts Mandate

Sponsors of clinical trials that will be submitted to the FDA should develop a Race and Ethnicity Diversity Plan and submit it to the agency early in clinical development, the FDA recommended in draft guidance released April 13.

In the draft guidance, "Diversity Plans to Improve Enrollment of Participants from Underrepresented Racial and Ethnic Populations in Clinical Trials," the agency recommended that a plan be submitted for medical products for which an investigational new drug (IND) application, a biologics license application, a new drug application (NDA), or investigational device exemption (IDE) is required and/or for which clinical studies are intended to support a device marketing submission (a premarket notification (510(k)), premarket approval (PMA) application, a de novo classification request, or a humanitarian device exemption (HDE) application).

The FDA said that it will evaluate the diversity plan "as an important part of the sponsor's development program."

"The U.S. population has become increasingly diverse, and ensuring meaningful representation of racial and ethnic minorities in clinical trials for regulated medical products is fundamental to public health," FDA Commissioner Dr. Robert Califf said in announcing the availability of the draft guidance. "Going forward, achieving greater diversity will be a key focus throughout the FDA to facilitate the development of better treatments and better ways to fight diseases that often disproportionately impact diverse communities."

While the draft guidance focused specifically on the racial and ethnic demographic characteristics of study populations, the agency advised sponsors to seek diversity in clinical trial enrollment beyond populations defined by race and ethnicity — including other underrepresented populations defined by demographics such as sex, gender identity, age, socioeconomic status, disability, pregnancy status, lactation status and comorbidity.

"The FDA encourages sponsors to also submit plans that help ensure the adequate participation of relevant and underrepresented populations and analyses of data collected from clinically relevant subpopulations," the draft guidance said.

While sponsors may discuss their strategy to enroll a diverse study population at any time throughout the medical product's development, the draft guidance offered recommendations specific to each medical product type for when a diversity plan should be submitted. In addition, the FDA recommended that sponsors include the plan in the marketing application for the medical product along with a description of the successes and challenges in implementing it.

The draft guidance also detailed recommended elements and contents for a diversity study plan.

The document was developed by the FDA Oncology Center of Excellence's Project Equity, which aims to ensure that the data submitted to the agency for approval of oncology medical products adequately reflects the demographic representation of participants for whom the medical products are intended. The FDA Center for Drug Evaluation and Research (CDER), the Center for Biologics Evaluation and Research (CBER), the Center for Devices and Radiological Health (CDRH) and the agency's Office of Minority Health and Health Equity also participated in the development of the draft guidance.

FDORA mandate. Under the Food and Drug Omnibus Reform Act of 2022 (FDORA), enacted as Title III of the Consolidated Appropriations Act, 2023 (Pub. L. No. 117-328), diversity action plans are required for Phase 3 drug trials as well as for "another study of a new drug (other than bioavailability or bioequivalence studies)."

The diversity action plan requirement also applies to most medical devices, and the plans must be submitted in any PMA application or 510(k). FDORA also specified requirements for FDA guidance concerning diversity action plans.

3. In Advisory Opinion, HHS OIG Interprets Anti-Kickback Statute To Bar Patient Assistance Plans; Charity Asks Court To Nullify Advisory Opinion

A charity seeking to help lower-income Medicare patients with cancer obtain Part D-covered drug treatments sued the Department of Health and Human Services (HHS) Office of Inspector General (OIG), alleging that the agency's conclusion in a Sept. 30 advisory opinion that the charity's patient assistance program might violate the Anti-Kickback Statute (AKS) was arbitrary and capricious and violated the charity's First Amendment rights (*Pharmaceutical Coalition for Patient Access v. United States,* No. 3:22-cv-00714 (E.D. Va.)).

The HHS OIG's Advisory Opinion No. 22-19 was the first to analyze a so-called "coalition model" of beneficiary cost subsidizing — an arrangement in which a coalition of drug manufacturers would subsidize cost sharing for their own drugs — in the context of the Part D program.

Proposed arrangement. The charity, the Glen Allen, Va.-based Pharmaceutical Coalition for Patient Access (PCPA), had proposed a patient assistance model based in part on the OIG's guidance in its Nov. 22, 2005, Special Advisory Bulletin on Patient Assistance Programs for Medicare Part D Enrollees (70 Fed. Reg. 70623).

The bulletin referred to "nascent efforts by some in the industry to develop arrangements through which multiple pharmaceutical manufacturers would join together to offer financially needy Part D enrollees a card or similar vehicle that would entitle the enrollees to subsidies of their cost-sharing obligations for the manufacturers' products."

"It is premature to offer definitive guidance on these evolving programs," the OIG said in the November 2005 special advisory bulletin. "Although these programs would operate so that the manufacturers effectively underwrite only the discounts on their own products, we observe that the risk of an illegal inducement potentially may be reduced if: (i) the program contains features that adequately safeguard against incentives for card holders to favor one drug product (or any one supplier, provider, practitioner, or Part D plan) over another; (ii) the program includes a large number of manufacturers, including competing manufacturers and manufacturers of both branded and generic products, sufficient to sever any nexus between the subsidy and a beneficiary's choice of drug; and (iii) each participating pharmaceutical manufacturer offers subsidies for all of its products that are covered by any Part D plan formulary. Other safeguards may also be needed to reduce the risk of an improper inducement."

Advisory opinion's conclusions. In its Sept. 30 advisory opinion, the OIG concluded that the cost-sharing subsidies under the PCPA's proposed arrangement "would present more than a minimal risk of fraud and abuse under the federal [AKS]."

An individual funding manufacturer's cost-sharing subsidies "would be contingent on the purchase of that particular funding manufacturer's oncology products," the OIG said in the advisory opinion. "This remuneration presents many of the hallmark risks of fraud and abuse that the federal [AKS] is designed to prevent."

Among other things, the OIG said, the cost-sharing subsidies proposed in the PCPA's arrangement "would leave funding manufacturers' prices for their products largely unconstrained by a key market control inherent to the current Medicare Part D drug benefit design, while the Medicare program and taxpayers would bear the financial brunt of those unchecked drug prices."

Charity cites OIG's guidance. In its Nov. 9 complaint for declaratory judgment and injunctive relief, filed in the U.S. District Court for the Eastern District of Virginia, the charity said that it had requested a favorable advisory opinion from the OIG "based on regulatory guidance that OIG itself issued which permits a coalition of manufacturers to provide assistance to Medicare Part D patients in financial need — exactly what PCPA stands ready to do."

Nevertheless, PCPA said, the OIG concluded in the Sept. 30 advisory opinion that the charity's proposal "constituted 'prohibited remuneration' that 'induces' the purchase of Medicare items and services under the federal [AKS]." The agency told the charity that there was "no pathway" forward for the plan, PCPA claimed.

Because the AKS is a felony criminal law, PCPA told the court, the charity and any prospective donors "cannot implement the program that would assist patients with cancer in immediate and dire need because OIG has refused to issue a favorable advisory opinion."

Alleged APA violations. The charity alleged that the OIG's conclusions in the advisory opinion were arbitrary and capricious, contrary to law, beyond statutory authority, and an abuse of discretion in violation of the Administrative Procedure Act (APA).

First, PCPA said, the advisory opinion was contrary to law because its proposed program does not violate the AKS. Under the statute, "any prohibited kickback [must] involve a quid pro quo 'in return for' or to 'induce' the purchase of a specific item or service," the charity told the court. "Under PCPA's program, a needy patient with cancer may receive assistance for any one of a broad range of drug and nondrug cancer services after a course of treatment independently has been approved by the patient's medical doctor. As such the proposed program cannot, as a matter of law, satisfy the parallel 'in return for' and 'to induce' requirements of the AKS."

"Where there are a wide range of options presented to a patient, as is the case here," the charity told the court, "OIG has itself conceded that the range of options would 'sever any nexus' between the offered remuneration and a subsequent purchase under the [statute]. In such circumstances, the remuneration is not 'in return for' and does not 'induce' a specific item or service."

"Contrary to the advisory opinion," the charity continued, "the PCPA program does not result in prohibited remuneration because it does not involve any element of corruption, which is an element of an illegal kickback as reflected in the language, structure and history of the AKS. … It is arbitrary and capricious to conclude that a charitable program offering a wide range of assistance to patients with documented financial need in an open and transparent fashion is corrupt, in any way."

Second, the charity asserted, the advisory opinion "treats PCPA fundamentally differently than other similarly situated parties in an arbitrary and capricious manner." The charity alleged that the OIG has allowed other charities to secure funding from manufacturers to support patients using those manufacturers' products, and that the office has allowed other providers to reduce or even completely waive copayments for their own patients.

Third, PCPA said, the advisory opinion was arbitrary and capricious "because it conflicts with OIG's own guidance" — the November 2005 special advisory bulletin. "OIG has specifically advised that, where certain safeguards are present in a 'coalition' of manufacturers working together, such a coalition may provide financial assistance without fear of AKS prosecution. That 2005 guidance has not been rescinded or modified in any way by OIG. … PCPA has, furthermore, complied in all respects with that 2005 guidance."

First Amendment argument. Finally, the charity asserted, in evaluating its proposal the OIG "failed to consider the First Amendment rights of PCPA, as a charitable entity, in seeking to engage in protected solicitation of funds and in the protected speech it would make in securing funds and then dispensing assistance."

Because the OIG's "sweeping advisory opinion conclusions … flatly prevent PCPA from proceeding with its charitable mission" and because the OIG "failed to consider or adopt any narrowly tailored alternative" to those conclusions, the charity argued, "OIG has violated PCPA's constitutional rights."

"OIG reads the AKS so broadly that it improperly criminalizes innocuous, or even beneficial conduct, that is itself protected by the First Amendment. The courts, including the Supreme Court, have not allowed the government to assert overly broad interpretations of criminal statutes [*citing Skilling v. United States, 561 U.S. 358 (2010), and Liparota v. United States,* 471 U.S. 419 (1985)]. This court should take the same step here."

PCPA asked the district court to enter declaratory judgments that the OIG's failure to issue a favorable advisory opinion to the charity was arbitrary and capricious in violation of the APA; that the proposed arrangement was not subject to enforcement under and did not violate the AKS; that the arrangement was entitled to a favorable advisory opinion with respect to enforcement under the AKS; and that the Sept. 30 advisory opinion was invalid in that it violated the First Amendment rights of the charity and its prospective donors to engage in protected free speech.

4. Final 510(k) Template Guidance Moves FDA Toward October 2023 Electronic Submission Mandate

With the finalization of agency guidance on its electronic template for 510(k) submissions and an Oct. 3 invitation to all device firms to use the template, the FDA took major steps toward requiring that all 510(k)s be submitted electronically beginning in October 2023.

The final guidance, "Electronic Submission Template for Medical Device 510(k) Submissions," represents "one of several steps in meeting FDA's commitment to the development of electronic submission templates to serve as guidance submission preparation tools for industry to improve submission consistency and enhance efficiency in the review process," the agency said in a *Federal Register* notice published Sept. 22 (87 Fed. Reg. 57910).

Agency commitments. Section 745A(b) of the FD&C Act requires that submissions and pre-submissions to the agency for devices be submitted in electronic format as specified by the FDA beginning on the date that the agency designates in final guidance (21 U.S.C. §379k-1(b)).

The statute also required the FDA to issue draft guidance by October 2019 providing standards for device submissions in electronic format, a timetable for establishing the standards, and criteria for waivers of and exemptions from the requirements.

In addition, the FDA commitment letter submitted to Congress following negotiations with the device industry that led to enactment of the Medical Device User Fee Amendments of 2017 (MDUFA IV) committed the agency to developing "electronic submission templates that will serve as guided submission preparation tools for industry." The letter also committed the FDA to drafting guidance by fiscal year 2020 on the use of electronic submission templates. In the commitment letter, the FDA said that it would issue a final version of the guidance within 12 months of the close of the comment period for the draft guidance.

In July 2020, the FDA issued a final "parent guidance" for electronic device submissions intended to satisfy these obligations. In the document, "Providing Regulatory Submissions for Medical Devices in Electronic Format — Submissions Under Section 745A(b) of the Federal Food, Drug, and Cosmetic Act," the agency said that it was not feasible to describe the electronic formats that would apply to all submission types in a single guidance document. Therefore, the July 2020 guidance laid out a plan for developing individual guidance documents to specify the formats for various specific submissions and the corresponding implementation timetables.

The Sept. 22 final guidance document is the first of these individual guidance documents to provide standards for the submission of 510(k)s in electronic format, a timetable for establishing further standards, and the criteria for waivers and exemptions.

Current electronic submission capabilities. "At this time," the FDA said in the *Federal Register* notice, "the electronic Submission Template And Resource (eSTAR) is the only electronic submission template available to prepare a complete 510(k) electronic submission using the guided prompts for the collection of structured and unstructured data."

As specified in the Sept. 22 guidance, all 510(k) submissions — including traditional, special and abbreviated 510(k)s, subsequent supplements and amendments (including all-to-files and appeals), and all other subsequent submissions related to an original submission (unless exempted in the guidance document) — will be required to be submitted electronically according to the specifications provided in the guidance.

"FDA is identifying Oct. 1, 2023, as the date on which the 510(k) electronic submission requirements will take effect," the agency said.

Changes to draft guidance. A draft version of the guidance was issued in September 2021.

The FDA said that it revised the draft guidance to update the criteria for exemptions and to clarify the technical screening hold put on electronic submissions (a process for verifying that the responses provided in the template accurately describe the device and that at least one relevant attachment is provided for each question that calls for an attachment). In the final guidance, the agency also revised the description of the transition period and effective date on which 510(k) electronic submissions will be required.

Questions about the final guidance may be directed to the FDA Center for Devices and Radiological Health Division of Industry and Consumer Education via email at DICE@fda.hhs.gov or by phone at (800) 638-2041 or (301) 796-7100.

5. Supreme Court Sets Tough Standard for Convictions on Illegitimate Prescription Charges Under CSA

The Supreme Court June 27 imposed a demanding standard of proof for the government to meet when it brings criminal charges against practitioners for allegedly dispensing or distributing controlled substances in violation of the Controlled Substances Act (CSA) (*Ruan v. United States,* 142 S. Ct. 2370 (2022)).

The decision is likely to strengthen the legal positions of some physicians who have been accused of writing illicit prescriptions for opioids and other controlled substances.

The Court held that for a person to be convicted under the statute for knowingly or intentionally distributing or dispensing a controlled substance without authorization, or intending to do so, once the defendant produces evidence that he or she was authorized to dispense the controlled substance, the government must prove beyond a reasonable doubt that the defendant knowingly or intentionally acted in an unauthorized manner or intended to do so.

Issue before the Court. The majority opinion of the Court, written by Associate Justice Stephen Breyer and joined by five other justices, addressed the question of the state of mind that is required for a conviction under 21 U.S.C. §841 for the unauthorized dispensing or distribution of controlled substances.

Under the CSA, "except as authorized" under the statute, it is unlawful "for any person knowingly or intentionally to manufacture, distribute, or dispense, or possess with intent to manufacture, distribute, or dispense, a controlled substance" (21 U.S.C. §841(a)(1)).

As stated by the Court, the issue was the following: "To prove that a doctor's dispensation of drugs via prescription falls within the statute's prohibition and outside the authorization exception, is it sufficient for the government to prove that a prescription was *in fact* not authorized, or must the government prove that the doctor knew or intended that the prescription was unauthorized?"

Facts of the consolidated cases. Two physicians, Dr. Xiulu Ruan and Dr. Shakeel Kahn, who both possessed licenses permitting them to prescribe controlled substances, had been convicted on charges of unlawfully dispensing and distributing controlled substances in violation of Section 841.

Ruan and a business partner were accused of writing hundreds of thousands of controlled substance prescriptions, mostly for Schedule II controlled substances, often without seeing the patients for whom the prescriptions were written. Kahn, a physician specializing in pain management, allegedly sold prescriptions for highly addictive drugs for cash. The prescriptions allegedly were frequently written without an examination of the patient or after only a perfunctory patient examination.

Physicians' defenses. The physicians had argued that their separate trials that their dispensing of drugs had been lawful because the drugs were dispensed pursuant to valid prescriptions. The government had argued that the prescriptions had not been issued for legitimate medical purposes

by practitioners acting in the usual course of professional practice, as required under 21 C.F.R. §1306.04(a).

Importantly, at trial the physicians argued that even if the prescriptions had not met the regulation's standard, the doctors had not knowingly or intentionally deviated from the standard.

In Ruan's case, the district court had denied his request for a jury instruction that would require the government to prove that he subjectively knew that the prescriptions fell outside the scope of his prescribing authority. Instead, the court instructed the jury under an objective standard, asserting that a doctor violates Section 841 when his or her actions "were either not for a legitimate medical purpose or were outside the usual course of professional practice."

Reviewing Ruan's conviction, the U.S. Court of Appeals for the 11th Circuit held that a physician's subjective belief that he is meeting a patient's medical needs by prescribing a controlled substances is not a "complete defense." Rather, it said, "whether a defendant acts in the usual course of his professional practice must be evaluated based on an objective standard, not a subjective standard" (*United States v. Ruan,* 966 F.3d 1101 (11th Cir. 2020)).

Before Kahn's conviction, the district court had instructed the jury that it should not convict if the physician had acted in "good faith" — i.e., in an attempt "to act in accordance with what a reasonable physician should believe to be proper medical practice." To find such "good faith," the court also said, the jury would have to conclude that he had "acted in an honest effort to prescribe for patients' medical conditions in accordance with generally recognized and accepted standards of practice."

"Good faith" would be a "complete defense," the court told the Kahn jury, because it "would be inconsistent with knowingly and intentionally distributing and/or dispensing controlled substances outside the usual course of professional practice and without a legitimate medical purpose."

Reviewing Kahn's conviction, the U.S. Court of Appeals for the 10th Circuit affirmed, holding that to convict under Section 841 the government most prove that the doctor "either: (1) subjectively knew a prescription was issued not for a legitimate medical purpose; or (2) issued a prescription that was objectively not in the usual course of professional practice" (*United States v. Kahn,* 989 F.3d 806 (10th Cir. 2021)).

The Supreme Court decided to review cases, which it consolidated to determine what state of mind applies to the Section 841's exception for "authorized" acts.

Interpreting the statute. In reaching its decision, the Court majority determined that Section 841's requirement for a knowing or intentional state of mind applies to the statute's "except as authorized" phrase.

Consequently, the Court said, "once a defendant meets the burden of producing evidence that his or her conduct was 'authorized,' the government must prove beyond a reasonable doubt that the defendant knowingly or intentionally acted in an unauthorized manner."

The Court based its determination on a number of factors, including the following:

- In Section 841 prosecutions, "it is the fact that the doctor issued an unauthorized prescription that renders his or her conduct wrongful, not the fact of the dispensing itself. … Authorizations plays a crucial role in separating innocent conduct — and, in the case of doctors, socially beneficial conduct — from wrongful conduct."

- The language of 21 C.F.R. §1306.04(a) defining an authorized prescription is "ambiguous, written in generalities, susceptible to more precise definition and open to varying constructions" (*Gonzales v. Oregon,* 546 U.S. 243 (2006)). The conduct prohibited by that language "is thus often difficult to distinguish from the gray zone of socially acceptable conduct."

- Section 841 imposes severe penalties upon those who violate it — incarceration for as much as a life term and fines of up to $1 million. "Such severe penalties counsel in favor of a strong scienter requirement," the Court said — i.e., a strong requirement that the defendant knows that the act is wrongful and intends to act despite this knowledge.

Rejecting the government's interpretation. The government had interpreted the statute to mean that it could convict "by proving beyond a reasonable doubt that [the defendant] did not even make an objectively reasonable attempt to ascertain and act within the bounds of professional medicine."

However, the Court noted, the statute "uses the familiar mens rea [(intention of wrongdoing)] words 'knowingly or intentionally.' It nowhere uses words such as 'good faith,' 'objectively,' 'reasonable,' or 'honest effort.'"

"Moreover," the Court continued, "the government's standard would turn a defendant's criminal liability on the mental state of a hypothetical 'reasonable' doctor, not on the mental state of the defendant himself or herself. We have rejected analogous suggestions in other criminal contexts."

Also, the government had argued that requiring it to prove that a doctor knowingly or intentionally acted in an unauthorized way "will allow bad-apple doctors to escape liability by claiming idiosyncratic views about their prescribing authority," the Court noted.

"The government, of course, can prove knowledge of a lack of authorization through circumstantial evidence," the Court continued. "And the regulation defining the scope of a doctor's prescribing authority does so by reference to objective criteria such as 'legitimate medical purpose' and 'usual course' of 'professional practice.' … The more unreasonable a defendant's asserted beliefs or misunderstandings are, especially as measured against objective criteria, the more likely the jury will find that the government has carried its burden of proving knowledge."

"But the government must still carry this burden," the Court stressed. "And for purposes of a criminal conviction under Section 841, this requires proving that a defendant knew or intended that his or her conduct was unauthorized."

Remands ordered. Rejecting the government's arguments, the Court vacated the judgments by the two courts of appeals and remanded the two physicians' cases for further proceedings.

"The court of appeals in both cases evaluated the jury's instructions under an incorrect understanding of Section 841's scienter requirements," the Court said. "We decline to decide in the first instance whether the instructions complied with the standard we have set today. We leave that and any harmlessness questions for the courts to address on remand."

Concurring opinion. In a separate opinion concurring in the Court's judgment, Associate Justice Samuel Alito, joined by Associate Justice Clarence Thomas and Associate Justice Amy Coney Barrett, disagreed with the majority opinion, concluding that "absolutely nothing in the text of the [CSA] indicates that Congress intended to impose a burden on the government to disprove all assertions of authorization beyond a reasonable doubt."

Alito said that he would have held that the CSA contains an exception for prescriptions issued in the course of professional practice — a carry-over from the CSA's processor. He noted that in a 1925 case interpreting the predecessor statute, the Court had held that a registered physician acts in the course of professional practice when he or she writes prescriptions in good faith (*Linder v. United States*, 268 U.S. 5 (1925)).

"I would hold that this rule applies under the CSA and would therefore vacate the judgments below and remand for further proceedings," Alito said.

6. Court Rejects FDA's Attempt To Regulate Procedures Performed by California Stem Cell Clinic

A federal district court in California rejected the FDA's attempt to enjoin a stem cell clinic from performing procedures involving what the agency alleged to be unapproved drugs and biological products. The court held that the clinic's current procedures did not involve products that were subject to FDA regulation (*United States v. California Stem Cell Treatment Center,* No. 5:18-cv-01005-JGB-KK, 2022 U.S. Dist. LEXIS 156714, 2022 WL 3756509 (C.D. Cal. Aug. 30, 2022)).

Acting on behalf of the FDA, the Department of Justice (DOJ) filed an injunction action in May 2018 seeking to permanently enjoin California Stem Cell Treatment Center, based in Rancho Mirage and Beverly Hills, and two physicians who co-owned the clinic from performing various stem cell treatments on patients.

The government alleged that the treatments violated the FD&C Act by causing the adulteration and misbranding of drugs and the receipt of misbranded drugs.

Three procedures. The center offered patients a procedure in which a physician targeted stromal vascular fraction (SVF) cells for extraction and then implanted the same cells back into the same patient. SVF cells are comprised of multiple types of stem cells and are the naturally occurring part of adipose tissue that does not contain adipocytes (fat cells). The procedure is intended to treat chronic and systemic conditions by increasing the number of available SVF cells in circulation or around an injured area.

The clinic also offered a procedure in which a patient's adipose tissue was removed and sent to a tissue bank to isolate mesenchymal stem cells (MSC cells). Those cells were then replicated and stored until the same patient requested that they be returned for implantation into his or her body. The procedure was intended for patients who had medical conditions that would require multiple treatments but who were unable or unwilling to undergo multiple liposuctions.

The clinic's two physicians also had studied the safety of an experimental procedure through which SVF cells were used to deliver ACAM2000, an oncolytic virus, to cancer patients. The federal government maintains exclusive control over ACAM2000 as part of the Strategic National Stockpile, and the virus may be distributed only by certain government agencies. Although the virus is not publicly available, researchers may request vials of the virus for clinical studies.

The two physicians at the clinic had obtained the ACAM2000 they used from the Centers for Disease Control and Prevention, and they had performed the treatment under institutional review board (IRB)-approved clinical study protocols. They had not performed the experimental treatment since August 2017, when U.S. marshals acting on behalf of the FDA entered a laboratory and seized five vials of the virus that had been earmarked for injection into cancer patients at the clinic.

"Muddy" line between drugs and procedures. The district court noted that surgical procedures — like drugs as defined in the FD&C Act (21 U.S.C. §321(g)(1)) — are intended for the diagnosis, cure, mitigation, treatment or prevention of disease. However, "when passing the [FD&C Act]," the court said, "Congress explicitly rejected any attempt to 'limit or interfere with the authority of a health care practitioner to prescribe or administer any legally marketed device to a patient for any condition or disease within a legitimate health care practitioner-patient relationship'" (21 U.S.C. §396).

"Indeed," the court continued, "Congress recognized the limitations of the FDA and rejected any intent to directly regulate the practice of medicine."

However, it noted, "the line between 'drug' and 'procedure' is muddy when licensed medical doctors enter a patient's body, extract that patient's cells, and reintroduce those cells to that patient after some amount of cellular processing."

The FDA contended that this scenario constitutes the production of drugs under the FD&C Act, the court said, while the clinic and the physicians argued that "this is mere surgery, the exclusive province of the medical practitioners, and not something which the [FD&C Act] may regulate."

The court concluded that neither the SVF surgical procedure nor the expanded MSC procedure were "drugs" within the meaning of the FD&C Act and therefore were not subject to the statute's adulteration and misbranding provisions. By contrast, the court said, the SVF/ACAM2000 treatment "involves the creation of a drug under the [FD&C Act]."

SSP exception. According to the court, neither the SVF procedure nor the MSC procedure involved creating "new drugs" or "prescription drugs" as defined in the FD&C Act.

Moreover, the court said, the SVF procedure (but not the MSC procedure) qualified for the "same surgical procedure" (SSP) exception, which exempts from FDA oversight any "establishment that removes [human cells, tissues, or cellular or tissue-based products (HCT/Ps)] from an individual and implants such HCT/Ps into the same individual during the same surgical procedure" (21 C.F.R. §1271.15).

"Because the entire SVP surgical procedure involves introducing the same HCT/Ps back into patients during a single outpatient procedure at the surgical clinic," the court said, "defendants' SVF surgical procedure involved introducing HCT/Ps back into patients during the 'same surgical procedure' as they were extracted, triggering the SSP exception."

"The same is not true of the expanded MSC procedure," the court continued. "Though the cells extracted for the SVF surgical procedure and the expanded MSC procedure are HCT/Ps, only the SVF surgical procedure qualifies for the SSP exception."

SVF procedure. The court concluded that because of the SSP exception, the SVF procedure did not involve an adulterated drug or prescription drug. Moreover, it concluded, the SVF procedure did not involve a "drug" as defined in the FD&C Act. Consequently, it said, the clinic and the physicians did not fall under the jurisdiction of the FDA and were not governed by the FD&C Act or FDA regulations.

The SVF surgical procedure was autologous, the court noted, "because it involves collecting a patient's cell population naturally occurring in the patient's adipose tissue and relocating that cell population back into the same patient."

Although the SSP exception does not have any requirement that an HCT/P be unaltered before reinsertion into the patient, the court noted, the SVP did not alter the biological characteristics of the SVF, and there was no evidence that the cells were "anything other than autologous cells removed from, belonging to, and returned back to the patient."

Rejecting an FDA argument, the court said that the SSP exception unambiguously did not require that the surgeon implant everything that had been removed for the exception to apply.

The physicians "may lawfully use FDA-cleared medical devices and FDA-approved pharmaceuticals in any manner that they determine is best to care for and treat their patients," the court added.

MSC procedure. With respect to the MSC procedure, the district court held that the cells involved in the procedure are not drugs but rather are "human cells removed from patients and then reintroduced into those same patients. They are not fungible goods that can be sold, mass produced, or patented."

"Defendants are engaged in the practice of medicine," the court said, "not the manufacture of pharmaceuticals."

SVF/ACAM2000 treatment. By contrast, the court said, "unlike the SVF surgical procedure, the SVF/ACAM2000 treatment constitutes the manufacture of a drug." The ACAM2000 had been shipped in interstate commerce from Georgia, the court noted (21 U.S.C. §331(k)).

However, it continued, the government had not met its burden of establishing standing to pursue injunctive relief regarding the procedure because the two physicians had stopped performing the treatment by June 2017, before the FDA's suit was filed and before ACAM2000 intended for use in the clinic had been seized on the agency's behalf.

"Defendants cannot perform the SVF/ACAM2000 treatment without the ACAM2000, which is in the exclusive control of the government and otherwise inaccessible to defendants," the court noted. "[The two physicians] have no desire or intention of performing the SVF/ACAM2000 treatment absent formal regulatory approval."

Accordingly, the court entered judgment in favor of the clinic and the two physicians on all the claims brought by the government.

7. DOJ Statement of Interest Links FD&C Act Violations to Possible Liability Under the False Claims Act; Court Rejects Using False Claims Act as 'Catch-All Statute for Targeting Weaselly Behavior'

The DOJ filed a statement of interest in a False Claims Act suit in which a whistleblower asserted that a medical device manufacturer's liability under the statute stemmed from its alleged violations of the FD&C Act and FDA regulations. The DOJ statement presented the department's views on possible links between FD&C Act violations and False Claims Act liability (*United States ex rel. Crocano,* No. 0:22-cv-60160-RAR (S.D. Fla.)).

The qui tam relator originally filed her False Claims Act complaint against Trividia Health Inc., a manufacturer of store brand diabetes-related products, in February 2017.

In her November 2021 amended complaint, the relator alleged that because of a manufacturing defect, beginning in 2013 the company produced thousands of vials of contaminated diabetes test strips — Class II medical devices cleared for marketing through the FDA's 510(k) procedure — that would not produce an accurate reading.

She alleged that the company "had actual knowledge of the defect and that the defective product was causing adverse health outcomes in unwitting diabetics that trusted the accuracy of Trividia's product." Instead of recalling the defective products or issuing a warning to patients, the relator asserted, the company "did nothing, kept quiet, and continued placing defective test strips into the stream of commerce for years and concealed evidence of adverse patient events."

Alleged violations of FDA requirements. The test strips were adulterated, the relator alleged, because they failed to meet performance standards and specifications and because their production did not comport with cGMP. Moreover, the devices were misbranded, she asserted, because the product label failed to warn patients that the product could fail and that its failure could be dangerous to health.

According to the amended complaint, the defect in the test strips was an adverse event that required disclosure to the FDA and remedial action by the manufacturer. "Nevertheless," she argued, "Trividia intentionally introduced and continued introducing this adulterated, misbranded product into the stream of commerce, causing public and private health insurance programs to pay for a false and, at best, entirely worthless product."

Specifically, she asserted, "when it placed these worthless, dangerous products into the stream of commerce knowing that it was unlawful to do so, Trividia also knew government health insurance programs would and, in fact, did pay for these unlawful products at great cost to state and federal taxpayers."

The relator asserted claims under the federal False Claims Act and the false claims acts of 26 states and the District of Columbia.

In September 2021, the DOJ declined to intervene in the case.

Motion to dismiss. The following December, the manufacturer filed a motion to dismiss. The company argued in part that "the sale of an approved device or drug that is allegedly adulterated or misbranded pursuant to FDA regulations cannot serve as the basis of a [False Claims Act] claim."

Specifically, the company asserted, "the relator has failed to allege how the purported [FD&C Act] violations highlighted in her complaint give rise to False Claims Act liability where there is no false statement to the government, or allegations that the regulatory violations caused a payment."

Citing a decision by the U.S. Court of Appeals for the 4th Circuit, the company stated that allowing a False Claims Act theory of liability "based merely on a regulatory violation would sanction use of the [False Claims Act] as a sweeping mechanism to promote regulatory compliance, rather than a set of statutes aimed at protecting the financial resources of the government from the consequences of fraudulent conduct" (*United States ex rel. Reshoulder v. Omnicare, Inc.,* 745 F.3d 694 (4th Cir. 2014)).

Also, the company stated, "it is well settled that the enforcement of the medical device regulations is exclusively the province of the federal government" (citing *Buckman Co. v. Plaintiff's Legal Committee,* 531 U.S. 341 (2001)).

Linking deficiencies to payment decision. In its June 3 Statement of Interest as to Defendant's Motion To Dismiss, the DOJ asserted that, despite the fact that it declined to intervene in the case, the United States "remains the real party of interest in this matter" because "the relator has asserted claims on behalf of the United States for harms purportedly suffered by the government."

Noting the company's assertion that alleged FD&C Act violations cannot serve as a basis for False Claims Act liability, the DOJ argued that "deficiencies in the affected product resulting from [FD&C Act] violations may, in certain circumstances, be material to the government's decision whether to pay for the affected product, and thus relevant in [a False Claims Act] case."

Specifically, the department stated, FD&C Act violations may be relevant in False Claims Act cases "where the violations are significant, substantial, and give rise to actual discrepancies in the composition, functioning, safety, or efficacy of the affected product" — for example, "where, as a result of the regulatory violations, the affected product's quality, safety and efficacy fell below what was specified to and cleared by the [FDA] through its approval processes."

"In some cases," the DOJ said, "manufacturing deficiencies could affect the quality, safety and efficacy of the affected products such that the FDA never would have approved or cleared the affect products — or allowed them to remain on the market — if it had known the truth, and claims involving those devices never would have been eligible for federal health care program reimbursement."

"For example," the department continued, "when a medical device manufacturer obtains FDA approval or clearance for a device and then palms off a defective version of that device both directly on the government itself and on the unsuspecting government payors, the manufacturer may be liable under the [False Claims Act] if the elements of the [False Claims Act] are sufficiently met."

Consequences of "an original fraud." Notably, the DOJ said that a claim can be false or fraudulent for purposes of the False Claims Act "if it is submitted under a contract or extension of government benefit that was originally obtained through false statements or fraudulent conduct." Under this theory, the department said, "subsequent claims are false because of an original fraud, even if the subsequent claim for payment is not false on its face and makes no false certification."

Consequently, the DOJ continued, "it is possible to articulate a viable [False Claims Act] claim based on materially false or fraudulent statements made to the FDA regarding drugs or medical devices for which the government provides payment or reimbursement."

The department noted that when deciding whether to cover a drug or device, federal health care programs "often rely on the FDA's decision as to whether the drug or device is sufficiently safe and effective to be sold in the United States" — a decision based on information provided by the manufacturer "and therefore the manufacturer's compliance with its reporting obligations, including reporting of adverse events."

Moreover, the government noted, "FDA approval or clearance of a drug or medical device is required for Medicare coverage."

Fraud on the FDA. Importantly, the DOJ asserted, "when a manufacturer perpetrates a fraud on the FDA by hiding material information concerning the safety or efficacy of a device — either during or after the approval process or to avoid a recall — and federal health care programs then pay for that device, that fraud may be integral to a causal chain leading to payment and can be actionable under the [False Claims Act]."

"In circumstances in which the defendant's false statements or material omissions masked problems that, for example, would have prompted the FDA to institute or require a product recall," the department stated, "subsequent claims relating to the affected devices could be rendered false or fraudulent because the government would not have paid the claims for those affected devices but for the defendant's conduct."

Effect of regulatory violations. "Further," the DOJ said, "in some situations, manufacturing deficiencies violating the [FD&C Act] or FDA regulations could materially affect the safety, efficacy, or performance of a device such that the product is essentially worthless and not eligible for payment by the government. Submitting claims (or causing claims to be submitted) to federal health care programs for products or services that are so deficient as to be essentially worthless may give rise to [False Claims Act] liability. That these manufacturing deficiencies might separately violate FDA regulations does not preclude [False Claims Act] liability arising from the claims for payment submitted for the affected products."

"However the court rules on the present motion," the department concluded, "the United States requests that the ruling not foreclose the possibility that, under certain circumstances, conduct giving rise to violations of the [FD&C Act] or FDA regulations could be material to the government's payment decisions and provide a basis for [False Claims Act] liability assuming all necessary [False Claims Act] elements are demonstrated."

Court grants motion to dismiss. On July 18, the district court granted the manufacturer's motion to dismiss (*United States ex rel. Crocano v. Trividia Health Inc.,* No. 0:22-cv-60160-RAR, 2022 U.S. Dist. LEXIS 126976, 2022 WL 2800380 (S.D. Fla. July 18, 2022)).

"The False Claims Act prohibits people from submitting claims to the federal government for amounts it does not owe," the court said, addressing the DOJ's arguments. "It is not a catch-all statute targeting any conceivable form of misconduct connected with the government's spending programs — particularly when such misconduct is proscribed by separate enforcement regimes."

"Here," the court continued, "relator alleges a pattern of illicit behavior concerning defendant's response to a serious defect in its products. But she alleges no conduct expressly contemplated by the False Claims Act, and the court must rein in relator's expansive view of the statute."

Agreeing with the manufacturer that the relator had failed to state a claim, the court said that the False Claims Act "is not a catch-all statute for targeting weaselly behavior. Rather, it has the singular purpose of placing the federal government on notice of potential fraudulent claims in relation to its assistance and other spending programs."

"There is no question that relator alleges a cornucopia of weaselly practices on the part of defendant," the court continued. "But, at bottom, these allegations amount to a series of regulatory violations whose connection to claims for payment by the government is tenuous at best."

"To be clear," the court cautioned, "a regulatory violation can rise to the level of creating liability under the False Claims Act. Indeed, if a statute governing certain claims expressly conditions reimbursement on compliance with specific regulatory obligations, violation of said obligations is material to the claims and therefore relevant to a defendant's liability. But allowing a theory of liability based merely on a regulatory violation would sanction use of the False Claims Act as a sweeping mechanism to promote regulatory compliance, rather than a set of statutes aimed at protecting the financial resources of the government from the consequences of fraudulent conduct."

The relator claimed that the manufacturer's test strips were statutorily ineligible for reimbursement and accordingly false because they were misbranded and adulterated, the court noted. "This argument fails," it responded, "because none of the alleged regulatory violations resulting in 'misbranded and adulterated' test strips were material to any claim for payment."

The relator did not allege that the statutes governing health care programs prohibited reimbursement for adulterated or misbranded medical products, the court also noted. "Rather," it said, "her central argument hangs on alleged violations of the [FD&C Act] and of FDA regulations":

- introducing adulterated or misbranded devices into interstate commerce; and

- failing to investigate adverse events, evaluate their causes, and furnish to the agency within 30 days information suggesting that a death or serious injury was linked to the devices, rendering the devices misbranded and therefore ineligible for reimbursement by government health insurance companies — meaning that "any claims for any test strip manufactured during this period were necessarily false."

However, the court said, even if the test strips were misbranded, the relator had cited no portion of the FD&C Act "closing the circuit" between misbranding and claims for reimbursement from the government. Instead, the relator offered merely the "conclusory assertion" that misbranding would be material to a decision to pay for the defective product because a defect rendering the product worthless and unmarketable "necessarily is … important to any decision to pay for the product."

The relator identified "no statutory condition tying adverse event reporting to eligibility for reimbursement," the court said, and she floated "a 'false certification' argument, but because compliance with FDA regulations is not required for payment by Medicare and Medicaid, defendant has not falsely stated such compliance to the government."

Finally, the court said, the relator had not identified any false statement or other fraudulent misrepresentation that the manufacturer made to the government. "What she alleges," it said, "is a long pattern of shady behavior designed to conceal a serious product defect from the relevant governing body."

"But unless such violations are material to the alleged fraudulent claims," the court stressed, "they do not create liability under the False Claims Act. They are proscribed by other statutes subject to their own enforcement regimes. The court will not expand the scope of the False Claims Act into the realm of regulatory enforcement."

Rejecting two more of the relator's contentions, the court said that:

- the faulty test strip units could not be ineligible for reimbursement due to being not "reasonable and necessary," because the "reasonable and necessary" standard "is applied at the product level, not the unit level"; and

- while "worthless services" have been found by some courts to be ineligible for reimbursement, "relator attempts to expand case law concerning 'worthless services' theory under the False Claims Act into the realm of 'worthless products.' The 11th Circuit has not endorsed this view, and the court declines to do so here."

For these reasons, the court found that the relator had failed to state a claim upon which relief may be granted.

The court declined to give the relator an opportunity to amend her complaint because "any amendment would be futile in light of the holding that adulterated devices are not barred from reimbursement by Medicare and Medicaid and, therefore, claims for reimbursement for these devices cannot be false under the False Claims Act."

Having dismissed the relator's federal False Claims Act claims, the court declined to exercise jurisdiction over the relator's state law claims, dismissing them without prejudice.

"To be clear," the district court said, "the court does not condone defendant's alleged violations of the FDA's reporting requirements and other practices designed to illicitly protect itself from the consequences of placing potentially dangerous medical products into the stream of commerce. But the court is convinced that the False Claims Act is not the proper avenue for holding defendant accountable for this behavior and is confident that the FDA's use of its regulatory enforcement powers may be exercised fully to ensure further compliance."

In its opinion, the district court acknowledged the filing of the DOJ's statement of interest, but it did not otherwise directly address the statement.

8. Biden Signs Legislation To Facilitate Research on Potential Health Benefits of Marijuana, CBD

President Biden Dec. 2 signed into law a bill intended to remove barriers that have impeded research into the potential health benefits of marijuana and cannabidiol (CBD).

The Medical Marijuana and Cannabidiol Research Expansion Act, Pub. L. No. 117-215, establishes DEA registration processes for practitioners conducting marijuana research and manufacturers of marijuana for research purposes. The processes include deadlines for DEA action on the registration applications.

The statute also directs the agency to register manufacturers and distributors of marijuana and CBD that are involved in the commercial production of FDA-approved drugs that contain marijuana or a marijuana derivative.

The measure (H.R. 8454) passed the House on July 26 by a vote of 325 to 95. The Senate approved the legislation without amendment by a voice vote on Nov. 16.

Practitioner registration to conduct research. The statute directs the DEA to register a practitioner to conduct research with marijuana if:

- the applicant's research protocol has been reviewed and allowed by the FDA, by the National Institutes of Health (NIH) or another federal agency funding the research, or under the DEA regulations on research protocols (21 C.F.R. §1301.18) and research on Schedule I substances (21 C.F.R. §1301.32); and

- the applicant has demonstrated to the DEA that effective procedures to safeguard against diversion are in place, "including demonstrating that the security measures are adequate for storing the quantity of marijuana the applicant would be authorized to possess."

The DEA may deny the application only if it determines that issuing the registration would be inconsistent with the public interest (21 U.S.C. §823(f)(1)).

The first of the five statutory public interest factors, the recommendation of the appropriate state licensing board or professional disciplinary authority, would be considered by the DEA if the state requires practitioners conducting research to register with a state board or other authority.

The DEA must either approve the registration or request more information from the applicant within 60 days. If more information is requested, the agency must approve or deny the application within 30 days after receiving the supplemental information. If the application is denied, the DEA must provide a written explanation of the reasons for the denial.

Research protocols. Also under the statute, a practitioner registered with the DEA to conduct research with marijuana may amend or supplement the research protocol without notice to or review by the agency if the registrant does not change:

- the quantity or type of marijuana or CBD;
- the source of the marijuana or CBD; or
- the conditions under which the marijuana or CBD is stored, tracked or administered.

The statute specifies procedures for the registrant and the DEA to follow in cases where a registrant wants to change the type of marijuana or CBD, to address additional security measures, or to change the quantity of marijuana needed for the research.

The FDA retains its authority over the research protocols, including (1) the method of administration or the dosing of the marijuana or CBD and (2) the number of individuals or patients involved in the research.

The DEA must promulgate regulations covering these research protocol provisions by December 2023.

Registration for manufacturers of marijuana for research. For applications to manufacture marijuana for research purposes, when the DEA places a notice in the *Federal Register* to increase the number of registered entities manufacturing marijuana to supply researchers, the agency has 60 days to approve the application or ask for additional information.

In its registration application, the manufacturer must document that it will limit the transfer and sale of marijuana to DEA-registered researchers and for purposes of preclinical research or clinical investigations pursuant to an IND.

The manufacturer also must document that:

- it will transfer or sell marijuana only with the DEA's prior written consent;
- it has completed the application and review process for the bulk manufacture of Schedule I controlled substances;
- it has established and begun operation of a process for storing and handling Schedule I controlled substances (including the statute's inventory control and monitoring security requirements); and
- it has satisfied any state marijuana manufacturing licensing requirements.

Once the DEA has received any supplemental information that it has requested, the agency has 30 days to approve or deny the manufacturer's application. The DEA must supply a written explanation for an application denial.

Ensuring a supply of marijuana for research. The statute also requires the DEA to work with the FDA to assess annually "whether there is an adequate and uninterrupted supply of marijuana, including of specific strains, for research purposes."

If the supply is found not to be adequate and uninterrupted, the DEA must within 60 days of the finding report to Congress on the factors contributing to the supply issues, the expected impacts on ongoing research protocols, and the steps that the agency will take to restore the supply.

Security. Researchers must store the marijuana and its components in "a securely locked, substantially constructed cabinet."

Any additional security measures imposed by the DEA must be consistent with those that apply to practitioners conducting research on Schedule I and Schedule II controlled substances that have "a similar risk of diversion and abuse."

No interdisciplinary review. The statute prohibits HHS from reinstating a review process under which the Public Health Service (PHS) had reviewed non-federally funded research protocols involving marijuana.

The PHS review had been instituted in May 1999 with publication of a guidance document titled "Guidance on Procedures for the Provision of Marijuana for Medical Research." In June 2015, HHS eliminated the PHS review process after finding that it overlapped the FDA's IND process (80 Fed. Reg. 35960).

The statute bars HHS from requiring any additional review of scientific protocols that is applicable only to marijuana research.

Medical research on CBD. "An appropriately registered covered institution of higher education, practitioner, or manufacturer may manufacture, distribute, dispense, or process marijuana or cannabidiol … for purposes of medical research for drug development or subsequent commercial production," the statute provides.

The legislation specifies that these activities are permitted notwithstanding any provisions of the CSA, the Safe and Drug-Free Schools and Communities Act, or any other federal law.

DEA registration for commercial production of drugs. The statute also requires the DEA to provide registrations for applicants that manufacture or distribute CBD or marijuana for purposes of the commercial production of FDA-approved drugs derived from marijuana.

The registration process must follow the requirements of the CSA (21 U.S.C. §823(a), 21 U.S.C. §823(b)).

Doctor-patient relationship. In addition, the statute specifies that it is not a violation of the CSA for a state-licensed physician to discuss the potential harms and benefits of treatments using marijuana derivatives, including CBD, with the legal guardians of children who are the physician's patients.

When talking with adult patients or their legal guardians, a physician may discuss the potential harms and benefits of marijuana as well as marijuana derivatives, including CBD, as treatments.

Federal report. The statute also directs HHS to work with the NIH and other relevant federal agencies to prepare a report on (1) the potential therapeutic effects of CBD or marijuana on serious medical conditions, including intractable epilepsy, and (2) the barriers associated with researching marijuana and CBD in states that have legalized the use of such substances.

The report must be submitted by December 2023 to the Senate Caucus on International Narcotics Control, the Senate Health, Education, Labor and Pensions Committee, the Senate Judiciary Committee, the House Energy and Commerce Committee, and the House Judiciary Committee.

9. District Court Upholds Majority of NBFDS Regulations But Rejects Text Message Disclosure Option

A federal district court in California Sept. 13 upheld the majority of the USDA's National Bioengineered Food Disclosure Standard (NBFDS) regulations but granted summary judgment to plaintiffs challenging the regulations' text message disclosure option. The court sent two sections of the NBFDS rules back to the USDA for reconsideration (*Natural Grocers v. Vilsack,* No. 3:20-cv-05151-JD, 2022 U.S. Dist. LEXIS 165437, 2022 WL 4227248 (N.D. Cal. Sept. 13, 2022)).

The NBFDS final rule was published by the USDA's Agricultural Marketing Service (AMS) in December 2018 (83 Fed. Reg. 65814). The standard requires food manufacturers,importers and certain retailers to ensure that bioengineered (BE) foods are appropriately identified to consumers. Disclosure of highly processed food ingredients derived from genetically engineered crops is not required. The final rule established a mandatory compliance date of Jan. 1, 2022.

Under the regulations, companies have four options for making bioengineered food disclosures: (1) on-package text, for example, "Bioengineered Food" or "Contains a Bioengineered Food Ingredient"; (2) a USDA-approved symbol; (3) electronic or digital disclosure — including instructions to "Scan here for more food information" or similar language, and including a phone number; and (4) text message disclosure — "Text [command word] to [number] for bioengineered food information."

Challenges raised. The plaintiffs — a group of food safety advocacy organizations and natural and organic food retailers — filed a complaint challenging a number of provisions in the NBFDS implementing regulations. In addition to constitutional concerns, the plaintiffs raised issues with the regulatory provisions that (1) permit a text message disclosure option as an alternative to an electronic or digital link disclosure, (2) require disclosures to use the word "bioengineered," and (3) exclude highly refined foods that do not contain detectable amounts of modified genetic material.

The court granted applications to intervene in the proceedings from the United States Beet Sugar Association, the American Sugarbeet Growers Association and the American Farm Bureau Federation, and the intervenors filed a consolidated opposition to the plaintiffs' motion for summary judgment.

Background. On July 29, 2016, President Obama signed into law legislation mandating the labeling of products containing ingredients made with genetically modified organisms. The legislation, Pub. L. No. 114-216, called for the creation of the NBFDS within two years of enactment.

In the disclosure provisions in the law, the district court stressed, Congress directed the USDA to conduct a study "to identify potential technological challenges that may impact whether consumers would have access to the bioengineering disclosure through electronic or digital disclosure methods."

In September 2017, the USDA released a report prepared under contract on the challenges of placing quick response (QR) codes or other electronic or digital links on food labels to aid in disclosures. The study, "Study of Electronic or Digital Link Disclosure: A Third-Party Evaluation of Challenges Impacting Access to Bioengineered Food Disclosure," revealed that technological challenges existed with respect to consumers' access to the BE disclosure through electronic or digital means.

The study identified three steps to address the challenges identified: (1) educate consumers and retailers about electronic and digital disclosure and bioengineered foods; (2) offer other/offline options to obtain the information (e.g., phone or text message); and (3) develop or endorse user-friendly scanner apps.

"The same subsection of the disclosure statute," the court said, "also required USDA to provide additional and comparable options to access the bioengineering disclosure" if it determined "that consumers, while shopping, would not have sufficient access to the bioengineering disclosure through electronic or digital disclosure methods."

Provision goes back to USDA. "AMS' decision to provide a separate text message disclosure option did nothing to fix the problem of inaccessible electronic disclosures," the court determined. "It merely provided a fourth disclosure option that regulated entities can select instead of the electronic disclosure method. … The result is that the stand-alone electronic disclosure suffices under the regulations, even though USDA determined that 'consumers would not have sufficient access to the bioengineering disclosure through electronic or digital means under ordinary shopping conditions at this time'" (83 Fed. Reg. 65828).

The court said that Congress' intent was clear and unambiguous in mandating a study on "whether consumers would have access to the bioengineering disclosure through electronic or digital disclosure methods precisely to ensure that those methods were accessible and would achieve the goal of disclosure."

The court ultimately agreed with the plaintiffs' claim that AMS' decision to implement a stand-alone text message disclosure option was "arbitrary, capricious, an abuse of discretion or otherwise not in accordance with law." The court remanded 7 C.F.R. §66.106 and §66.108 of the NBFDS regulations to the USDA for reconsideration.

The court did not vacate the two regulatory provisions, however. The court stated that although the "text message disclosure decision was a significant error, ... the government urges a remand without vacatur so that the status quo is maintained while AMS revisits the issue." AMS argued that vacatur would disrupt consumer access to bioengineering disclosures and disrupt the food industry.

The court rejected the plaintiffs' other challenges to provisions of the NBFDS regulations.

10. FDA Allows Makers of Six COVID-19 Drugs To Provide Safety, Efficacy Results in Promotional Material

The FDA determined that it would allow the manufacturers of six COVID-19 drugs granted emergency use authorizations (EUAs) to provide some safety and efficacy results in promotional materials.

An Oct. 27 CDER memorandum revised "certain conditions on printed, advertising and promotional materials" in the EUAs for baricitinib, Actemra, Evusheld, Paxlovid, Lagevrio and bebtelovimab.

In the memorandum, CDER Office of New Drugs Director Dr. Peter Stein noted that "the epidemiological landscape for COVID-19, specifically with emerging viral variants of SARS CoV-2, has shifted multiple times and in a few instances, relatively quickly."

"In addition," Stein continued, "the rates of infection and public health impact of the virus continue to change. Each of these factors has contributed to a shifting clinical context, of which health care providers and patients, alike, should be aware; underscoring the importance for accurate and non-misleading information on the authorized COVID-19 therapeutics being available to advance the public health."

Previously, a condition included in the EUA letters of authorization had stated: "No descriptive printed matter, advertising, or promotional materials relating to the use of Drug X under this authorization may represent or suggest that Drug X is safe or effective when used for [authorized use]."

"This condition, in combination with other conditions on advertising and promotion currently included in EUAs for COVID-19 therapeutics, already authorize the dissemination of product-specific, truthful, and non-misleading information relating to the use of the product when consistent with the authorized labeling," Stein noted.

"Current conditions on advertising and promotional materials included in EUAs for COVID-19 therapeutics require that any such materials clearly and conspicuously state that the product (or use) is not FDA-approved, but rather has been authorized for such use for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of drugs and biological products during the COVID-19 pandemic … unless the declaration is terminated or authorization revoked."

However, Stein said, CDER "was recently made aware that there may be benefit in clarifying the condition for EUA sponsors that wish to include in promotional materials information about the safety and efficacy data that supported the issuance of a particular EUA — for example, in promotional materials disseminated to health care providers and patients. CDER has considered this and has determined that it is appropriate to make clarifying revisions."

New EUA condition. The new condition states: "Company A may disseminate descriptive printed matter, advertising, and promotional materials relating to the emergency use of DRUG X that provide accurate descriptions of safety results and efficacy results on a clinical endpoint(s) from the clinical trial(s) summarized in the authorized labeling. Such materials must include any limitations of the clinical trial data as described in the authorized labeling. Company A may not imply that DRUG X is FDA approved by making statements such as 'DRUG X is safe and effective for [authorized use].'"

"While the authorized labeling for an EUA should serve as the primary resource for information on the authorized product," Stein said in the memorandum, "dissemination of truthful and non-misleading printed matter, advertising, and promotional materials containing scientific information related to the authorized use of the product, when consistent with the terms and conditions of the respective authorization, can further enhance the public's awareness of and understanding on the authorized COVID-19 therapeutic."

The FDA required that any promotional material be submitted to the agency for consideration at least 14 calendar days before initial dissemination or first use. The submission "will provide CDER the opportunity to provide feedback on the submitted materials, as appropriate, to ensure consistency with the terms and conditions of the EUA, including the authorized labeling," Stein said.

"The inclusion of accurate descriptions of safety and efficacy information that underlies the issuance of a particular EUA in printed matter, advertising and promotional materials is authorized," he specified.

Noting that "there may be uncertainties regarding the safety and effectiveness data supporting an EUA for COVID-19 therapeutics," the FDA advised that printed, advertising and promotional materials "need to include a description of any limitations of the clinical trial data, consistent with the limitations described in the authorized labeling." The information, the agency said, "is necessary to facilitate health care providers and patients in making informed decisions on the use of the authorized COVID-19 therapeutics."

The FDA said that it will continue to assess the circumstances and appropriateness of EUAs covering authorized COVID-19 therapeutics "and will make additional revisions, when appropriate."

Predictions for 2023

Courts To Address Challenges to the Government's Interpretation of the Anti-Kickback Statute

Challenges to the government's interpretation of the AKS presented in recent HHS OIG advisory opinions addressing proposed patient assistance programs are likely to be addressed by the courts during 2023.

One such challenge addressed by federal appellate courts during 2022 came from Pfizer Inc., which had sought to implement a "Direct Co-Pay Assistance Program" through which the company would provide funds directly to eligible patients to ease the high co-payment cost of the company's drug tafamidis, sold under the brand names Vyndaquel and Vyndamax, used to treat transthyretin amyloid cardiomyopathy, a rare heart condition.

In September 2020, the HHS OIG issued an advisory opinion in which it concluded that the co-pay assistance program could violate the AKS "if the requisite intent to induce or reward referrals for, or purchases of, items or services reimbursable by a federal health program were present" (OIG Advisory Opinion No. 20-05). The OIG said that the proposed program could "operate as a quid pro quo" for Pfizer and seemed designed in induce "a Medicare beneficiary [who] otherwise may be unwilling or unable to purchase [tafamidis] due to his or her cost-sharing obligations … to purchase [the drug]." The office added that the proposed program presented "more than a minimal risk of fraud and abuse" because of the drug company's elimination of patient cost-sharing, which the OIG said is "one of the key pricing controls" of Medicare Part D.

Pfizer then sought a declaratory judgment from the U.S. District Court for the Southern District of New York holding that the proposed program would not violate the AKS. The company contended that to violate the statute, the patient assistance program would have to constitute an improper quid pro quo in which Pfizer directly influenced a doctor's or patient's decision to prescribe or purchase tafamidis. In the district court's words, the company argued that "because it lacks such an intent and because there is no monetary benefit," the proposed program "cannot violate the AKS."

The district court rejected Pfizer's contention, disputing the company's argument that it would have to have a corrupt intent to violate the statute. "The AKS requires only that payments are made with an intent to influence a decision about medical care or purchases and does not require any further proof of intent or purpose," the court said. "The only showing of intent necessary for a person to be liable under the AKS is that remuneration be given to induce a beneficiary to purchase or receive medical services" (*Pfizer Inc. v. U.S. Department of Health and Human Services,* No. 1:20-cv-04920-MKV, 2021 U.S. Dist. LEXIS 189381, 2021 WL 4523676 (S.D.N.Y. Sept. 30, 2021)).

In July 2022, the U.S. Court of Appeals for the Second Circuit affirmed the district court's decision, rejecting Pfizer's contention that a quid pro quo was required for there to be liability under the AKS. The statute's prohibition against "any remuneration … to induce" "implies a one-way transaction," the appeals court said. The 2nd Circuit also rejected the company's argument that the OIG's view of the AKS "criminalizes a range of beneficial activities" (*Pfizer, Inc. v. U.S. Department of Health and Human Services,* 42 F.4th 67 (2022)).

Pfizer filed q petition for a writ of certiorari with the Supreme Court on Oct. 7, 2022. The petition was supported in amicus briefs filed by the Pharmaceutical Research and Manufacturers of America (PhRMA), Johnson & Johnson Patient Assistance Foundation Inc. and Janssen Pharmaceuticals Inc., among others. However, in January 2023, the Supreme Court declined to review the Second Circuit's decision (*Pfizer, Inc. v. Department of Health and Human Services,* No. 22-339, 214 L. Ed. 2d 370, 2023 U.S. LEXIS 312, 2023 U.S. 124415 (U.S. Jan. 9, 2023)).

It may be that the Court was reluctant to consider the issues raised by Pfizer because virtually the same issue was being litigated in *Pharmaceutical Coalition for Patient Access v. United States,* No. 3:22-cv-00714 (E.D. Va.). A decision by the U.S. District Court for the Eastern District of Virginia, a subsequent decision on appeal by the U.S. Court of Appeals for the 2nd Circuit, and parallel litigation in other courts may tee up reconsideration of the issue by the Supreme Court.

FDA Will Ramp Up Cybersecurity Requirements for Medical Devices

A revised April 2022 FDA draft guidance on addressing QS considerations relating to medical device cybersecurity and presenting cybersecurity information in device premarket submissions emphasized the importance of addressing cyber risks throughout the product life cycle, including at the IDE phase, in the face of increased cyber threats to which interconnected devices are vulnerable.

Even as the agency set finalizing the revised draft guidance as a top priority for 2023, a white paper released by Sen. Mark Warner, D-Va., identified possible policy options for improving medical cybersecurity, including addressing the problem of cybersecurity vulnerabilities among legacy medical equipment.

At the end of 2022, FDORA gave the FDA new authorities for regulating device cybersecurity.

Under FDORA, a sponsor of a "cyber device" — defined as a device that (1) includes software validated, installed or authorized by the sponsor as a device or in a device, (2) can connect to the internet, and (3) contains technological characteristics that could be vulnerable to cybersecurity threats — must include in its premarket submission to the agency:

- a plan to monitor postmarket cybersecurity vulnerabilities and exploits;
- design and develop procedures for maintaining the device's cybersecurity and providing updates and patches; and
- a software bill of materials — a list of commercial, open source, and off-the-shelf software components.

The sponsor also must comply with other requirements that the FDA may enact "to demonstrate reasonable assurance that the device and related systems are cybersecure."

Also under FDORA, a failure to comply with requirements relating to ensuring device cybersecurity is deemed a prohibited act under 21 U.S.C. §331.

Urgency Grows for Clarification of DEA Requirements for Suspicious Orders; Final Rule, Litigation May Provide Some Answers

At the end of 2022, DEA-regulated companies were still awaiting a final rule from the agency that will revise requirements for the steps that registrants must take upon receiving suspicious orders of controlled substances.

A November 2020 DEA notice of proposed rulemaking (85 Fed. Reg. 69282) proposed two options for how registrants should respond to suspicious orders: (1) immediately file a suspicious order report with the DEA and decline to fill the suspicious order; or (2) resolve each suspicious circumstance surrounding a suspicious order within seven days through due diligence and fill the order without filing a suspicious order report with the agency.

The proposed rule would define "due diligence" to broadly specify the actions that a registrant would need to take to resolve the suspicious circumstances.

A final version of the rule has been delayed. Projected in early 2022 to be issued in June 2022, in early 2023 the final rule was projected to be published in March 2023.

Meanwhile, even while the DOJ's litigation against the giant retailer Walmart Inc. alleging violations of CSA suspicious order handling requirements by the company's pharmacies continued, at the end of 2022 the department filed a parallel suit against giant pharmaceutical distributor AmerisourceBergen Corp. (*United States v. AmerisourceBergen Corp.,* No. 2:22-cv-05209 (E.D. Pa.)).

The government alleged that the distributor violated its obligations under the CSA to scrutinize controlled substance orders and to report each suspicious order to the DEA. The DOJ's complaint closely scrutinized AmerisourceBergen's order monitoring systems and the resources that the company devoted to CSA compliance — raising again questions of exactly what the DEA expects from registrants when it comes to identifying and reporting suspicious orders.

The proposed DEA rule, the Walmart litigation, the AmerisourceBergen litigation, and future litigation that the DOJ may file in enforcement actions linking regulatory noncompliance by controlled substance manufacturers, distributors and dispensers to the U.S. opioid addiction crisis may offer some clarification of companies' requirements when dealing with suspicious orders — or may raise even more questions at a time when more transparency is needed.

More Scrutiny of Medical Product Endorsements

During 2023 there will be more scrutiny of endorsements in medical product marketing — with both the FDA and the Federal Trade Commission (FTC) examining how companies use celebrity endorsements in their advertisements and other promotional materials.

The FTC announced on July 26, 2022, that it was updating its Guides Concerning the Use of Endorsements and Testimonials in Advertising (87 Fed. Reg. 44288). FTC Chairwoman Lina M. Khan said that three changes included in proposed revisions to the guides were "especially important":

- ***Guidance on platforms' relationships with influencer marketing.*** "Digital platforms profit from influencer marketing and should bear greater responsibility in this area," Khan said. "The revised guides warn that some platforms' disclosure tools are inadequate and may expose influencers to liability or, in some instances, leave platforms themselves open to liability."

- ***Explicit guidance on consumer reviews, including a discussion of how encouraging fake reviews and suppressing negative reviews can violate the law.*** "This guidance reflects recent enforcement actions the agency has taken," Khan said.

- ***A warning that child-directed influencer advertising is of special concern to the commission.*** "Those who market to children cannot assume that compliance with these guides is a safe harbor," Khan said. "There is currently no clear or consistent approach to addressing the problem, and Congress and advocacy groups have called on the FTC to provide guidance on this issue. While we presently lack the full evidentiary record to support specific guidance or to propose best practices, I am eager for more input that will support more concrete action in this important area."

Meanwhile, researchers with the FDA's Office of Prescription Drug Promotion are examining four types of direct-to-consumer television ad endorsers (celebrity, physician, patient, and noncelebrity influencer) in two studies and studying whether a disclosure of their payment status influences participant reactions (87 Fed. Reg. 58099).

FDA To Update Criteria for 'Healthy' Nutrient Content Claim, Consider Standards for Voluntary Front-of-Package Food Labeling

On Sept. 27, 2022, the Biden administration issued a National Strategy on Hunger, Nutrition and Health that included ideas for a new front-of-package (FOP) labeling scheme.

FOP labeling systems — such as "star ratings" or "traffic light schemes" — can promote equitable access to nutrition information and healthier choices and could also prompt industry to reformulate foods to be healthier, according to the administration's 44-page strategy document.

The administration called for the FDA to conduct research and propose developing a standardized FOP labeling system for food packages to help consumers, particularly those with lower nutrition literacy, quickly and easily identify foods that are part of a healthy eating pattern.

On Aug. 4, 2022, the Center for Science in the Public Interest (CSPI), together with the Association of SNAP Nutrition Education Administrators and the Association of State Public Health Nutritionists, petitioned the FDA to implement "an easy-to-understand, standardized front-of-package nutrition labeling system that is mandatory, nutrient-specific, includes calories, and is interpretive with respect to the levels of added sugars, sodium and saturated fat per serving."

On Sept. 29, 2022, the FDA published a proposed rule that would update the "healthy" nutrient content claim (87 Fed. Reg. 59168). The current claim limits a food's total fat, saturated fat, cholesterol and sodium and requires the food to provide at least 10% of the Daily Value (DV) for one or more of the following nutrients: vitamin A, vitamin C, calcium, iron, protein and fiber.

To meet the proposed updated definition of "healthy," a food (1) would need to contain a certain amount of food from at least one of the food groups or subgroups (such as fruit, vegetables, grains, dairy and protein foods) and (2) would need to limit added sugars, saturated fat and sodium to certain levels based on the percentage of the DV for the nutrients.

On a separate track, the FDA is exploring the possibility of developing a graphic symbol that industry can use to voluntarily label food products that satisfy the definition of the term "healthy." In May 2021, the FDA issued a notice that provided an overview of the consumer research that the FDA intended to conduct on symbols that could be used for such a purpose and sought comments (86 Fed. Reg. 24629).

In a March 28, 2022, *Federal Register* notice, the agency summarized and responded to the comments submitted and announced two consecutive quantitative research studies to explore consumer responses to draft FOP symbols that companies could voluntarily use on a food product as a graphic representation of the nutrient content claim "healthy" (87 Fed. Reg. 17300).

FDA To Harmonize Its Clinical Trial Regulations with the Revised Common Rule

The FDA will harmonize its clinical trial regulations with the revised Federal Policy for the Protection of Human Subjects (revised Common Rule), which was finalized in January 2017.

On Sept. 28, 2022, the agency published a proposed rule intended to "reduce regulatory burden on IRBs, sponsors, and investigators" (87 Fed. Reg. 58733).

The proposed rule would amend 21 C.F.R. Part 50 and Part 56 in the following ways:

- It would revise the content, organization and presentation of information included in the informed consent form and process to aid a prospective subject's decision about whether to participate in the research.
- It would add new basic and additional elements of informed consent, including a statement as to how private information or biospecimens collected during the research may be used for commercial profit and whether the subject will or will not share in this commercial profit; whether clinically relevant results will be disclosed to study subjects; and for research involving biospecimens, whether the research involves whole genome sequencing.
- It would add a provision allowing IRBs to eliminate continuing review of research in certain circumstances.
- It would require U.S. institutions participating in cooperative research to rely on approval by a single IRB.
- It would revise the IRB recordkeeping requirements for certain determinations related to the need for continuing review and for research that takes place at an institution in which IRB oversight is conducted by an IRB that is not operated by the institution.

The agency also proposed revising 21 C.F.R. Part 812 regarding progress reports submitted by investigators and sponsors to a reviewing IRB for consistency with the revisions in 21 C.F.R. Part 56 relating to the continuing review process.

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