Top 10 FDA & DEA Developments of 2021 — And Predictions for 2022

THOMPSON FDA
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During 2021, the Food and Drug Administration (FDA) continued to focus on dealing with the ongoing COVID-19 pandemic. By the end of the year, more than 55 million Americans had been infected with the virus, and more than 824,000 Americans had died from COVID-19.

Much as in 2020, plans that the FDA had for the year necessarily were postponed as the agency responded to the impact of multiple variants of SARS-CoV-2, the virus that causes COVID-19.

Moreover, although the FDA had worked to bring its enforcement activity back up to pre-pandemic levels, some oversight work — including, critically, the agency's product approval-related inspections — continued to lag behind the levels of activity seen before the public health emergency.

Developments during 2021 related to FDA and Drug Enforcement Administration (DEA) regulatory and enforcement activities — including the FDA's activities related to the pandemic — are likely to reverberate throughout 2022.

Below is our list of the 10 most important FDA and DEA developments of 2021 — and some predictions of what to expect during 2022.

Top 10 FDA & DEA Developments of 2021

1. Biden Administration Reverses Trump-Era FDA Regulatory and Enforcement Policies

Following the inauguration of President Joe Biden, the FDA and the Department of Justice (DOJ) reversed or nullified a number of regulatory and enforcement policies that had been implemented during the administration of former President Donald Trump.

510(k) exemptions. In April 2021, the Biden administration withdrew a Trump administration proposal to exempt 83 types of Class II medical devices and one unclassified device type from the FDA's premarket notification (510(k)) requirements. The Department of Health and Human Services (HHS) had selected the devices for possible 510(k) exemptions given the lack of adverse event reports in the FDA's Manufacturer and User Facility Device Experience (MAUDE) database for the products.

In withdrawing the proposed exemptions, HHS and the FDA said that the Trump administration had not considered the factors that the FDA has followed for decades when dealing with 510(k) exemptions and that it had relied inappropriately on adverse event data.

FDA's Unapproved Drugs Initiative. In May 2021, HHS and the FDA withdrew a November 2020 HHS notice that had terminated the FDA's Unapproved Drugs Initiative (UDI).

Through the initiative, launched in 2006, the FDA has called for companies illegally marketing drugs without FDA approval to submit applications to the agency showing that the products are safe and effective before continuing to market them.

The agencies said that the November 2020 notice terminating the UDI "contained multiple legal and factual inaccuracies."

During the Trump administration, HHS had said that the UDI, "while well-intentioned," had "distorted markets and produced the unintended consequences of price spikes and drug shortages."

Under the UDI, since September 2011 unapproved new drugs introduced onto the market had been subject to enforcement action at any time. In reinstating the UDI, the agencies said that the FDA planned to issue guidance on how it intended to prioritize its enforcement priorities for marketed unapproved drugs.

DOJ policies on agency guidance. In a July 2021 memorandum, Attorney General Merrick Garland rescinded two DOJ memoranda issued during the Trump administration that had sought to restrict the department's use of guidance documents issued by the DOJ and other federal agencies in its enforcement actions.

Garland nullified a November 2017 order issued by then Attorney General Jeff Sessions directing DOJ components not to issue guidance documents "that purport to create rights or obligations binding on persons or entities outside the executive branch (including state, local and tribal governments)." Sessions had stated that guidance could not be used as a substitute for rulemaking and could not "create binding standards by which the department will determine compliance with existing regulatory or statutory requirements."

Also, Garland nullified a January 2018 memorandum issued by then Associate Attorney General Rachel L. Brand that had prohibited the department from attempting to "convert agency guidance documents into binding rules" through civil enforcement litigation and from treating noncompliance with an agency guidance document "as presumptively or conclusively establishing that the party violated the applicable statute or regulation."

Garland said that from now on, DOJ attorneys handling enforcement actions or other litigation "may rely on relevant guidance documents in any appropriate and lawful circumstances, including when a guidance document may be entitled to deference or otherwise carry persuasive weight with respect to the meaning of the applicable legal requirements" — even though guidance alone "cannot impose any legally binding requirements on private parties."

The changes meant that department enforcement officials could rely on guidance issued by the FDA and other agencies in certain circumstances when they bring and pursue enforcement actions.

DOJ policies on the criminal prosecution of business organizations. In October 2021, the DOJ announced three policy changes intended to bolster federal prosecutions of corporate crime — including changes that, according to Deputy Attorney General Lisa O. Monaco, reflected the department's "first priority" in corporate criminal cases: "to prosecute the individuals who commit and profit from corporate malfeasance."

The changes were contained in a memorandum from Monaco to DOJ divisions, the FBI, and U.S. attorneys.

In the first policy change, Monaco ordered the DOJ "to restore prior guidance making clear that to be eligible for any cooperation credit, companies must provide the department with all nonprivileged information about individuals involved in or responsible for the misconduct at issue."

"To be clear," she said, "a company must identify all individuals involved in the misconduct, regardless of their position, status or seniority."

The memorandum said that the DOJ would reinstate the September 2015 memorandum issued by then Deputy Attorney General Sally Quillian Yates, "Individual Accountability for Corporate Wrongdoing."

The change nullified a policy announced by then Deputy Attorney General Rod J. Rosenstein in November 2018 under which companies were given the opportunity to be eligible for some cooperation credit from the DOJ even if they could not identify every relevant individual or provide all the relevant information connected with allegedly illegal activity. Specifically, the November 2018 policy had mandated that cooperation credit would be available in criminal cases only to companies that identified every individual who was "substantially" involved in or responsible for the misdoing.

A second Biden administration change in DOJ policy focused on a company's prior misconduct and how it affected the department's decisions on reaching "appropriate" criminal resolutions.

Under a new policy, Monaco said, "all prior misconduct needs to be evaluated when it comes to decisions about the proper resolution with a company, whether or not that misconduct is similar to the conduct at issue in a particular investigation."

The policy revised one of the 11 so-called Filip factors included in the DOJ's Principles of Federal Prosecution of Business Organizations (Justice Manual §9-28.300, §9-28.600), which has specified that prosecutors should consider "the corporation's history of similar misconduct, including prior criminal, civil, and regulatory procedures against it." The factors were established in an August 2008 memorandum issued by then Deputy Attorney General Mark Filip.

"Going forward," Monaco said, "prosecutors will be directed to consider the full criminal, civil and regulatory record of any company when deciding what resolution is appropriate for a company that is the subject or target of a criminal investigation."

She stressed that prosecutors should consider "the full range" of prior misconduct, "not just a narrower subset of similar misconduct — for instance, only the past [Foreign Corrupt Practices Act (FCPA)] investigations in an FCPA case, or only the tax offenses in a Tax Division matter."

The third DOJ policy change announced by Monaco dealt with independent corporate monitors in corporate criminal matters. Monitors are engaged to encourage and verify a company's compliance where the basis for the firm's commitment to improved compliance "is limited or called into question."

"To the extent that prior Justice Department guidance suggested that monitorships are disfavored or are the exception," Monaco said, "I am rescinding that guidance. Instead, I am making clear that the department is free to require the imposition of independent monitors whenever it is appropriate to do so in order to satisfy our prosecutors that a company is living up to its compliance and disclosure obligations under [a deferred prosecution agreement (DPA)] or [nonprosecution agreement (NPA)]."

The change affected part of an October 2018 Criminal Division memorandum issued by then Assistant Attorney General Brian A. Benczkowski, "Selection of Monitors in Criminal Division Matters."

In addition, Monaco said that the DOJ planned to look into "how to account for companies who have a documented history of repeated corporate wrongdoing. In certain cases, the department sees the same company become the subject of multiple investigations — not just in the same office or section, but in multiple sections and divisions across the department."

Also of concern, Monaco said, was "whether companies under the terms of an NPA or DPA take those obligations seriously enough. … We have no tolerance for companies that take advantage of pretrial diversion [through an NPA or DPA] by going on to continue to commit crimes, particularly if they then compound their wrongdoing by knowingly hiding it from the government."

HHS policy on laboratory developed tests. In November 2021, HHS withdrew an August 2020 Trump administration policy barring the FDA from requiring premarket review of laboratory developed tests (LDTs).

The former policy had directed the FDA not to require premarket review for LDTs "even in situations where they have poor performance," HHS Secretary Xavier Becerra said. "By withdrawing the policy, HHS is helping to ensure that COVID-19 tests work as intended." "Effective today," he stated, "HHS no longer has a policy on LDTs that is separate from FDA's long-standing approach in this area."

Becerra announced the policy change as the FDA toughened its requirements for COVID-19 tests, including COVID-19-related LDTs. The FDA said that going forward it would issue emergency use authorizations (EUAs) for only a few types of tests and would require marketing authorization for other tests through traditional device review pathways such as 510(k)s and de novo classifications.

2. FDA Inspections: Agency Expands Use of Alternative Oversight Tools as COVID-19 Pandemic Continues To Rage

The FDA entered 2021 struggling to return its inspection programs to full capacity after the COVID-19 pandemic had severely limited the agency's ability to conduct on-site oversight of the companies that it regulates.

GAO report. In January 2021, the U.S. Government Accountability Office (GAO) presented a wide-ranging report on the federal government's response to the COVID-19 public health emergency that sounded the alarm on the restraints that the pandemic had placed on the FDA's ability to conduct inspections.

"Without regular inspections or alternative tools to fully assess an establishment's compliance with quality standards," the watchdog agency said, "FDA could be faced with a backlog of inspections, threatening the agency's goal of shifting toward exclusively risk-driven surveillance inspections."

Typically, for example, the FDA conducts more than 1,600 drug manufacturing facility inspections each year. However, the GAO reported, the total number of domestic and foreign drug establishment inspections was 56 percent lower in fiscal year (FY) 2020, which ended on Sept. 30, 2020, as compared with each of the previous two fiscal years.

The GAO noted that the FDA had expanded its use of alternative inspection tools during the pandemic, including its reliance on inspections conducted by foreign regulators and on requesting and reviewing records and other information as substitutes for FDA inspections. However, the GAO said, at the time these alternative inspection tools were "not a long-term or comprehensive substitute" for inspections, and the FDA had not fully assessed how the tools could be used to support its drug oversight activities.

The watchdog agency said that a continued pause in preapproval inspections might lead to delays in FDA drug approvals, and that continued postponement of surveillance inspections might create a backlog that would prevent the FDA from inspecting all the drug establishments that it had prioritized through its risk-based site selection model.

Guidance on remote interactive evaluations: FDA guidance released in April 2021 on the agency's remote interactive evaluations of drug facilities during the COVID-19 public health emergency offered a view of how the agency was using the oversight tools that had taken the place of on-site inspections of medical product facilities during the pandemic — tools that the FDA was likely to use more frequently in the future.

The guidance — "Remote Interactive Evaluations of Drug Manufacturing and Bioresearch Monitoring Facilities During the COVID-19 Public Health Emergency" (https://www.fda.gov/media/147582/download) — was expected to form one basis for the expansion of the FDA's use of record requests in advance of or in lieu of inspections, information from non-U.S. regulatory authorities, remote livestreaming video, teleconferences, screen sharing of data and documents, and other tools past the end of the COVID-19 emergency.

"Resiliency Roadmap" identifies alternative oversight tools. In May 2021, the FDA issued a detailed report on the impact of the COVID-19 public health emergency on its inspectional oversight activities. The report set forth what acting FDA Commissioner Dr. Janet Woodcock called the agency's "detailed plan for a more consistent state of operations" and its inspection priorities going forward.

The document, "Resiliency Roadmap for FDA Inspectional Oversight" (https://www.fda.gov/media/148197/download), was intended to show how the FDA planned to address the inspectional work that the agency postponed due to safety concerns arising from the pandemic. Woodcock said that the FDA was committed to tackling the postponed inspections "as quickly as possible."

The FDA reported in the document that it had looked to a range of its available alternative oversight tools to "weave new approaches into [its] oversight scheme." Among these tools are the following:

- ***Review of facility records and other information in advance or in lieu of some drug and biological product inspections***. The FDA has this record review authority under Section 704(a)(4) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. §374(a)(4)). The FDA has used this authority to make application approval decisions, to identify areas of focus for future inspections, to determine that certain products must be placed on Import Alerts, and to help review the compliance histories of facilities to help prioritize future oversight.

- ***Remote assessments dealing with Foreign Supplier Verification Program (FSVP) requirements***. The FDA had stepped up its use of remote inspections of human and animal food importers to evaluate FSVP compliance. From March 2020 through March 2021, the agency reported, it had conducted approximately 1,183 remote FSVP inspections, including 102 inspections dealing with situations in which agency inspections of foreign suppliers were postponed. The FDA reported that remote FSVP inspections "have been an effective way to ensure importer compliance" and have led to the placement of several importing companies on an FSVP Import Alert.

- ***Inspections conducted by state, local, tribal and territorial (SLTT) regulatory authorities.*** Between March 2020 and March 2021, the FDA's SLTT partners conducted 4,273 human food and 1,295 animal food inspections on the agency's behalf.

- ***Information from foreign regulatory partners provided through mutual recognition and confidentiality agreements.*** The agency said that in response to the pandemic it had assessed expanding the use of its mutual recognition agreements with the European Union and the United Kingdom "beyond in-country inspections to include third-country inspections and had begun to accept and classify third-party inspections conducted by countries deemed capable" under 21 U.S.C. §384e. Also, under the Medical Device Single Audit Program (MDSAP), regulatory audits were conducted at 2,842 device manufacturing facilities during FY 2020, and 536 more regulatory audits had been conducted during FY 2021 as of March 2021.

- ***Sampling and analytical testing of FDA-regulated products.*** The use of product sampling and analysis resulted in the placement of 65 foreign drug establishments, 30 filtering facepiece respirator companies, five ready-to-eat food manufacturers, and some seafood manufacturers on FDA Import Alerts. Sampling and analysis also led to the issuance of an Import Alert covering alcohol-based hand sanitizers manufactured in Mexico, with 130 of 347 product samples determined by laboratory analysis to be in violation of agency requirements.

- ***Refusal of unsafe imported products at the U.S. border.*** The FDA said that the use of its authority at ports of entry "plays a critical role in keeping dangerous and defective products out of U.S. commerce."

In the report, the FDA constructed three possible near-term scenarios (reflecting various degrees of pandemic severity) to estimate how many surveillance inspections could be completed through the remainder of FY 2021.

Return to "standard operating levels." Following the roadmap's release, the FDA in July 2021 moved to "standard operating levels" for domestic surveillance inspections and resumed investigations and sample collections based on its considerations of risk and on FDA priorities — even as the agency continued to conduct mission-critical inspections, as it had throughout the COVID-19 public health emergency.

During the course of the public health emergency, mission-critical FDA inspections had included:

- inspections related to potential drug shortages, approvals of novel drugs, or drugs that potentially could be treatments for COVID-19;

- Bioresearch Monitoring (BIMO) inspections conducted to evaluate the integrity of data submitted to the FDA in support of premarket or prelicense applications or to ensure that the rights and safety of research subjects are protected;

- inspections conducted as a follow-up to product recalls; and

- inspections conducted to collect environmental samples in response to outbreaks of foodborne illnesses.

Update to "Resiliency Roadmap." In November 2021, the FDA reported in an update to its May 2021 "Resiliency Roadmap" report (https://www.fda.gov/media/154293/download) that, despite the ongoing COVID-19 pandemic, it had far exceeded its projection for the number of domestic surveillance oversight inspections that it could conduct during FY 2021 — with the agency conducting more than twice the number of inspections that it had set as a goal in May 2021.

Between April and September 2021, the FDA also reported, the agency completed 124 foreign inspections — 50 human and animal food inspections and 74 human and animal medical product inspections — in 23 countries.

With most foreign surveillance inspections on hold due to COVID-19 travel and other restrictions, the agency "continued to focus primarily on mission-critical inspections in foreign countries," but it managed to conduct some non-mission-critical foreign inspections as well, according to the report.

The FDA stated that it was "currently developing a plan for resuming prioritized foreign inspections, including surveillance and application-related inspections, starting in February 2022 for all commodities."

The agency also said that it had "exceeded all established goals" when it came to following up on compliance actions related to prior domestic inspections that had been classified as official action indicated (OAI).

"FDA's development of new oversight approaches and expanded use of a variety of surveillance tools significantly contributed to the agency's ability to exceed these goals," the agency said. The FDA credited the alternative oversight tools that informed its domestic surveillance work and other oversight activities.

For example, between April 1 and Sept. 30, 2021, the agency conducted more than 600 domestic and more than 200 foreign remote regulatory assessments — remote reviews of the records that companies are required to maintain for review by the agency.

However, of all medical product applications received by the FDA since March 2020, as of Sept. 30, 2021, decisions on 60 applications had been delayed solely because of the agency's inability to conduct inspections or facility assessments. Among those 60 applications, four were considered mission-critical, and nearly 90% required foreign inspections or assessments.

Omicron variant forces inspection cutbacks. At the end of the year, the continuing COVID-19 public health emergency once again forced the FDA to cut back on its on-site inspections.

As of Dec. 29, 2021, the agency announced in early January 2022, the FDA had "implemented temporary changes to its inspectional activities to ensure the safety of its employees and those of the firms it regulates" as the agency "further adapts to the evolving COVID-19 pandemic and the spread of the omicron variant."

Although mission-critical inspectional work would continue, the FDA said, the agency had "temporarily postponed certain inspectional activities." The FDA added that it hoped to restart these activities "as soon as possible."

With respect to foreign inspections, the agency said that it would continue to conduct mission-critical inspections and would "reassess plans as needed based on its monitoring [of] foreign travel conditions." However, the FDA said that it was postponing its plans to make prioritized surveillance foreign inspection assignments, which had been scheduled to begin in February 2022.

3. D.C Circuit: FDA May Not Ban a Medical Device for a Particular Purpose

The FDA may not ban electrical stimulation devices to treat aggressive or self-injurious behaviors, the U.S. Court of Appeals for the District of Columbia Circuit held in July 2021. In a 2-1 decision, the court ruled that banning a medical device for a particular purpose constitutes the illegal regulation of the practice of medicine (*The Judge Rotenberg Educational Center, Inc. v. FDA*, 3 F.4th 390 (D.C. Cir. 2021)).

The FDA regulates electric stimulation devices and other aversive conditioning devices as Class II devices (21 C.F.R. §882.5235). In April 2016, the FDA proposed banning electrical stimulation devices for self-injurious or aggressive behavior, citing what the agency called "psychological and physical risks," including depression, fear, worsening of underlying symptoms, or bursts of self-injury (81 Fed. Reg. 24386). A final rule promulgated by the FDA in March 2020 amended 21 C.F.R. §882.5235 to ban electrical stimulation devices for self-injurious or aggressive behavior (85 Fed. Reg. 13312).

The Judge Rotenberg Educational Center, a Canton, Massachusetts, facility that treats patients with severe mental disabilities, had used a graduated electronic decelerator, a type of electrical stimulation device, to treat some of its patients. The device briefly shocks patients, causing them to reduce or cease their self-injurious behaviors. The center admitted patients whom other facilities could not successfully treat and was the only facility in the country that used electric shock therapy to treat individuals who severely injured themselves or who were aggressive.

Under the FD&C Act, the FDA — upon a finding that "a device intended for human use presents substantial deception or an unreasonable and substantial risk of illness or injury" and that the risk cannot be "corrected or eliminated by labeling" — may promulgate a regulation "to make such device a banned device" (21 U.S.C. §360f(a)).

At the same time, under the FD&C Act the agency is prohibited from regulating the practice of medicine. Specifically, the statute states that nothing in the Act "shall be construed 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). Section 396 specifies that it does not limit "any existing authority" to impose restrictions on the sale or distribution of a device that are promulgated through regulations.

In the majority opinion, written by Senior U.S. Circuit Judge David B. Sentelle, the court said that Section 396 preserves the flexibility of health care providers "to draw on their expertise to prescribe or administer the device for any condition or disease, not just the use the FDA approved — in short, to practice medicine." The court said that Section 396 "protects the liberty of doctors and patients to use approved devices in any manner they wish," including off-label uses.

According to the court, the "natural reading" of Section 360f's statement that the FDA may make "such device a banned device" "suggests that a device either is banned or it is not. It speaks of no authority to place a device in an intermediate state of 'banned in some uses.'"

On the other hand, the court acknowledged, the agency's analysis of the various risks presented by a device "could … be reasonable in some cases but not for others."

"However," the court said, "Section 396 expressly denies the FDA authority to construe any part of the [FD&C Act], including its authority to ban devices under Section 360f, to permit the FDA to limit or interfere with practitioners' authority to prescribe or administer legally marketed devices to patients."

Consequently, the court said, the questions posed in the case were (1) whether a ban "limits or interferes" and (2) whether a device that the FDA has attempted to ban for a particular purpose is "legally marketed."

The court concluded that (1) a use-specific ban indeed does limit or interfere with a practitioner's authority by restricting the available range of devices through regulatory action, and (2) a device is legally marketed if it is lawful for the manufacturer to sell the device or for a practitioner to prescribe or administer it.

"The statute does not suggest, [nor] should we read into it, a limitation that the device must be marketed for the particular use for which the practitioner wants to utilize the device," the court said. "Indeed, that would eviscerate the statute's protection of off-label use."

Electrical stimulation devices are legally marketed, the court reasoned, and banning them for a particular use limits or interferes with a practitioner's ability to administer or prescribe them as the practitioner sees fit.

"The plain meaning of the first sentence of Section 396 demonstrates that the FDA does not have the authority to limit practitioners' use of a device for a particular purpose," the court concluded.

In September 2021, the DOJ, acting on behalf of the FDA, called for the full U.S. Court of Appeals for the District of Columbia Circuit to review the ruling. The government's petition for rehearing en banc was denied in November 2021.

4. FDA Issues Notices of Noncompliance for Failure To Report Trial Results

Fourteen years after Congress authorized the FDA to take enforcement action in response to clinical trial sponsors' failure to report applicable trial results on ClinicalTrials.gov, the agency issued its first notice of noncompliance for the violation.

In April 2021, the agency issued a notice of noncompliance to Acceleron Pharma Inc. over its failure to submit results for a Phase 2 randomized, double-blind study of Dalantercept and Axitinib compared to placebo and Axitinib in patients with advanced renal cell carcinoma.

In addition, in July 2021 the agency issued a notice of noncompliance to Accuitis Inc. over its failure to submit to ClinicalTrials.gov the results of a trial on the efficacy of ACU-D1 in the treatment of acne rosacea.

Although the Food and Drug Administration Amendments Act of 2007 (FDAAA) required responsible parties to submit clinical trial registration and results information to ClinicalTrials.gov for applicable clinical trials, the National Institutes of Health did not publish a final rule for clinical trials registration and results information submission until September 2016. The final rule set a compliance date of April 18, 2017 (81 Fed. Reg. 64982).

In August 2020, the FDA issued final guidance on civil money penalties for ClinicalTrials.gov reporting violations (https://www.fda.gov/media/113361/download).

In announcing the notice to Acceleron Pharma, acting FDA Commissioner Woodcock noted that the agency had sent more than 40 prenotices of noncompliance "to encourage voluntary compliance with the ClinicalTrials.gov requirements."

In a July 2020 prenotice letter to Acceleron Pharma, the FDA asked the company to review its records for the clinical trial and submit all required results information promptly. The agency said that it intended to further review and assess the clinical trial beginning 30 calendar days after the company received the letter and that the agency might take regulatory action if it determined that the company was not in compliance at that time.

A similar prenotice letter had been sent to Accuitis in October 2020.

In the notices of noncompliance, the FDA said that the companies had failed to submit results information for the trials and were not in compliance with FDAAA's results information submission requirements. The agency gave the companies 30 days after receipt of the notices to remedy the noncompliance by submitting the required clinical trial results information.

The notices informed the companies that the FDA might initiate administrative actions seeking civil monetary penalties of up to $10,000 for each set of violations adjudicated in a single proceeding. "If your company does not submit the required clinical trial results information in the manner and format specified … within 30 calendar days after receiving this notice," the agency said in the notices, "FDA may also seek additional civil monetary penalties … of not more than $10,000 for each day of the violation until the violation is corrected."

The notices informed the companies that the violations could result in additional regulatory action, such as injunction or criminal prosecution.

"The FDA takes its role in enforcing the ClinicalTrials.gov registration and results information submission requirements extremely seriously, and we will continue to encourage voluntary compliance with these requirements," Woodcock said. "When necessary, the FDA will take appropriate actions to help ensure that required information is available on ClinicalTrials.gov as required by law and for the benefit of clinical trial participants and public health."

5. USDA Proposes Rule for Labeling Cell Cultured Meat, Poultry

The U.S. Department of Agriculture (USDA) Food Safety and Inspection Service (FSIS) published an advance notice of proposed rulemaking (ANPR) in September 2021 seeking public comment on how best to label meat and poultry products containing cultured cells derived from animals subject to the Federal Meat Inspection Act or the Poultry Products Inspection Act (86 Fed. Reg. 49491).

"This ANPR is an important step forward in ensuring the appropriate labeling of meat and poultry products made using animal cell culture technology," said USDA Deputy Under Secretary for Food Safety Sandra Eskin. "We want to hear from stakeholders and will consider their comments as we work on a proposed regulation for labeling these products."

Animal cell culture technology employs a small number of cells from living animals that are grown in a controlled environment to create many things, including food. After the cells have multiplied, additional inputs such as growth factors, new surfaces for cell attachment, and additional nutrients are added to enable the cells to differentiate into various cell types. Once produced, the harvested cells can be processed, packaged and marketed in the same or a similar manner as slaughtered meat and poultry products.

In March 2019, the USDA and the FDA announced a formal agreement to jointly oversee the production of human food products made using animal cell culture technology and derived from the cells of livestock and poultry to ensure that such products are safe, unadulterated and truthfully labeled.

Under the agreement, the FDA oversees cell collection, growth and differentiation. The FDA then transfers oversight at the cell harvest stage to FSIS, which regulates the cell harvest and the processing, packaging and labeling of products. The agencies agreed to develop joint principles for the labeling of products made using cell culture technology under their respective jurisdictions. Seafood, other than *Siluriformes* fish, falls under the FDA's jurisdiction, whereas meat, *Siluriformes* fish and poultry are under the jurisdiction of FSIS.

The ANPR focused on issues raised by the labeling of meat and poultry products produced using animal cell culture technology, including how these products were to be identified and how their nature, source or characteristics should be described. Input offered in the comments was to inform future rulemaking to establish labeling requirements for these products, according to FSIS. This ANPR also discussed how FSIS would generally evaluate labels for these products if they were submitted before completion of the rulemaking.

Other than new labeling regulations, FSIS indicated that it would not issue any new food safety regulations for cell cultured food products.

The ANPR referred to such foods as cultured meat and poultry products or as containing cultured animal cells. The use of the term "cultured," FSIS cautioned stakeholders, was not intended to establish or suggest nomenclature for labeling purposes.

In the ANPR, FSIS requested comment on topics to be addressed during the rulemaking, including consumer expectations about the labeling of the products, especially considering nutritional composition and certain product qualities (taste, color, odor or texture); names for the products that would be neither false nor misleading; economic data; and any consumer research related to labeling nomenclature for products made using animal cell culture technology.

FSIS already had received thousands of comments on the topic in response to a 2018 joint public meeting with the FDA and in connection with related petitions for rulemaking from the United States Cattlemen's Association (Petition No. 18-01) and the Harvard Law School Animal Law and Policy Clinic (Petition No. 20-03).

6. After Six Years, FDA Finalizes Rule on Determining the Intended Uses of Devices

In August 2021, the FDA published final versions of regulations outlining the types of evidence that the agency considers when determining the intended uses of a medical device or drug (86 Fed. Reg. 41383). The final rule, which amended the FDA's 21 C.F.R. Part 201 and Part 801 labeling regulations, was effective Sept. 1, 2021.

With the publication of the final rule, the FDA withdrew portions of a January 2017 final rule that never went into effect. The final rule "provide[s] more clarity and direction to regulated industry and other stakeholders regarding the types of evidence relevant to determining a product's intended uses," the agency said.

The evolution of the finalized intended use regulations dated back to September 2015 with the publication of a proposed rule that was drafted to help determine when a tobacco product was subject to regulation by the agency as a drug, device or combination product (80 Fed. Reg. 57756, Sept. 25, 2015).

The September 2015 proposed rule was intended to change how the agency determined the intended use of a device by removing language that required a device manufacturer to provide labeling to cover uses to which the manufacturer knew a marketed device was being put. The labeling requirement applied even if the manufacturer did not intend the product to be used in those ways.

In January 2017, the FDA published a final rule including a new version of 21 C.F.R. §801.4, under which the intended uses of devices were to be determined by "the objective intent of the persons legally responsible for the labeling of devices" (82 Fed. Reg. 2193, Jan. 9, 2017).

That intent, according to the January 2017 final rule, was "determined by such persons' expressions or may be shown by the circumstances surrounding the distribution of the article," such as labeling claims, advertising matter, or oral or written statements. "It may be shown, for example," the final rule stated, "by circumstances in which the article is, with the knowledge of such persons or their representatives, offered and used for a purpose for which it is neither labeled nor advertised."

"If the totality of the evidence establishes that a manufacturer objectively intends that a device introduced into interstate commerce by him is to be used for conditions, purposes, or uses other than ones for which it has been approved, cleared, granted marketing authorization, or is exempt from premarket notification requirements (if any)," the January 2017 final rule provided, "he is required … to provide for such device adequate labeling that accords with such other intended uses."

The final rule was scheduled to go into effect in February 2017. However, in response to criticism of the final rule, the FDA delayed its effective date twice (82 Fed. Reg. 9501, Feb. 7, 2017; 82 Fed. Reg. 14319, March 20, 2017). In March 2018, the agency delayed the effective date indefinitely (83 Fed. Reg. 11639, March 16, 2018).

In a September 2020 proposed rule (85 Fed. Reg. 59718), the FDA said that it was repealing and replacing the intended use regulations "to clarify the regulatory language describing the types of evidence [that the agency considers] relevant to determining a product's intended use," according to then FDA Commissioner Dr. Stephen M. Hahn.

Hahn said that the proposed changes did not reflect a change in the agency's policies and practices, but rather "better reflect[ed] the FDA's long-standing approach to intended use and provide greater clarity for regulated parties."

The final rule remained largely unchanged from the September 2020 proposed rule. However, the FDA modified the intended use regulation for devices to clarify that the regulation applied to devices that are approved, cleared, granted marketing authorization, or exempted from premarket notification by the agency. The proposed version had referred solely to "an approved or cleared device."

7. Supreme Court Will Consider Physician Good Faith Defense to Illegitimate Prescription Charges Under Controlled Substances Act

The Supreme Court agreed in November 2021 to consider whether and to what extent a physician charged with prescribing a controlled substance illegitimately in violation of the Controlled Substances Act (CSA) may assert as a defense that he or she reasonably believed or subjectively intended the prescription to be legitimate (*Ruan v. United States, cert. granted*, 142 S. Ct. 457 (U.S. Nov. 5, 2021) (No. 20-1410); *Kahn v. United States, cert. granted*, 142 S. Ct. 457 (U.S. Nov. 5, 2021) (No. 21-5261)).

The Court granted writs of certiorari in two cases on appeal from separate federal appeals courts and consolidated the cases for purposes of briefing and oral argument.

At issue in the cases is the question of a so-called good faith defense to charges of violating 21 U.S.C. §841(a)(1), under which a physician may be convicted if the government proves that he or she knowingly prescribed controlled substances outside the usual course of professional practice (21 C.F.R. §1306.04(a)).

Many of the federal courts of appeals permit a physician charged with such a violation of the CSA to assert a good faith defense. However, the courts of appeals have established different definitions of what "good faith" means in such a case and how a jury should be instructed as to the defense.

The U.S. Courts of Appeals for the Second, Fourth and Sixth Circuits have set an objective standard, holding that a physician should be acquitted if he or she "reasonably believed" that the prescription was within the usual course of professional practice.

By contrast, the U.S. Courts of Appeals for the First, Seventh and Ninth Circuits have set a subjective standard, holding that any sincere belief, whether it is reasonable or not, that a prescription was within the bounds of professional practice is grounds for acquittal.

Dr. Xiulu Ruan, a Mobile, Alabama, physician and a partner in a pain clinic, was convicted of unlawfully distributing controlled substances. In his petition, Ruan said that the question presented to the Court, "on which the circuits are deeply divided," is "whether a physician alleged to have prescribed controlled substances outside the usual course of professional practice may be convicted under Section 841(a)(1) without regard to whether, in good faith he 'reasonably believed' or 'subjectively intended' that his prescriptions fall within that course of professional practice."

Dr. Shakeel Kahn was convicted on 22 criminal counts related to his issuing of prescriptions for controlled substances, primarily opioids, between 2011 and 2016, including illegal distribution or aiding and abetting illegal distribution. Kahn's petition to the Court formulated the questions presented as the following:

1. Where the government prosecutes a medical practitioner under the [CSA] for issuing a prescription outside "the usual course of professional practice," is the government required to prove that the doctor knew or intended that the prescription be outside the scope of professional practice?

2. Does a good faith defense in the context of a licensed medical practitioner prosecuted under the [CSA] protect doctors who have an honest but mistaken belief that they have issued the charged prescription in "the usual course of professional practice"; and, if so, must that belief be objectively reasonable?

3. Should the "usual course of professional practice" and "legitimate medical purposes" prongs of [21] C.F.R §1306.04(a) be read in the conjunctive or the disjunctive?

Walmart litigation put on hold. In the wake of the Court's action, the U.S. District Court for the District of Delaware put on hold the government's massive civil suit against Walmart Inc. for alleged violations of the CSA by the company's pharmacies pending the Court's rulings in the two cases (*United States v. Walmart Inc.*, No. 1:20-cv-01744-CFC (D. Del.)).

In the civil suit, filed in December 2020, the DOJ alleged that Walmart unlawfully dispensed controlled substances from the pharmacies that it operates across the United States and that it unlawfully distributed controlled substances to those pharmacies.

8. D.C. Circuit: FDA Lacks Broad Discretion To Choose To Regulate a Product as Either a Drug or a Device

If a medical product satisfies the statutory definitions of both a drug and a device, the overlapping definitions do not grant the FDA broad discretion to regulate the product under either regime, the U.S. Court of Appeals for the District of Columbia Circuit held in April 2021 (*Genus Medical Technologies L.L.C. v. U.S. Food and Drug Administration*, 994 F.3d 631 (D.C. Cir. 2021)).

The decision affirmed a grant of summary judgment by a federal district court in December 2019 (*Genus Medical Technologies, L.L.C. v. U.S. Food and Drug Administration*, 427 F. Supp. 3d 74 (D.D.C. 2019)).

The appeals court's decision may bolster some companies' attempts to have the agency regulate their products under the generally less demanding device regime rather than as drugs.

Since 2017, the FDA had classified Genus Medical Technologies L.L.C.'s line of diagnostic contrast agents — products used in medical imaging to improve the visualization of tissues, organs and physiological processes — as drugs rather than as devices, despite the agency's recognition that the products appeared to satisfy the definition of a medical device under the FD&C Act.

The statute defines a device in relevant part as a product "intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease … and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purpose" (21 U.S.C. §321(h)(1)).

A drug is defined under the FD&C Act to include "articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals" (21 U.S.C. §321(g)(1)(B)).

The company sought FDA clearance to market the products as devices or as grandfathered drugs, which — unlike new drugs — do not require premarket approval.

However, after a June 2016 inspection of the company's Chesterfield, Missouri, distribution facility, the FDA issued the company a May 2017 Warning Letter alleging that the products constituted drugs under the FD&C Act.

Genus objected to the agency's position. The FDA responded that, although the products appeared to meet the definition of a device, they also met the FD&C Act's definition of a drug because they were intended for use in the diagnosis of disease.

The company then submitted a request for designation to the FDA Office of Combination Products (OCP) requesting that the agency classify its products as devices. OCP's response reiterated the FDA's position that the products would be regulated as drugs.

In February 2019, the company sued the FDA in the U.S. District Court for the District of Columbia, contending that the agency's decision was arbitrary and capricious and in excess of its statutory authority under the FD&C Act and the Administrative Procedure Act.

In December 2019, the district court granted summary judgment to the company, holding that the FD&C Act requires that "a product that meets the device definition must be regulated as such."

On appeal, the FDA argued before the D.C. Circuit that, because it is possible for a product to satisfy both the drug definition and the device definition in the FD&C Act, Congress must have granted the FDA discretion in such a situation to choose a classification for the product. The statute is silent on how to treat products that meet both definitions, the agency argued, and therefore the court should read the statute to be ambiguous and defer to the FDA's interpretation under *Chevron U.S.A., Inc. v. Natural Resources Defense Council, Inc*., 467 U.S. 837 (1984).

The company argued that, because the drug and device definitions are broadly similar except for the mode-of-action clauses in the device definition — which exclude products that achieve their primary intended purposes through chemical action or metabolization — products like its contrast agents that satisfy both definitions but do not achieve their primary intended purpose through either excluded mode must be regulated as devices.

In addition, the company urged the appeals court panel to rely on "two traditional canons of statutory construction": the rule that "the specific governs the general," and the principle that a statute "should be construed to give effect to all its provisions, so that no part will be inoperative or superfluous, void or insignificant."

The appeals court agreed with the company. "This is a case where the specific must govern the general," it said. "The FDA does not dispute that [the FD&C Act's] definition of a device is drawn more narrowly than its definition of a drug. Indeed … the set of products that satisfy the device definition is necessarily encompassed by, but narrower than, the set of products that satisfy the drug definition. … The device definition's instrument and mode-of-action clauses make it a classic candidate for application of the canon that the specific governs the general, and to the extent the drug and device definitions conflict, it is the narrower definition — the device definition — to which we must give effect."

Rejecting the FDA's argument that the two definitions do not actually conflict, the appeals court said, "In theory, it may be possible for a product to satisfy both definitions at once. What the FDA omits, however, is that the [FD&C Act's] statutory definitions are meaningful only insofar as they carry concrete regulatory regimes for drugs and devices. And each scheme is mandatory. … In short, it is not textually possible to say that an item is a drug (or a device) but need not be regulated as such. … The statute, then, is clear: a product may be regulated as a drug or a device, but not both, and while a single product may simultaneously satisfy the linguistic elements of two definitions, it is not possible for the FDA to give simultaneous effect to both."

Moreover, the court concluded, the statute's structure, purpose and legislative history "make plain that the Congress did not grant the FDA near-limitless discretion to classify any device as a drug. Rather, the Congress has elaborated separate regulatory tracks for drugs and devices and, to the extent that the FDA possesses the discretion to choose one track or the other, such discretion must be exercised in a manner consistent with the statutory drug and device definitions."

"We do nothing to restrict the agency's discretion to determine, in close cases, whether a particular product satisfies the device definition," the D.C. Circuit said. "We necessarily address only the FDA's conclusion that the [FD&C Act] grants it discretion to classify as a drug any product that meets the statutory definition of a device. We hold that it does not. Excepting combination products, devices must be regulated as devices, and drugs — if they do not also satisfy the device definition — must be regulated as drugs."

Effect on previously approved products. In the wake of the court's decision, the FDA acknowledged that the ruling may require some approved products to transition from drug status to device status, and the agency called for comments on how such transitions should be handled (86 Fed. Reg. 43553, Aug. 9, 2021).

In the *Federal Register* notice, the FDA announced that it would not appeal the D.C. Circuit's decision.

"Going forward, in accordance with *Genus*," the agency said, "FDA intends to regulate products that meet both the device and drug definition as devices, except where the statute indicates that Congress intended a different classification."

In addition, it said, the agency "intend[s] to bring previously classified products into line with the *Genus* decision." As a result, the FDA planned to review past product classifications in light of the court's ruling.

"We expect the determining factor in many cases to be whether the product achieves its primary intended purposes through chemical action within or on the body or is dependent upon being metabolized for the achievement of its primary intended purposes," the FDA said.

In addition, the agency said that it would examine whether other statutory definitions (beyond the drug and device definitions) "indicate Congress intended a type of product to be regulated under either the drug or device authorities."

For products that need to be transitioned from drug status to device status, the FDA said that it would act "in a way that does not disrupt the supply of these important medical products or place undue burden on manufacturers or on the health care delivery system."

The agency planned to publish in the *Federal Register* a list of drug products that it tentatively selects to be transitioned to device status and to give stakeholders an opportunity to comment.

Because of the differing regulatory compliance obligations of the two types of medical products — including differing labeling requirements, differing current good manufacturing practice requirements, and the need to prepare for different kinds of inspections — "sponsors of transitioning marketed products will need time to transition" from compliance with drug requirements to compliance with device requirements, the FDA recognized. The agency called for comments on the timelines needed for the transitions.

The *Federal Register* notice also called for comments on considerations related to user fee transitions, including requests for refunds that may be submitted by payors of the annual FY 2022 fees under the Prescription Drug User Fee Amendments (PDUFA) or the Generic Drug User Fee Amendments (GDUFA).

The FDA vowed to create "a process for the orderly and efficient determination of which products currently regulated as drugs must be regulated as devices under *Genus*."

9. Supreme Court: FTC Cannot Obtain Restitution, Disgorgement Without a Prior Administrative Proceeding

In April 2021, the Supreme Court limited one of the statutory enforcement tools available to the Federal Trade Commission (FTC), ruling that the commission cannot rely on a provision of the statute governing the FTC to obtain equitable monetary remedies such as restitution or disgorgement (*AMG Capital Management, L.L.C. v. Federal Trade Commission*, 141 S. Ct. 1341 (2021)).

The Court's unanimous decision bars the FTC from using Section 13(b) of the Federal Trade Commission Act, 15 U.S.C. §53(b), to obtain restitution or disgorgement from a federal district court when the commission has not previously initiated an administrative proceeding against the defendant.

The FTC has relied on the statutory provision to bring dozens of cases every year seeking not only permanent injunctions, which are expressly authorized by Section 13(b), but also the return of illegally obtained funds. As the FTC told the Court, the commission has pursued far more consumer protection cases in court than through administrative process.

For example, during FY 2019, the FTC filed 49 complaints in federal court and obtained 81 permanent injunctions and orders that resulted in $723.2 million in consumer redress or disgorgement. By contrast, that year the commission issued 21 new administrative complaints and 21 final administrative orders.

The case before the Supreme Court involved several companies that provided short-term payday loans to borrowers. According to the FTC, language included in fine print in the loan agreements provided that a loan would be automatically renewed unless the customer took affirmative steps to opt out of it. More than 5 million loans made by the companies allegedly resulted in more than $1.3 billion in deceptive charges.

The FTC filed suit against the companies in 2012, asserting that the companies' practices were likely to mislead consumers. The commission did not first use its administrative options but rather filed a complaint against the companies in federal district court under Section 13(b). The court granted a summary judgment motion filed by the FTC and directed the companies to pay approximately $1.27 billion in restitution and disgorgement.

On appeal, the companies argued that Section 13(b) does not authorize the monetary relief granted by the district court. The U.S. Court of Appeals for the Ninth Circuit ruled against the companies, relying on its own precedent interpreting the section as "empower[ing] district courts to grant any ancillary relief necessary to accomplish complete justice, including restitution" (*Federal Trade Commission v. AMG Capital Management, L.L.C.*, 910 F.3d 417 (9th Cir. 2018)).

The Supreme Court granted a writ of certiorari in the case. In its opinion, the Court noted the differences that have emerged among federal courts of appeal as to the scope of Section 13(b) (*see Federal Trade Commission v. Credit Bureau Center L.L.C.*, 937 F.3d 764 (7th Cir. 2019); *Federal Trade Commission v. AbbVie Inc*., 976 F.3d 327 (3d Cir. 2020)).

The Court said that "several considerations, taken together," convinced it that Section 13(b)'s "permanent injunction" language "does not authorize the commission directly to obtain court-ordered monetary relief."

First, it said, the language of the section refers only to injunctions, and "an 'injunction' is not the same as an award of equitable monetary relief" — although the Court acknowledged that it has sometimes "interpreted similar language as authorizing judges to order equitable monetary relief." Second, the Court said, "the language and structure of Section 13(b), taken as a whole, indicate that the words 'permanent injunction' have a limited purpose — a purpose that does not extend to the grant of monetary relief." The Court noted that the section focuses on "relief that is prospective, not retrospective" — specifically, "stopping seemingly unfair practices from taking place while the commission determines their lawfulness."

"To read those words as allowing what they do not say, namely, as allowing the commission to dispense with administrative proceedings to obtain monetary relief as well, is to read the words as going well beyond the provision's subject matter," the Court said. "In light of the historical importance of administrative proceedings, that reading would allow a small statutory tail to wag a very large dog."

Third, the Court pointed to the structure of the FTC Act beyond Section 13(b). In the other enforcement sections of the statute, it said, Congress "gave district courts the authority to impose limited monetary penalties and to award monetary relief in cases where the commission has issued cease-and-desist orders, i.e., where the commission has engaged in administrative proceedings."

"Since in these provisions Congress explicitly provided for 'other and further equitable relief' and for the 'refund of money or return of property,'" the Court reasoned, "it likely did not intend for Section 13(b)'s more cabined 'permanent injunction' language to have similarly broad scope."

"Nothing we say today … prohibits the commission from using its authority under Section 5 and Section 19 to obtain restitution on behalf of consumers," the Court said. "If the commission believes that authority is too cumbersome or otherwise inadequate, it is, of course, free to ask Congress to grant it further remedial authority." Indeed, the Court noted, "the commission has recently asked Congress for that very authority. … We must conclude, however, that Section 13(b) as currently written does not grant the commission authority to obtain equitable monetary relief."

Reacting to the ruling, acting FTC Chair Rebecca Kelly Slaughter said, "With this ruling, the Court has deprived the FTC of the strongest tool we had to help consumers when they need it most. We urge Congress to act swiftly to restore and strengthen the powers of the agency so we can make wronged consumers whole."

In testimony before the House Energy and Commerce Committee Subcommittee on Consumer Protection and Commerce, Slaughter urged passage of H.R. 2668, which she said would ensure that the commission could obtain equitable monetary relief through Section 13(b) and that the FTC could seek equitable relief under the section in cases where the unlawful conduct is no longer occurring.

10. Medicrea Settlement Continues Emerging DOJ Trend of Including Open Payments Violation Allegations in Settlements

In May 2021, Medicrea International, a medical device manufacturer based in France, and its American affiliate, Medicrea USA Inc., agreed to pay $1 million to resolve kickback and false claims allegations and an additional $1 million to resolve related allegations that they failed to fully report the alleged kickbacks to the Centers for Medicare and Medicaid Services (CMS) as required by the physician Open Payments Program (*United States ex rel. Frain v. Medicrea USA Corp.*, No. 2:16-cv-01986-MMB (E.D. Pa.)).

The DOJ said that this was among the first settlements into which the department had entered to resolve allegations under both the False Claims Act and the Open Payments Program.

According to a whistleblower suit filed in the U.S District Court for the Eastern District of Pennsylvania, Medicrea USA Inc. entertained U.S.-based physicians during the Scoliosis Research Society's 2013 Congress, held in Lyon, France, providing the physicians meals, alcoholic beverages and travel expenses.

"The United States alleged that Medicrea provided the benefits to induce the physicians to purchase or order Medicrea's spinal devices, and that this resulted in false payment claims to federal health care programs," the DOJ said in announcing the settlement.

According to federal enforcement officials, the alleged payments violated the Anti-Kickback Statute, which prohibits medical product manufacturers from directly offering or paying anything of value to induce the referral of items or services, such as product orders or purchases, covered by federal health care programs. The resulting claims for reimbursement submitted to those programs violated the federal False Claims Act, the DOJ said.

The department noted that the claims involved in the settlement were allegations only and that there had been no determination of liability.

Allegations of violations of Open Payment Program requirements have been highlighted in a number of recent DOJ settlements.

In October 2020, the department reached a settlement with Medtronic USA Inc. in which the company agreed to pay $8.1 million to resolve allegations that at the request of a South Dakota neurosurgeon it paid for social events, including expensive meals, at a restaurant that he owned to induce him to use the manufacturer's SynchroMed II intrathecal infusion pumps.

As part of the settlement, Medtronic agreed to pay an additional $1.11 million to resolve allegations that the company violated the Open Payments Program by failing to accurately report to CMS the payments made to the restaurant.

In a separate False Claims Act suit, filed by a whistleblower in August 2016, the DOJ alleged that the neurosurgeon received kickbacks to induce his use of certain implants in his spinal surgeries. The suit resulted in a May 2021 settlement in which the neurosurgeon and two medical device distributorships that he owned agreed to pay $4.4 million to resolve the False Claims Act allegations and an additional $100,000 for allegedly failing to report to CMS the neurosurgeon's ownership interests and the payments made to him. The DOJ had intervened in the case in June 2019 and filed its own complaint in November 2019 (*United States ex rel. Bechtold v. Asfora*, No. 4:16-cv-04115-LLP (D.S.D.)).

In March 2019, the Senate Finance Committee asked CMS and the HHS Office of Inspector General to investigate acts of noncompliance with the Open Payments Program on the part of physician-owned distributorships and to pursue enforcement actions against alleged violators of the program's requirements.

Predictions for 2022

FDA's Use of Alternative Oversight Tools Will Increase, Whatever Course the COVID-19 Pandemic Takes

Although it was the COVID-19 public health emergency and the resulting suspension or restriction of on-site inspections that prompted the FDA's increased use of alternative oversight tools, the agency has signaled that beyond the pandemic it will continue its use of its authority to request records in advance of or in lieu of onsite inspections under FD&C Act Section 704(a)(4), remote interactive evaluations, remote regulatory assessments, and other tools upon which the agency has relied heavily since early 2020.

FDA-regulated companies should watch carefully to see how the agency expands its use of these tools and stay informed about any legal challenges brought against the agency that may result from these developments.

In addition, as with on-site FDA inspections, companies should develop clear policies and standard operating procedures in anticipation of the agency's use of these tools. Companies also should be on the lookout as best practices for responding to the use of the tools emerge within the regulated community, and they should explore other ways to be prepared to act effectively as the FDA continues, as it is able, to bring its inspection program up to speed and expands its use of these alternative oversight tools.

FDA's Regulation of Devices Will Balance Ongoing COVID-19 Response with Efforts To Move Beyond the Pandemic

Even as medical device regulators at the FDA continue to grapple with the continuing COVID-19 public health emergency — for example, by examining the effectiveness of existing and new SARS-CoV-2 tests in detecting emerging variants of the virus — the agency is beginning to deal with how it will regulate COVID-19-related devices beyond the pandemic.

Through two draft guidance documents released in December 2021, the FDA began to address the questions raised by the need to transition back to "normal operations" the agency's regulation of devices that have been marketed during the COVID-19 public health emergency through policies providing enforcement discretion or through EUAs.

For devices marketed under enforcement policies or EUAs issued during the emergency, the agency proposed detailed recommendations for the transition processes, including recommendations for filing marketing submissions with the FDA for the devices.

Also, in January 2022 the FDA issued draft guidance on the requirement that device manufacturers notify the agency about a permanent discontinuance or an interruption in the manufacturing of a device during or in advance of future public emergencies to help prevent or mitigate device shortages.

When finalized, the draft guidance, meant to help stakeholders deal with the reporting mandate outside of the COVID-19 public health emergency, will implement authorities granted to the FDA under the Coronavirus Aid, Relief, and Economic Security Act (CARES Act). Previously issued guidance on complying with the reporting mandate during the COVID-19 public health emergency will remain in effect until the COVID-19 emergency declaration expires or is withdrawn.

The FDA Center for Devices and Radiological Health (CDRH) will also continue to grapple with what agency officials have called "a sustained increase in workload" as the pandemic continues.

In a December 2021 FDA Voices posting, Dr. Jeffrey E. Shuren, the center's director, and CDRH Office of Product Evaluation and Quality Director Dr. William Maisel said, "Given the heavy workload from conventional submissions that pre-dated COVID-19 and COVID-19 response work, we continue to experience some delays in meeting review timelines for certain submissions, including files tied to Medical Device User Fee Agreement (MDUFA) timelines."

"While CDRH's response to the pandemic remains a top priority," the two officials said, "we anticipate a gradual transition back toward normal review timelines in 2022. Our ability to reach and sustain 'normal' review times will depend on the course of the pandemic and adequate resources."

Return of Dr. Robert Califf as FDA Commissioner Will Focus Agency on Emergency Preparedness, Patient Protection, Modernization and Innovation

In November 2021, President Biden nominated Dr. Robert M. Califf to return to the FDA as the next commissioner of food and drugs — a post that he had held at the end of the Obama administration.

In announcing his intention to nominate Califf, Biden called him "one of the most experienced clinical trialists in the country."

With Califf's return as FDA commissioner, the agency's policies on clinical trials would likely reflect his advocacy for streamlining the clinical trial process, making the process more transparent, and ensuring that trials can generate enough reliable data to assure that the FDA's decisions about medical products are truly evidence-based.

Citing his extensive career experience in clinical research, Califf told members of the Senate Committee on Health, Education, Labor and Pensions during a December 2021 confirmation hearing, "Like clinical decisions, FDA decisions are best made when the evidence is robust. My career has been focused on developing better systems for generating reliable evidence to support the everyday decisions that consumers, patients, clinicians and policymakers must make to achieve better health."

He told the senators that his personal life has shown "how important it is to find a critical balance between appropriate safeguards for patients and innovative treatments." He reported that his mother had directly benefited from the accelerated approval of new drugs for treating multiple myeloma, which he said "without a doubt added meaningful years to her life."

Specifically, Califf told the committee members that if confirmed he would have three priorities as FDA commissioner:

- ***Emergency preparedness and response***. As it continues to battle COVID-19, Califf told the senators, the agency "must have infrastructure in place that reflects lessons learned from this pandemic so it is ready for the next one."

- ***Consumer and patient protection***. "Now is the time to develop a systematic approach to evidence generation that will improve patient safety and provide a much more efficient way to understand the benefits and risks of medical products when used in practice," Califf said. "The FDA must continue to build the science base needed to give people confidence that their food is safe and their medical products are safe and effective."

- ***Modernization and innovation***. The agency "must stay current on the latest advances in science and technology in order to provide guidance to industry and stakeholders on everything from clinical trial development to best practices for protecting the safety of the U.S. food supply," Califf told the committee. "The scientific and technical world is moving quickly. The FDA needs the talent to keep up and protect the public while supporting scientific innovation."

Walmart Litigation, Final DEA Rule on Suspicious Orders of Controlled Substances May Clarify Pharmacy, Pharmacist Obligations

In the Biden administration's Fall 2021 Unified Agenda of Regulatory and Deregulatory Actions, which reported the regulatory actions that federal agencies were planning to take in the near future, the DEA projected that by June 2022 it will issue a final rule revising agency requirements for the steps that registrants must take upon receiving suspicious orders of controlled substances.

In a November 2020 notice of proposed rulemaking (85 Fed. Reg. 69282), the DEA 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.

Following an initial comment period on the proposed rule that ended in January 2021, the DEA reopened the comment period for an additional month (until late March 2021) after recognizing that the registrants that would be primarily affected by the proposed rule were preoccupied with dealing with COVID-19, in particular with distributing COVID-19 vaccines.

Meanwhile, the civil litigation initiated by the DOJ against Walmart, focused on pharmacy and pharmacist responsibilities under the CSA, will proceed in 2022 following decisions in the two pending cases regarding physician responsibilities under the statute that were accepted for review by the Supreme Court in November 2021.

A final DEA rule and the course of the Walmart litigation, along with DEA registration proceedings and settlements dealing with pharmacies' and pharmacists' responses to red flags of diversion, may continue to clarify to some extent registrants' specific obligations under the CSA.

FDA's Ad Promo Enforcement Will Continue To Focus on Public Health, But Changes in DTC Policy May Be on the Horizon

With the naming of Califf as the next FDA commissioner, the agency's regulation of advertising and promotion will maintain the status quo in terms of policies and level of enforcement, according to Wayne L. Pines, the president of health care at APCO Worldwide L.L.C. and the author and editor-in-chief of Thompson FDA's *FDA Advertising and Promotion Manual*.

In a December 2021 FDA Intelligence article posted online on Thompson's FDA Compliance Expert (https://fda.complianceexpert.com/), Pines said that maintaining the status quo was likely "because the positions on ad promo regulation taken by the new FDA leaders" — including Califf; FDA Center for Drug Evaluation and Research (CDER) Director Dr. Patrizia Cavazzoni, who became director in February 2019 after Woodcock became acting commissioner; and Catherine (Katie) Gray, who succeeded Thomas Abrams as permanent director of CDER's Office of Prescription Drug Promotion (OPDP) in June 2021 — "are fairly predictable based on their previous actions and views."

Among the policies likely to continue, according to Pines, is the enforcement approach taken by the FDA on alleged ad promo violations since the tenure of Dr. Scott Gottlieb as FDA commissioner, which has focused on alleged violations that affect public health and safety. Woodcock clarified at the time that the alleged ad promo violations cited in enforcement letters would have public health or safety implications and not be mere "technical violations."

"The violations that have been the subject of these letters have been regarded as somewhat egregious and worthy of regulatory attention," Pines observed, and the letters "have reiterated long-standing policies with regard to issues such as risk minimization, the need to have safety/risk depictions 'reasonably comparable' to the benefits statements, [and] the need to support claims with substantial evidence."

A major change in the status quo may come, however, with respect to direct-to-consumer (DTC) television and radio advertisements for prescription drugs, Pines noted. In the Fall 2021 Unified Agenda, the FDA projected that in September 2022 it would issue a final rule on the presentation in DTC ads of the major statement relating to the side effects and contraindications of a prescription drug.

A March 2010 proposed rule (75 Fed. Reg. 15376) was intended to ensure that the major statement is "presented in a clear, conspicuous, and neutral manner," as required by FDAAA Section 901(d)(3)(A) (21 U.S.C. §352(n)), according to the FDA. The agency also proposed standards for it to consider when determining whether the major statement meets the requirement. The most recent of three comment periods on the proposed rule closed in April 2012.

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