SPECIAL REPORT

FDA 2018 YEAR IN REVIEW

JANUARY 7, 2018

McDermott Will & Emery

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INTRODUCTION

The US Food and Drug Administration's (FDA's) 2018 regulatory agenda spurred significant activity throughout the year, including implementation of several initiatives and mandates required by the 21st Century Cures Act (Cures Act). FDA continues to take measures to reduce regulatory barriers to market entry for innovative products, and it is leveraging traditional administrative processes, such as the citizen petition process, to advance its policy goals, including increasing generic competition. FDA initiated targeted enforcement actions in areas of traditional focus, such as good manufacturing practice (GMP) compliance, but it also signaled renewed focus on tobacco advertising, unapproved stem cell procedures, and compounding. FDA also issued important guidance documents throughout 2018.

This *Special Report* reviews notable actions that shaped FDA-regulated industries and products last year and offers insight into the agency's 2019 priorities and expected actions.

DRUGS

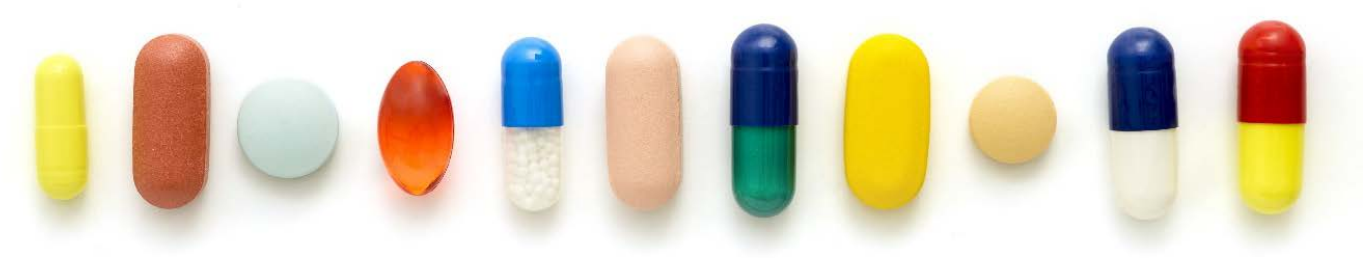
DEVELOPMENTS IN 2018

Citizen Petitions and Petitions for Stay of Action Subject to § 505(q)

On December 4, 2018, the Federal Trade Commission (FTC) commented on FDA's revised draft guidance, Citizen Petitions and Petitions for Stay of Action Subject to Section 505(q) of the Federal Food, Drug, and Cosmetic Act. In addition to reiterating FDA's authority under § 505(q) of the Federal Food, Drug, and Cosmetic Act (FDCA) to summarily deny certain citizen petitions, the revised draft guidance describes considerations FDA will use to determine whether a petition was submitted primarily to delay approval of a competing drug. These considerations include the following:

- The petition was submitted unreasonably long after the petitioner learned or knew about the relevant information
- The petitioner submitted multiple and/or serial petitions
- The petition was submitted close in time to expiration of a known patent or exclusivity
- The petition's scientific positions were unsupported by data or information
- The petition was the same or substantially similar to a prior petition to which FDA had already substantively responded
- The petitioner had not commented during other opportunities for input
- The petition requested a standard more onerous or rigorous than the standard applicable to the petitioner's product
- Other relevant considerations, such as the petitioner's history with the FDA

In a statement approved in a 5-0 vote, FTC indicated that it "shares the FDA's concerns about patient access to lower-cost generic drugs and biosimilars" and "has a longstanding interest in sham petitioning and other abuses of the government processes that



may inhibit competition." FTC noted its investigations regarding complaints of abuses of the citizen petition process as potential violations of federal antitrust law. FTC indicated that it "stand[s] ready to work closely with the FDA on citizen-petition abuse and other issues that may harm competition," suggesting that citizen petitions submitted by competitors are likely to face a high level of scrutiny from both FDA and FTC.

> FTC stated that it "shares the FDA's concerns about patient access to lower-cost generic drugs and biosimilars."

New Drug Development Modernization Plan

In July, FDA announced its new drug development modernization plan to provide the structural framework necessary to advance many goals of the Cures Act. As part of the plan, the Center for Drug Evaluation and Research (CDER) will add new review divisions organized more closely around disease types. A central goal of the plan is the implementation of multidisciplinary teams to enhance internal collaboration and external collaboration with scientists, expert physicians, patients and other stakeholders.

Patient-Focused Drug Development

Section 3002 of the Cures Act requires FDA to develop one or more guidance documents over a period of five years regarding the collection of patient experience data (*i.e.*, data collected by any person that is intended to provide information about patients' experiences with a disease or condition, including the impact on patient lives and patient preferences with respect to treatment). FDA launched a Patient Focused Drug Development (PFDD) initiative in response to this and commitments under the Prescription Drug User Fee Act V (PDUFA V), and issued the first draft guidance under the PFDD, Patient-Focused Drug Development: Collecting Comprehensive and Representative Input: Guidance for Industry, Food and Drug Administration Staff, and Other Stakeholders, in June.

Framework for Real-World Evidence Program for Drugs and Biologics

In December, FDA issued a Framework for FDA's Real-World Evidence Program under section 3022 of the Cures Act for assessing the potential use of real world evidence (RWE) in connection with the agency's drug and biologic review program. Click here for an in-depth discussion of the Framework. Additionally, in furtherance of its efforts to encourage multi-stakeholder collaboration that supports the generation of more and better RWE for medical devices and regulatory decision making, FDA continues to build out the National Evaluation System for health Technology (NEST). NEST will generate evidence across the total product lifecycle of medical devices by leveraging RWE from clinical registries, electronic health records, medical billing claims and other sources and apply advanced analytics to the data tailored to the data needs and innovation cycles of medical devices.

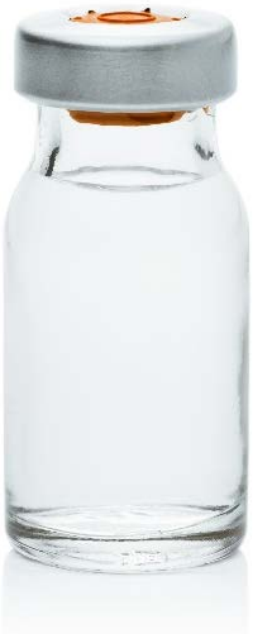
Biologics INTERACT Program

In June, FDA also announced its INitial Targeted Engagement for Regulatory Advice on CBER products (INTERACT) program to enable sponsors of biologics products to obtain preliminary informal

consultation with FDA at an early stage of development, prior to a pre-investigational new drug application (IND) meeting. Through an INTERACT meeting, sponsors can obtain initial, nonbinding advice from FDA regarding chemistry, manufacturing and controls, pharmacology/toxicology and/or clinical aspects of the development program. This may assist sponsors in conducting early product characterization and preclinical proof-of-concept studies, initiating discussion for new delivery devices, staying informed about overall early-phase clinical trial design elements, and identifying critical issues or deficiencies to address in the development of innovative products. Sponsors should submit (1) a summary of the product and disease being treated, (2) information about the product development to date and future development plans, if appropriate and (3) questions the sponsor wishes to have addressed. The Center for Biologics Evaluation and Research (CBER) will attempt to hold INTERACT meetings within 90 calendar days of receiving requests, depending on other resource constraints.

INDICATIONS AND USAGE Section of Labeling

FDA released an Indications and Usage Section of Labeling draft guidance in July, intended to help applicants draft proposed indications for use (including limitations for use, where appropriate) for prescription drug and biological products. The INDICATIONS AND USAGE section is intended to enable health care practitioners (HCPs) to readily identify appropriate therapies for patients by communicating the drug's approved indication(s). Therefore, the draft guidance is also intended to help ensure that the INDICATIONS AND USAGE section is consistent within and across drug and therapeutic classes, which is particularly relevant to indexing of



indications in electronic drug databases and searchability in electronic medical information systems, both of which facilitate clinical decision making and HCP awareness of available therapies.

LOOKING AHEAD TO 2019

Significant discussion around drug pricing will likely continue as the new Congress is seated in January 2019. On October 18, 2018, the US Department of Health and Human Services (HHS) published a proposed rule, Medicare and Medicaid Programs; Regulation To Require Drug Pricing Transparency, 83 Fed. Reg. 52,789, to require direct-to-consumer television advertisements of prescription drugs and biologics covered by Medicare or Medicaid to include the Wholesale Acquisition Cost or "list price" for a 30-day supply of any product that costs more than $35 a month. The list price must be written in a type size legible to television viewers. The proposed rule does not require that the list price be read aloud.

Proponents argue the proposed rule would prompt consumers to become more price sensitive, in turn slowing the rise of drug costs. Drugmakers that fail to comply would be penalized by being named on a list issued by HHS and through possible enforcement action.

The same day that HHS announced the proposed rule, the Pharmaceutical Research and Manufacturers of America (PhRMA) announced a new voluntary action that would direct consumers to company websites with pricing information. The announcement appears to be an effort to propose an alternative to more aggressive federal regulation. The initiative will begin by April 15, 2019, and it would provide consumers with pricing information that includes the list price, the expected out-of-pocket costs of the drug and available patient assistance programs.

DIGITAL HEALTH

DEVELOPMENTS IN 2018

In 2018, FDA focused on executing its 2017 Digital Health Innovation Action Plan, which laid the foundation for the digital health pre-certification pilot program and several cross-cutting guidance documents. The agency presented a "working model" for the pilot Digital Health Software Precertification (Pre-Cert) Program, which is intended to be a voluntary pathway to enable a more streamlined review for software as a medical device (SaMD). The model described proposed criteria to pre-certify companies, the pre-market review process for companies that successfully complete the pre-certification process and post-market surveillance obligations for SaMD under the program. The proposed Pre-Cert Program elements include:

- An "Excellence Appraisal" and determination of the pre-certification level
- Review of pathway determination
- Streamlined pre-market review process
- Monitoring real-world performance

The Excellence Appraisal is among the more forward-thinking aspects of the proposed pre-certification program. It involves a comprehensive assessment of the sponsor's compliance culture, operations and infrastructure with respect to five excellence principles: patient safety, product quality, clinical responsibility, cybersecurity responsibility and proactive culture. FDA proposes to assign one of two pre-certification levels based on how a company or sponsor satisfies the excellence principles and whether it has demonstrated a track record in delivering software products.

> The Excellence Appraisal involves a comprehensive assessment of the sponsor's compliance culture, operations and infrastructure.

FDA also plans to rely upon the SaMD risk classification criteria described in the International Medical Device Regulators Forum[1] (IMDRF) risk categorization guidance to determine the pre-

[1] The IMDRF is a voluntary group of medical device regulators from around the world that have come together to reach harmonization on medical device regulation. IMDRF develops internationally agreed upon documents related to a wide variety of topics affecting medical devices.

certification level and the appropriate review pathway. Review pathways could include streamlined versions of traditional market pathways such as 510(k) review or other approaches. FDA is also developing plans to collect and interpret real-world data about SaMD marketed under the pre-certification program to facilitate post-market surveillance requirements. In 2019, FDA plans to provide a progress update and further details regarding the proposed pre-certification program derived in part on its ongoing collaboration with current pilot program participants.

While the pre-certification pilot program featured heavily in FDA's 2018 digital health agenda, the agency also issued notable guidance documents on cross-cutting topics for digital health and traditional medical devices. The following is a list of notable guidance and activities in 2018:

- Content of Premarket Submissions for Management of Cybersecurity in Medical Devices draft guidance (Oct. 2018): provides recommendations to sponsors on ways to address cybersecurity in pre-market submissions for medical devices with cybersecurity risks
- Federal Register Notice "Prescription Drug-Use-Related Software" (Nov. 2018): announced the establishment of a docket to seek early input from the public on the agency's proposed framework for prescription drug-use-related software
- The FDA Memorandum of Agreement (MOA) with the US Department of Homeland Security: implements a framework for greater coordination and information sharing about potential or confirmed medical device cybersecurity vulnerabilities and threats

LOOKING AHEAD TO 2019

Data strategy and cybersecurity will continue to be a significant area of regulatory focus for FDA in 2019. Cybersecurity risk management principles and strategies are becoming a key component of quality management for SaMD and traditional medical devices in the wake of hacking incidents and related recalls. FDA will also focus on developing criteria and guidelines for developing and "tuning" algorithms and other tools that incorporate artificial intelligence (AI) or machine learning. FDA may seek input from thought leaders on criteria and processes to assess the safety and effectiveness of AI-driven SaMD prior to launch and to conduct ongoing or predictive risk assessments as the tools "learn" in a post-market environment.

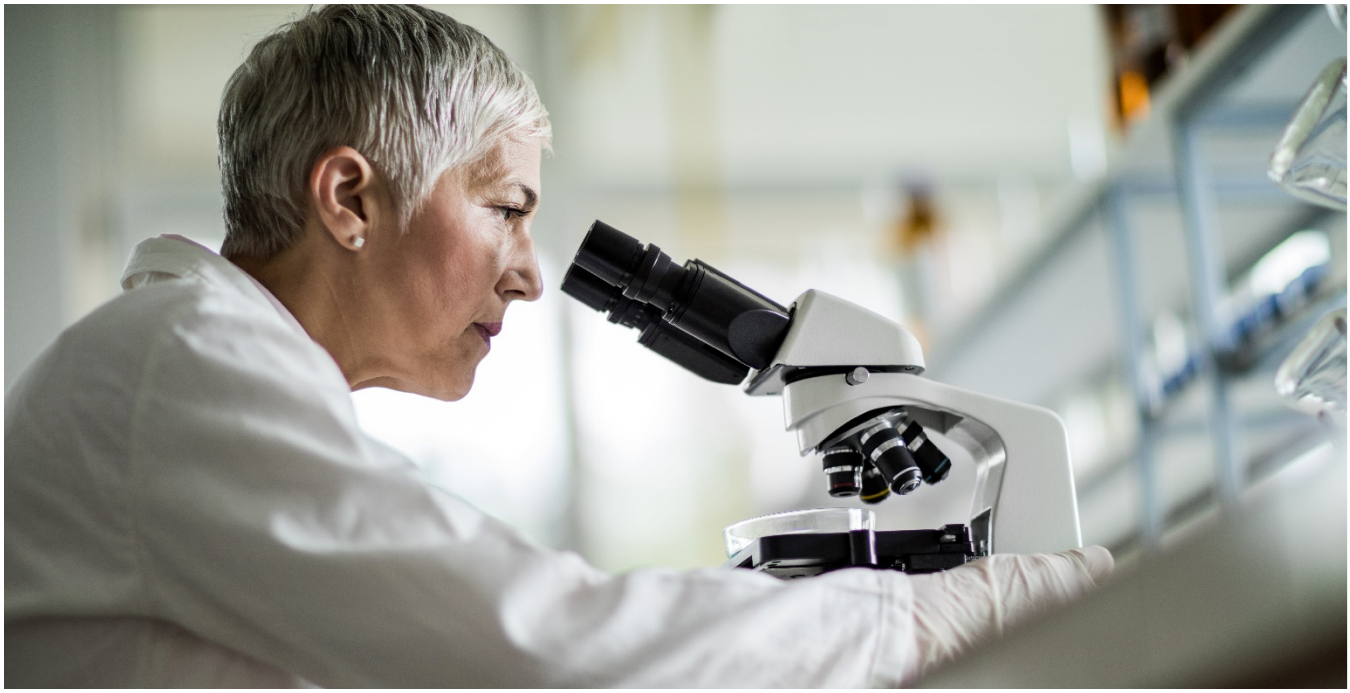
DRUG QUALITY SECURITY ACT IMPLEMENTATION

DEVELOPMENTS IN 2018

Compounding

In 2018, FDA issued six final and three draft or revised draft guidance documents on compounded drugs. The final guidance documents address:

- Compounded drug products that are essentially copies of commercially available drug products under FDCA sections 503A (compounding by licensed pharmacists or physicians for identified individual patients based on valid prescription orders) and 503B (compounding in an outsourcing facility) (collectively, copies)
- The facility definition under section 503B



- The compounding and repackaging of radiopharmaceuticals by state-licensed nuclear pharmacies, federal facilities and outsourcing facilities
- Adverse event reporting for outsourcing facilities

The draft and revised draft guidance documents cover insanitary conditions, evaluation of bulk drug substances under section 503B, and current good manufacturing practice (cGMP) for 503B outsourcing facilities. Below, we address three guidance documents with significant implications for 503A and 503B compounders, the 503A and 503B copies final guidance documents, and the revised draft guidance on insanitary conditions.

Sections 503A and 503B contain different statutory provisions regarding what constitutes a compounded drug product that is essentially a copy of a commercially available drug product. Under 503A, a compounder must not compound regularly or in inordinate amounts drug products that are essentially copies of a commercially available drug. A drug is not essentially a copy if there is a change, made for an identified individual patient that produces for that patient a significant difference, as determined by the prescribing practitioner, between the compounded drug and the commercially available drug. In the Compounded Drug Products That Are Essentially Copies of a Commercially Available Drug Product Under Section 503A of the Federal Food, Drug, and Cosmetic Act guidance (503A Copies Guidance), FDA explains its interpretations of statutory terms, such as "essentially a copy," and describes the ways in which a prescriber must document his or her determination that the compounded drug will produce a significant difference for the identified individual patient (*e.g.*, no dye, patient allergy). The significant difference must be produced by the change between the compounded drug and the commercially available drug. Compounding pharmacists and physicians will need to examine their documentation practices in light of this guidance.

Under 503B, a compounded drug must not be essentially a copy of one or more approved drugs. A compounded drug is essentially a copy if it is identical or nearly identical to a marketed unapproved over-the-counter (OTC) drug or an approved drug that is not on FDA's shortage list at the time of compounding, distributing or dispensing. A compounded drug is also essentially a copy if it is not identical or nearly identical, but has a bulk drug substance that is a component of a marketed unapproved OTC drug or an approved drug, unless the prescriber determines that there is a change in the compounded drug that produces a clinical difference for an individual patient. In the Compounded Drug Products That Are Essentially Copies of Approved Drug Products Under Section 503B of the Federal Food, Drug, and Cosmetic Act guidance (503B Copies Guidance), FDA stated that it will consider a compounded drug identical or nearly identical if the compounded drug and the FDA-approved drug have the same active ingredient(s), route of administration, dosage form, dosage strength and excipients. If the approved drug is on FDA's drug shortage list at the time of compounding, distributing or dispensing, then the compounded drug will not be essentially a copy and may be compounded, provided that section 503B's other requirements are satisfied.

As with the 503A Copies Guidance, the 503B Copies Guidance details what documentation of a prescriber's determination of clinical difference is acceptable if the compounded drug is not identical or nearly identical but contains the same bulk drug substance as a marketed unapproved OTC drug or an approved drug. Outsourcing facilities must obtain statements from prescribers that specify the change between the compounded drug and the approved drug, and such statements must indicate that the compounded drug will be administered or dispensed only to patients for which the drug will produce a clinical difference. Outsourcing facilities and prescribers must ensure that their documentation for individual patients complies with FDA's suggested documentation practices.

Neither 503A nor 503B compounding facilities are exempt from FDCA requirements with respect to drugs that are prepared, packed or held under insanitary conditions whereby the drugs may have been contaminated or rendered injurious to health. In September, FDA released its revised draft Insanitary Conditions at Compounding Facility guidance, which sets forth detailed examples of insanitary conditions (*e.g.*, visible microbial contamination, failing to disinfect or change gloves frequently to prevent contamination). State board of pharmacy inspections frequently document conditions such as those identified in the insanitary conditions guidance, and compounders should be aware of that the presence of insanitary conditions poses federal risks as well if compounders do not implement appropriate corrective actions. The guidance reiterates that FDA may take enforcement actions if compounders prepare, pack or hold drugs under insanitary conditions.

LOOKING AHEAD TO 2019

In 2019, the agency may finalize some or all of the above draft or revised draft guidances, as well as the 2016 draft guidance on hospital and health system compounding. We also anticipate that FDA will propose rules on the bulk drug substances list under section 503A and modifications to the withdrawn or removed list under sections 503A and 503B. Additionally, FDA is developing a revised draft memorandum of understanding (MOU) in consultation with the National Association of Boards of Pharmacy on the distribution of inordinate amounts of compounded drug products interstate that, once finalized, may be signed by the

states. Under the MOU, a state must provide for appropriate investigations of complaints related to compounded drug products distributed outside the state. The comment period on the MOU recently ended, and FDA will publish the final MOU and offer it to states to consider signing it before FDA begins to enforce the statutory five percent limit on distribution out-of-state for compounders in states that have not signed the MOU.

THE DRUG SUPPLY CHAIN SECURITY ACT

DEVELOPMENTS IN 2018

In 2018, FDA issued two final and five draft guidance documents to further implement and clarify certain aspects of Title II of the Drug Quality Security Act—the Drug Supply Chain Security Act (DSCSA). DSCSA was enacted by Congress on November 27, 2013, and it provides steps to build a system to identify and trace certain prescription drugs as they are distributed in the United States and to improve detection and removal of potentially harmful drugs from the drug supply chain. The effective compliance date applicable to manufacturers and repackagers for product identifier requirements was November 27, 2018. The effective compliance dates applicable to wholesalers and dispensers for authentication and verification requirements are November 27, 2019, and November 27, 2020, respectively. The deadline for complete unit level traceability is November 27, 2023.

Section 582 of the FDCA, added by section 202 of DSCSA, requires that each package and homogenous case of product in the pharmaceutical distribution supply chain bear a product identifier that is encoded with the product's standardized numerical identifier, lot number and expiration date.

FDA finalized two guidance documents related to the DSCSA. In the first guidance, Product Identifier Requirements Under the Drug Supply Chain Security Act—Compliance Policy Guidance for Industry, regarding the implementation of the product identifier requirements, FDA stated its intention not to take action against manufacturers that did not affix or imprint a product identifier to each package and homogenous case of product before November 27, 2018 (representing a one-year delay in enforcement of the requirement). In the second guidance, Grandfathering Policy for Packages and Homogenous Cases of Product Without a Product Identifier, FDA specified whether and under what circumstances such packages and homogenous cases of product that are not labeled with a product identifier and are in the pharmaceutical distribution supply chain at the time of the effective date shall be subject to the grandfathering exemption from certain requirements. The effective date, as mentioned, was extended to November 27, 2018, for manufacturers. The original effective date of November 27, 2018, remained the same for repackagers.

To further clarify the product identifier requirements under section 582 of the FDCA, FDA issued the Product Identifiers Under the Drug Supply Chain Security Act: Questions and Answers draft guidance.

FDA also issued the Waivers, Exceptions, and Exemptions from the Requirements of Section 582 of the Federal Food, Drug, and Cosmetic Act Guidance for Industry, which outlines the process for submitting requests to FDA for waivers, exceptions or exemptions to the requirements related to the traceability and security of prescription drugs. Section 582 also requires that manufacturers, wholesale distributors, dispensers and repackagers have verification systems in place to comply with tracing and verification requirements. The Verification Systems Under the Drug Supply Chain Security Act for Certain Prescription Drugs draft

guidance provides the industry with the agency's interpretation of the requirements regarding verification systems, recommendations for a robust verification system, recommendations for submitting cleared product notifications, and a discussion of the statutory requirements for verification. The Definitions of Suspect Product and Illegitimate Product for Verification Obligations Under the Drug Supply Chain Security Act draft guidance further clarifies relevant terms for verification requirements under section 582. A related draft guidance, Standardization of Data and Documentation Practices for Product Tracing, provides insight to industry on how to standardize the data contained in the product tracing information and how to understand the data elements that should be included in the product tracing information.

LOOKING AHEAD TO 2019

The effective compliance date applicable to manufacturers and repackagers for product identifier requirements was November 28, 2018. In 2019, industry can expect FDA to take action against noncompliant entities. The effective compliance date for wholesalers will be November 27, 2019, so wholesalers should be certain to make all necessary changes prior to that date.

MEDICAL DEVICES

DEVELOPMENTS IN 2018

FDA Focus

According to its Medical Device Enforcement and Quality Report, FDA has expanded its oversight through increased inspections both in the United States and abroad, bolstered by the Medical Device Single Audit Program, which involves a single regulatory audit of a device manufacturer's quality management system to satisfy the requirements of multiple jurisdictions, including the United States, Australia, Brazil, Canada and Japan. As codified in section 510(h) of the FDCA (21 USC § 360(h)), the agency reiterated that it continues to take a risk-based enforcement approach to address specific device areas of concern, citing its enforcement and related regulatory action around infusion pumps, automatic external defibrillators and radiation therapy devices in the past several years. FDA also noted that it has taken a more "interactive" approach with violative firms, using tools such as untitled letters and regulatory and other meetings in lieu of warning letters. The agency stated that it recognizes this can be more effective in achieving more timely and effective corrective action. Finally, FDA also noted that its focus on 21 CFR Part 806 Medical Devices Reports of Corrections deficiencies during inspections has resulted in an increased number of reported voluntary recalls and adverse event reporting.

510(k) Exemptions

FDA has continued to use its streamlined authority under the Cures Act to exempt more than 70 class I medical device types and more than 1,000 class II medical device types from the requirement to submit a 510(k). These devices may still be subject to other regulatory controls, such as cGMP, being adequately packaged and properly labeled and having current establishment registration and device listings with FDA.

Multiple Function Device Products

FDA issued its Multiple Function Device Products: Policy and Considerations guidance as part of the agency's continued efforts to develop a practical and risk-based approach to regulating medical devices and

digital health and to interpret the medical software provisions in section 3060(a) of the Cures Act. Click here for a detailed summary.

Unique Device Identification

In recognition of the complexity of implementing the unique identification system and the fact that medical devices often remain in inventory for long periods of time, FDA deferred enforcement of direct marketing deadlines in its Unique Device Identification: Policy Regarding Compliance Dates for Class I and Unclassified Devices and Certain Devices Requiring Direct Marking guidance (Nov. 2018), which was effective immediately. The new compliance dates and guidelines for the standard date formatting, unique device identifier (UDI) and Global UDI Database (GUDID) submission requirements under 21 CFR §§ 801.18, 801.20, 801.50 and 830.300 are as follows:

DEVICE CLASS	COMPLIANCE DATE
Finished Class I and Unclassified Medical Devices (other than implantable, life-sustaining or life-supporting (I/LS/LS) devices) labeled on or after September 24, 2018	September 24, 2020
Finished Class I and Unclassified Medical Devices (other than I/LS/LS devices) labeled before September 24, 2018	September 24, 2021 (unchanged)
Class I and Unclassified Medical Devices (except LS/LS devices)	September 24, 2022
Class I and Unclassified Devices manufactured or labeled prior to September 24, 2022, that remain in inventory	FDA does not plan to enforce these requirements, provided that the UDI can be derived from other information directly marked on the device, such as catalog number, lot number or serial number. This information should be documented in GUDID accordingly.
Class II Non-Sterile Devices labeled prior to September 24, 2018, that remain in inventory	FDA does not plan to enforce these requirements, provided that the UDI can be derived from other information directly marked on the device, such as catalog number, lot number or serial number. This information should be documented in GUDID accordingly.
Class III LS/LS Devices labeled prior to September 24, 2016, that remain in inventory	FDA does not plan to enforce these requirements, provided that the UDI can be derived from other information directly marked on the device, such as catalog number, lot number or serial number. This information should be documented in GUDID accordingly.

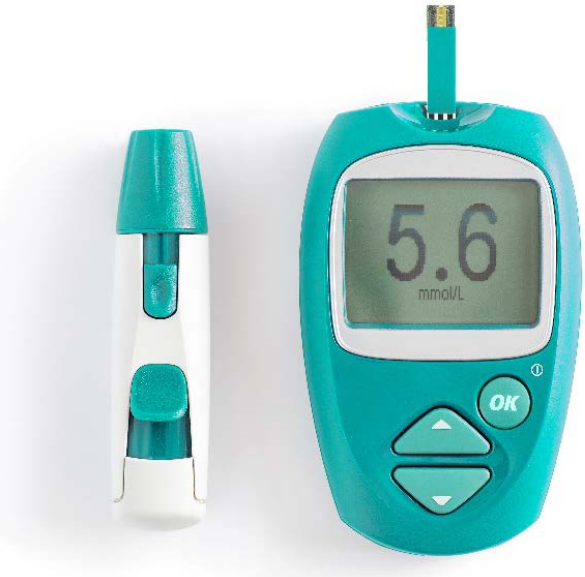
Special 510(k) Program

On September 28, 2018, FDA issued The Special 510(k) Program draft guidance, the first guidance the agency has issued on the Special 510(k) Program in 20 years. If finalized, the draft guidance will supersede The New 510(k) Paradigm – Alternate Approaches to Demonstrating Substantial Equivalence in Premarket Notifications guidance, issued on March 20, 1998. The original 1998 guidance introduced the Special 510(k): Device Modification option, which allows a manufacturer to use summary information that results from the design control process as the basis for clearing a device modification when a new 510(k) is needed, provided the modification does not affect the intended use of the device or alter the fundamental scientific technology of the device.

As an incentive to use the Special 510(k) process, FDA stated that it intends to process Special 510(k)s within 30 days of receipt (rather than a traditional 90-day goal review timeframe). In the new draft guidance, FDA proposes to expand on the types of changes eligible for the Special 510(k) Program. Specifically, if finalized as proposed, it includes certain changes to the indications for use (*i.e.*, labeling) and clarifications on the types of technological (*i.e.*, design) changes eligible to be reviewed as a Special 510(k). SaMD developers may be able to use the Special 510(k) pathway, provided that the original 510(k) appropriately identified the verification and validation approaches used. In the draft guidance, FDA reiterates that only the original manufacturer may avail itself of the Special 510(k) Program, because only a manufacturer that modifies its own legally marketed device is able to conduct the risk analysis and necessary verification and validation activities to demonstrate that the design outputs of the modified device meet the design input requirements in a streamlined 510(k) submission. The draft guidance also proposes, however, that a design or labeling change to an existing device (including changes to indications for use) may be appropriate for a special 510(k) if:

- Performance data are unnecessary, or if performance testing is required to evaluate a change, a well-established method must be used to evaluate the change
- Data submitted with a Special 510(k) must be reviewable in a summary or risk analysis format

Section 523 of the FDCA authorizes FDA to accredit third parties to review pre-market notification (510(k)) submissions and recommend classification of certain devices, specifically class I devices and class II devices, except those intended to be permanently implantable or life sustaining or life supporting, or combination drug/device products. As compared to submissions sent directly to FDA, the program provides expedited FDA review, as FDA will issue a substantial equivalence determination within 30 days' receipt of a recommendation from a Third Party (3P) Review Organization rather than in 90 days. On September 14, 2018, FDA issued a revised 510(k) Third Party Review Program draft guidance, in which FDA seeks to harmonize terms used by the IMDRF Medical Device Single Audit Program. The draft guidance primarily discusses how a 3P Review



Organization should apply for recognition and re-recognition, and the 3P Review Organization's 510(k) review process itself. The latter remains largely unchanged from the previous guidance, but FDA now offers substantially more guidance on recognition or re-recognition (previously accreditation or re-accreditation) requirements. Notably, FDA advises 3P Review Organizations to submit applications for recognition within six months after the finalization of the draft guidance.

Abbreviated 510(k) Program

When there is a recognized standard specific to a type of device, an abbreviated 510(k) may be an appropriate pathway to gain regulatory approval. The April Expansion of Abbreviated 510(k) Program – SE Through Performance Criteria draft guidance describes an optional pathway for certain types of devices, where a submitter would demonstrate that a new device meets FDA-identified performance criteria to demonstrate that the device is as safe and effective as a legally marketed device. Specifically, a submitter could demonstrate conformance to objective performance criteria established in FDA guidance, FDA-recognized consensus standards or special controls in lieu of providing data from direct comparison testing between the submitter's device and the legally marketed device. The use of performance criteria is only appropriate when FDA has determined that (1) the new device has indications for use and technological characteristics that do not raise different questions of safety and effectiveness than the identified predicate, (2) the performance criteria align with the performance of one or more legally marketed devices of the same type as the new device and (3) the new device meets the performance criteria. FDA plans to maintain a list of device types appropriate for the Expanded Abbreviated 510(k) program, which would include guidance documents that identify the performance criteria for each device type.

Q-Submission Program

In June, FDA issued its Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program draft guidance, which replaces the 2017 Requests for Feedback on Medical Device Submission: The Pre-Submission Program and Meetings with Food and Drug Administration Staff guidance. The new draft guidance captures changes under the Medical Device User Fee Amendments of 2017 (MDUFA IV). FDA will communicate with the applicant regarding whether a Q-Submission (Q-Sub) application—which includes Pre-Submission Requests, Submission Issue Requests, Study Risk Determination Requests, Informational Meeting Requests, Premarket Approval (PMA) Day 100 Meetings, Agreement Meeting and Determination Meeting Requests, Designation Requests for a Breakthrough Device, Qualification of Medical Device Development Tools requests, Accessory Classification Requests, requests for recognition of publicly accessible genetic variant database requests, combination product agreement meeting requests and requests for waivers under 21 CFR § 812.28. The guidance also provides several general clarifications about the Q-Sub program.

LOOKING AHEAD TO 2019

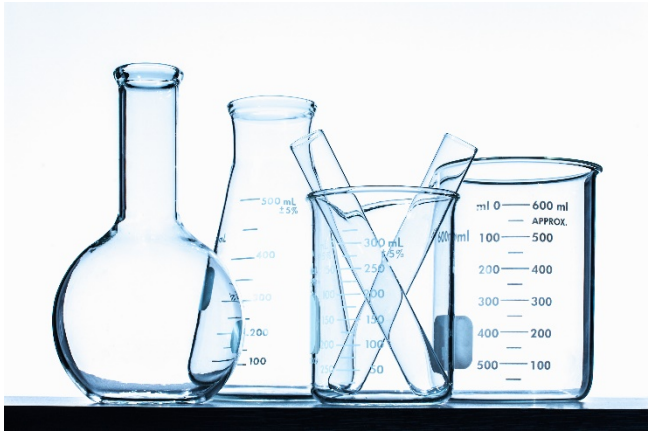
FDA stated that it will continue to focus on collaboration with industry and other stakeholders to drive compliance and promote device quality. CDER launched a voluntary quality maturity appraisal pilot, which uses third-party teams certified by the Capability Maturity Model Integration Institute (CMMI) to conduct quality system maturity appraisals to drive continuous improvement and organizational excellence among participating device manufacturers. The agency will evaluate whether to continue the pilot

through a formal appraisal program to complement its traditional oversight activities.

LABORATORY-DEVELOPED TESTS AND PRECISION MEDICINE

DEVELOPMENTS IN 2018

In 2018, FDA continued to express its interest in overhauling the regulatory framework applicable to in vitro diagnostic tests, including the laboratory-developed tests (LDTs) for which the agency currently exercises enforcement discretion. Notably, 2018 saw the FDA release long-awaited Technical Assistance on the House Energy and Commerce Committee's draft Diagnostic Accuracy and Innovation Act. The Technical Assistance reflects several notable changes in the agency's position—most notably with respect to the agency's willingness to "grandfather" many currently marketed LDTs into a new diagnostic-specific regulatory scheme (i.e., not to require that such products comply with many of FDA's regulatory requirements, such as pre-market review). Moreover, FDA indicated its support for the review and approval of prospective protocols, under which test developers would identify types of changes and procedures for test validation following such changes, and if the agency approved such protocols, developers could make such modifications without a supplemental pre-market filing.



LOOKING AHEAD TO 2019

In December 2018, the US House of Representatives Energy and Commerce Committee released an updated draft bill related to in vitro clinical tests (IVCT)—now titled the Verifying Accurate Leading-edge IVCT Development (VALID) Act of 2018—that is largely consistent with the FDA Technical Assistance. The Energy and Commerce Committee is accepting comments on the draft VALID Act from interested stakeholders until mid-February 2019, and is expected to hold hearings on diagnostic regulatory reform early in 2019. Stakeholders should stay apprised of the status of this bill and other legislative developments, which may have a substantial impact on FDA's oversight of diagnostics.

FOOD

DEVELOPMENTS IN 2018

The Food Safety Modernization Act (FSMA) of 2011 amended the FDCA to require persons who import food to the United States to perform risk-based foreign supplier verification activities. The activities are for the purpose of verifying that:

- Food is produced in compliance with hazard analysis and risk-based preventive control requirements, or in compliance with standards for the safe production and harvesting of certain fruits

and vegetables that are raw agricultural commodities.

- Food is not adulterated.
- Food is not misbranded.

The FSMA amendments also directed FDA to issue regulations on the content of foreign supplier verification programs (FSVP). These regulations were finalized in November 2015 (see 21 CFR §§ 1.500 and 1.514). In January 2018, FDA published a number of guidance documents related to the FSVP, including:

- Policy Regarding Certain Entities Subject to the Current Good Manufacturing Practice and Preventive Controls, Produce Safety, and/or Foreign Supplier Verification Programs: Guidance for Industry: states FDA's intent to exercise enforcement discretion with respect to the preventive controls requirements (and, in some cases, the cGMP requirements) of 21 CFR Parts 117 and 507 for certain facilities until completion of future rulemaking related to farm activities
- Draft Guidance for Industry: Foreign Supplier Verification Programs for Importers of Food for Humans and Animals: covers a range of topics, including the requirements of an FSVP and qualifications of individuals who develop an FSVP, hazard analyses and evaluation for foreign supplier approval, foreign supplier verification activities and hazard controls
- Draft Guidance for Industry: Considerations for Determining Whether a Measure Provides the Same Level of Public Health Protection as the Corresponding Requirement in 21 CFR part 112 or the Preventive Controls Requirements in part 117 or 507: includes considerations for determining whether a measure or procedure used

in lieu of an FDA requirement in 21 CFR Parts 112, 117 or 507 provides the same level of public health protection as the corresponding FDA requirement

- Guidance for Industry: Foreign Supplier Verification Programs for Importers of Food for Humans and Animals: What You Need to Know About the FDA Regulation; Small Entity Compliance Guide: contains modified procedures for a "very small importer" as well as importers of food from certain small foreign suppliers
- Hazard Analysis and Risk-Based Preventive Controls for Human Food: Draft Guidance for Industry, Chapter 15: Supply-Chain Program for Human Food: contains supply-chain program requirements, including the role of a corporate parent in establishing and implementing a supply-chain program

TOBACCO

DEVELOPMENTS IN 2018

The deadline for implementing warning labels on cigars and pipe tobacco under 21 CFR §§ 1143.3 and 1143.5 originally was August 10, 2018, but it has been delayed until 60 days after the US Court of Appeals for the DC Circuit decides the *Cigar Association of America, et al. v. U.S. Food and Drug Admin., et al.*, No. 1:16-cv-01460 (D.D.C. July 5, 2018). Cigar and pipe tobacco firms may choose to comply voluntarily with warning label requirements in the interim.

While statements by Commissioner Scott Gottlieb in 2017 suggested that FDA would take a fresh approach to nicotine regulation and the potential impact of delivery mechanism on addiction—*i.e.*, evaluation of products on a spectrum of risk—2018 represented a significant shift in agency policy regarding tobacco products.

FDA is expected to pursue the removal of ENDS products that are marketed to children or are appealing to youth.

In April, FDA issued more than 40 warning letters for violations related to youth sales of e-cigarettes. FDA also took steps to foreclose online sales of electronic nicotine delivery systems (ENDS) products to minors and examine youth appeal of ENDS products. In May, FDA and FTC jointly issued 13 warning letters to manufacturers, distributors and retailers for selling e-liquids "with labeling and/or advertising that cause them to resemble kid-friendly food products, such as juice boxes, candy, or cookies, some of them with cartoon-like imagery." After a call for voluntary manufacturer action in September, and the release of the 2018 National Youth Tobacco Survey, which demonstrated a dramatic increase in youth use of ENDS products, Commissioner Gottlieb announced that FDA would be seeking to take the following actions and to provide more guidance around:

- Limiting in-person sales of flavored ENDS products (other than tobacco, mint, menthol and non-flavored products) to age-restricted locations
- Limiting internet sales of flavored ENDS products (other than tobacco, mint, menthol and non-flavored products) to online retailers with heightened age verifications
- Banning marketing of ENDS products to children
- Banning menthol in combustible tobacco products, including cigarettes and cigars
- Banning flavored cigars

LOOKING AHEAD TO 2019

FDA is expected to revise its compliance policy for ENDS products that are flavored, including by providing additional guidance on "age-restricted locations" and "heightened age verifications." FDA is also expected to pursue the removal of ENDS products that are marketed to children or are appealing to youth, such as those using popular children's cartoon or animated characters, or names of products favored by youth, such as brands of candy or soda.

Finally, FDA is expected to issue a Notice of Proposed Rulemaking that would seek to ban menthol in combustible tobacco products, including cigarettes and cigars, and to propose a product standard that would ban flavors in all cigars.

CANNABIS

DEVELOPMENTS IN 2018

This year, FDA took two significant actions related to the cannabis plant: (1) the agency approved the first drug with an active ingredient (cannabidiol or CBD) derived from the cannabis plant; and (2) the Commissioner issued a lengthy public statement on FDA's stance with respect to hemp-derived products, including CBD, after President Trump signed the Agricultural Improvement Act of 2018, Pub. Law 115-334 (2018 Farm Bill) into law. The law signifies continuing momentum for the cannabis industry in terms of what it is lawful to grow and market in the US, and the law will impact the marketability of hemp-derived products. As the 2018 Farm Bill did not amend the FDCA, the cannabis industry still faces significant hurdles with respect to future plans to add hemp-derived substances to food, beverages, and dietary supplements. The Commissioner's announcement makes clear that FDA will exercise its existing authorities to take enforcement actions against hemp-derived CBD or THC products. Though the Commissioner's statement has tempered the cannabis industry's enthusiasm for such products, his contemporaneous announcement that three hemp ingredients may be lawfully marketed under the agency's Generally Recognized as Safe (GRAS) notice process will spark innovation in the form of new food and beverage products that use such ingredients.

First Drug Approved

In June, FDA approved the CBD oral solution for patients two years of age and older who have seizures associated with two forms of severe epilepsy. According to the US Drug Enforcement Administration (DEA) and FDA, the CBD in the approved drug is extracted from the cannabis plant and is a purified drug substance. The FDA-approved drug has no more than 0.1 percent residual tetrahydrocannabinol (THC), marijuana's psychoactive component. In September, DEA announced an order scheduling the drug under the least restrictive schedule of the Controlled Substances Act (CSA), schedule V, and noted that all other CBD products remain under the most restrictive schedule, schedule I. Although FDA did not post any warning letters for illegally marketed CBD-related products in 2018, the Commissioner noted in June that FDA has taken actions against the illegal marketing of such products. In his statement issued after the Farm Bill became law, the Commissioner cited past warning letters and reiterated that FDA will take enforcement actions to protect the public from illegally marketed cannabis-derived products.

The cannabis industry still faces significant hurdles with respect to future plans to add hemp-derived substances to food, beverages, and dietary supplements.

Ramifications of the 2018 Farm Bill

On December 20, President Trump signed the 2018 Farm Bill into law. The law permits a state or Indian tribe that wants primary regulatory authority over hemp production within the state or territory to submit plans to the Secretary of the US Department of Agriculture (USDA) for monitoring and regulating that production. Importantly, the law creates a new definition of "hemp" that differentiates hemp from the schedule I drug marijuana, but does not amend the FDCA. As a result, FDA will continue to regulate hemp-derived products under FDA's existing authority to regulate food, drugs, and dietary supplements, and the cannabis industry will encounter federal restrictions on such products, even if derived from hemp. The law makes two changes to the CSA:

- Creates a carve out for hemp from the CSA's definition of marijuana, such that marijuana would be limited to the cannabis plant and its derivatives with a THC of 0.3 percent or more on a dry weight basis
- Excludes THC in hemp from schedule I of the CSA

> The law would create a new definition of "hemp" that differentiates hemp from the schedule I drug, marijuana.

As a result, the law appears to exclude all cannabinoids (which include CBD) with less than 0.3 percent THC on a dry weight basis from the CSA's definition of marijuana. Though hemp is now a legal substance under federal law, FDA will still regulate the addition of cannabis and derivatives of cannabis (*e.g.*, CBD, THC) to food and drinks, deem foods with such derivatives to be adulterated and require agency approval of new drug applications. Finally, the 2018 Farm Bill includes a rule of construction that states that nothing in the applicable title of the law or an amendment made by the applicable title prohibits the interstate commerce of hemp or hemp products. However, the law did not change the FDCA's statutory provision on interstate commerce. That provision presumes the existence of the connection with interstate commerce that is required for FDA to exercise its jurisdiction to enforce the FDCA with respect to products including food, drugs, and cosmetics.

The Commissioner issued an announcement concurrent with President Trump's signing of the 2018 Farm Bill. The statement:

- Explained that FDA will continue to treat cannabis-derived compounds like any other drug, food or dietary supplement that the agency regulates, regardless of the source of the cannabis-derived substance, *e.g.*, plants classified as hemp
- Reminded industry that even if the cannabis-derived substance is hemp-derived, it is unlawful to introduce foods that contain added CBD or THC into interstate commerce
- Noted that it is a violation of the FDCA to market CBD and THC products as dietary supplements
- Asserted that FDA will take enforcement action against companies illegally selling any cannabis and cannabis-derived products that put consumers at risk and that are marketed in violation of the FDCA

- Indicated that FDA will update its guidance on cannabis products to address questions under the 2018 Farm Bill

The Commissioner also announced that FDA evaluated three hemp ingredients and determined they could be lawfully marketed: hulled hemp seeds, hemp seed protein, and hemp seed oil. We expect to see a substantial increase in the number of marketed foods and beverages that contain such ingredients.

LOOKING AHEAD TO 2019

Though FDA reaffirmed its jurisdiction with respect to cannabis derivatives in food, the agency did not address the addition of CBD or other cannabis derivatives to cosmetics in the Commissioner's announcement and has not addressed cosmetics in its current cannabis guidance. We expect FDA to weigh in on the addition of hemp-derived substances to cosmetics products next year. FDA also announced it will hold a public meeting on appropriate hemp products in the near future. Additionally, FDA, USDA and the US Department of Justice (DOJ) likely will issue guidance interpreting the 2018 Farm Bill's provisions on hemp and interstate commerce in hemp and hemp products. After the passage of the 2014 Farm Bill, the three government entities issued a Statement of Principles on Industrial Hemp, which reaffirmed that the 2014 law did not change any FDA authorities in the FDCA. The 2014 Farm Bill legalized the growing and cultivating of industrial hemp for research purposes in states where such conduct was legal despite federal restrictions on hemp production, but like the 2018 Farm Bill, it did not amend the FDCA. We anticipate that FDA will be asked to review an increased number of new drug applications and other regulatory submissions for products that contain cannabinoids (including CBD).

ADVERTISING AND PROMOTION

DEVELOPMENTS IN 2018

In June, FDA finalized its guidance on Medical Product Communications That Are Consistent with the FDA-Required Labeling. The guidance explains how manufacturers, packers, distributors and their representatives may communicate information in promotional materials and data about approved or cleared uses of a product that are not included in the FDA-required labeling. The guidance is narrowly tailored and defines "FDA-required labeling" to include labeling reviewed and approved by FDA as part of the medical product marketing application review process. The guidance does not address off-label communications about unapproved uses.

The guidance sets forth a three-factor test that FDA will use to determine if a drug, biological product or device firm is communicating information about its product consistent with FDA-required labeling. The factors are summarized as follows:

- Does the information provided differ from or conflict with the information about the conditions of use in the FDA-required labeling?
- Will the information in the communication increase the potential for harm to health, when compared to the information in the FDA-required labeling?
- Do the directions for use in the FDA-required labeling enable the product to be safely and effectively used under the conditions discussed in the communication?

The guidance emphasizes that communicating information in a manner consistent with FDA-required labeling is not enough to avoid an enforcement action; firms must also comply with FDA's other labeling and advertising provisions.

In June, FDA also finalized its Drug and Device Manufacturer Communications With Payors, Formulary Committees, and Similar Entities — Questions and Answers guidance, providing a clearer framework around the dissemination of information regarding prospective patient utilization and dissemination of the results of studies. Click here for an in-depth discussion.

In its draft guidance Presenting Quantitative Efficacy and Risk Information in Direct-to-Consumer Promotional Labeling and Advertisements, FDA states that quantitative efficacy or risk information presented in direct-to-consumer promotional materials may lead to greater consumer comprehension than qualitative information. FDA offers multiple recommendations with regard to presenting quantitative efficacy or risk information in a consumer-friendly manner:

- **Use Absolute Probability Presentations:** Firms should convey information in terms of absolute frequencies (*e.g.*, 57 out of 100) or percentages (57 percent). If relative frequency information is provided (*e.g.*, 50 percent reduction of risk), absolute probability measures should also be provided (*e.g.*, 50 percent reduction of risk—1 percent had a stroke compared to 2 percent in the control group).
- **Choose a Consistent Format:** Presentations should be consistent throughout a piece, frequencies should use the same denominator (preferably a multiple of 10), and when possible, whole numbers should be used.
- **Use Appropriate Visual Aids:** Visual aids help consumer comprehension and should be carefully and clearly labelled and defined, should include information proportionate to the quantity described (bar graphs representing appropriate proportions), and should include both the numerator and denominator of ratios or frequencies.
- **Include Comparator Numbers:** Both the treatment and the control groups should be represented to improve consumer perceptions about a drug's efficacy and risk.

In 2018, CDER's Office of Prescription Drug Promotion (OPDP) issued a recent historical low number of warning letters (two) and untitled letters (five) to pharmaceutical manufacturers. Both warning letters were related to failure to present or present adequate risk information—violations that FDA cited in untitled letters as well. Notably, OPDP issued an untitled letter alleging that a manufacturer made false or misleading claims or representations about the efficacy of its product, the first of its kind since the ultimately withdrawn Pacira Pharmaceuticals warning letter.

Violations cited in the remaining untitled letters included off-label promotion (promotion of unapproved uses for an approved product), lack of adequate directions for use in labeling, and pre-approval promotion of investigational drugs. One of the warning letters and one of the untitled letters resulted from complaints submitted to OPDP's Bad Ad Program, which is designed to educate HCPs about the role they can play in helping FDA ensure that prescription drug advertising and promotion is truthful and not misleading. The Center for Device Evaluation

and Research (CDER) Office of Compliance did not issue any letters related to advertising or promotion violations in 2018.

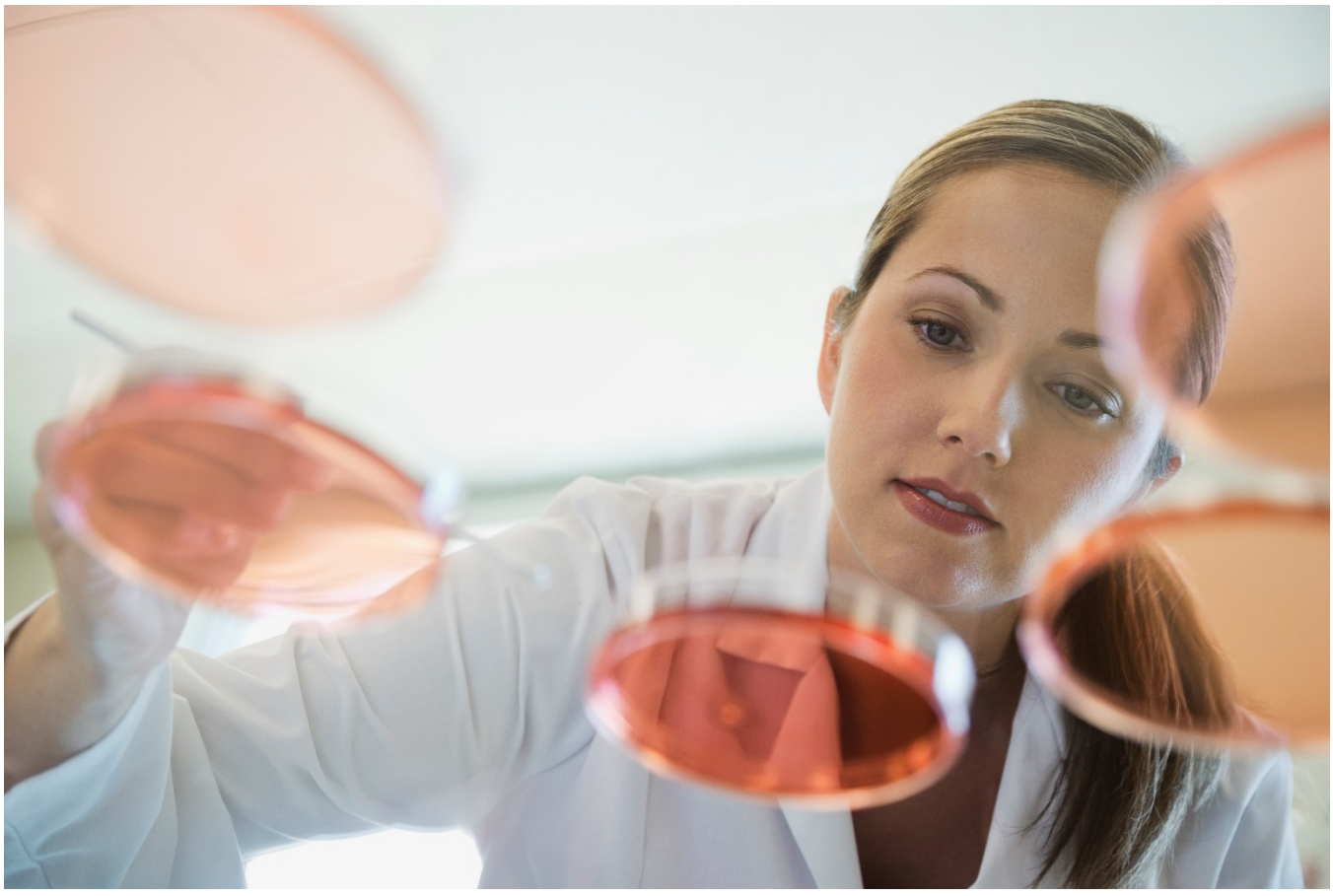
CLINICAL INVESTIGATIONS

DEVELOPMENTS IN 2018

On October 12, FDA published guidance offering interim direction for researchers, sponsors and Institutional Review Boards (IRBs) engaging in both FDA-regulated clinical trials and federally sponsored human subjects research regulated by the overarching rule known as the Common Rule. The Cures Act directed the Secretary of HHS to work to harmonize FDA's clinical research regulations with the Common Rule . This effort is of increased importance as the numerous federal agencies and departments that have adopted the Common Rule adopted sweeping revisions to the law, which are fully effective on January 21, 2019.

While the guidance document, Impact of Certain Provisions of the Revised Common Rule on FDA-Regulated Clinical Investigations, only provides limited guidance while more extensive FDA rulemaking is forthcoming, it provides FDA's current position and thinking on two important topics:

- **Informed Consent.** The updated Common Rule includes several new requirements for informed consent, including changes to the content,



organization and presentation of information to human subjects. FDA clarified that such additional elements could be built into the consent process for FDA-regulated clinical trials and that two consent forms would not be required, as the two rules are not inconsistent.

- **IRB Review.** The updated Common Rule presumes that studies that meet a list of eligible categories will not involve more than minimal risk, permitting them to qualify for expedited review by an IRB, while FDA's rules require an IRB to affirmatively make a risk determination. Similarly, the updated Common Rule eliminated the requirement for continuing IRB review for certain studies, whereas FDA's rules require continuing review. FDA acknowledged these changes but confirmed that FDA-regulated clinical trials must still follow the FDA's rules, which would not permit studies subject to both laws to benefit from the new pathways for decreased IRB oversight built into the new Common Rule.

At a high level, FDA also confirmed that in the event of a conflict between its regulations and the Common Rule, researchers are to follow the regulations that offer the greatest protection to human subjects. Given FDA's signal that the agency is "actively working" to harmonize its regulations with the Common Rule, additional formal rulemaking could be on the horizon in 2019, particularly on the topics addressed in the guidance.

MANUFACTURING AND GOOD MANUFACTURING PRACTICE

DEVELOPMENTS IN 2018

European Mutual Recognition Agreement

In 2017 FDA and the European Union entered into a Mutual Recognition Agreement to use one another's GMP inspection results for pharmaceutical manufacturing facilities. The initiative became effective November 2, 2017. FDA is currently in the process of evaluating each of the 28 EU countries' drug inspectorates to determine whether they are capable of meeting FDA's requirements. As of the date of publication, the following 20 countries' regulatory authorities have been deemed capable: Austria, Belgium, Croatia, Czech Republic, Denmark, Estonia, Finland, France, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Malta, Portugal, Romania, Spain, Sweden and the United Kingdom. The Mutual Reliance Initiative will enable FDA to avoid duplication, reduce costs and focus its resources in other parts of the world where there is greater public health and safety risk.

GMP for 503B Outsourcing Facilities

In December, FDA issued the Current Good Manufacturing Practice – Guidance for Human Drug Compounding Outsourcing Facilities Under Section 503B of the FD&C Act draft guidance, which describes the agency's policies regarding cGMP for facilities that compound human drugs and register as outsourcing facilities under section 503B of the FDCA (503B facilities). FDA intends to promulgate specific cGMP regulations for 503B facilities. The draft

guidance is intended to outline the conditions under which FDA does not intend to take enforcement action against 503B facilities until the agency issues the 503B-specific cGMP regulations. The draft guidance replaces the July 2014 Current Good Manufacturing Practice – Interim Guidance for Human Drug Compounding Outsourcing Facilities Under Section 503B of the FD&C Act draft guidance. It includes considerations for non-sterile compounded drug products and differentiates between requirements applicable to sterile and non-sterile compounded drug products where appropriate. The draft guidance also includes changes relating to stability testing (adding a "beyond-use date" as an expiration date) and release testing requirements. Finally, the draft guidance addresses reserve samples and provides guidance on "in-use times."

ENFORCEMENT

DEVELOPMENTS IN 2018

Overview

FDA's enforcement actions—including warning letters, civil monetary penalties, no-tobacco-sale orders, import alerts, seizures, injunctions and criminal prosecutions—tapered in 2018, a continued indication of the agency's current focus on deregulation and its continuing focus on risk-based decision-making. Overall warning letter numbers decreased, including in key areas of historical focus, such as medical device quality and labeling and prescription drug marketing and promotion.

FDA focused enforcement on unapproved stem cell therapies, filing lawsuits with the DOJ seeking permanent injunctions against two clinics. The agency had previously issued warning letters to the clinics citing violations that the clinics did not correct. Inspections of the clinics revealed failure to comply with GMP for cellular therapies along with marketing of unapproved stem cell treatments. The permanent injunctions would require the clinics to cease their stem cell treatments and remediate their manufacturing procedures.

FDA also increased its focus on foreign entities that manufacture or distribute products for the US market. In 2012, the Food and Drug Administration Safety and Innovation Act, which amended FDCA section 510(h), eliminated the distinction between domestic and foreign inspections and directed FDA to take a risk-based approach to inspecting both domestic and foreign drug manufacturing establishments. FDA formalized its process for selecting establishments for inspection based on risk factors specified by FDCA section 510(h) in 2015. Thus, 2018 reflected this increased focus on foreign-regulated entities.

Escobar and the Implied False Certification Theory

Alleged violations of FDA and health care laws continue drive False Claims Act (FCA) liability based on the "implied false certification theory." In 2016, the Supreme Court of the United States held that "the implied false certification theory can be a basis for

FCA liability when a defendant submitting a claim makes specific representations about the goods or services provided, but fails to disclose noncompliance with material statutory, regulatory, or contractual requirements that make those representations misleading with respect to those goods or services." *Universal Health Services v. United States ex rel. Escobar*, 579 U.S. ___ (2016). The resolution of these cases may influence FCA cases based on alleged

violations of cGMP, quality and other FDA requirements for reimbursed products.

In 2018, federal courts at both the trial and appellate level grappled with the practical application of the Supreme Court's ruling in *Escobar*. At issue is the case-by-case determination of whether a plaintiff has met the pleading standard for specificity and materiality in federal FCA cases to withstand a defendant's motion to dismiss. District court and appellate decisions came down on both sides of the fence in 2018. For example, the courts of appeal are deciding differently the question of whether a "specific representation" must be made to the government about the allegedly false goods or services in order to establish at the pleading stage a false certification theory of liability. The Second, Fourth and District of Columbia Circuits have held that allegations of specific representations are not a necessary condition to assert implied false certification claims that may withstand a defendant's Rule 9(b) motion to dismiss. In the Seventh and Ninth Circuits, however, plaintiffs must sufficiently allege specific representations were made in order to move on to the discovery phase of the case.

Federal courts at both the trial and appellate level grappled with the practical application of the SCOTUS's ruling from 2016's *Escobar* decision.

Courts are also applying the *Escobar* materiality test with sufficient rigor to defeat relator claims at the pleading stage. The "materiality" test continues to be heavily litigated, and the circuit courts are split over whether regulatory violations are "material" to government reimbursement. Some circuits have set a high bar for materiality. For example, the Fourth Circuit has held that FDA GMP violations by themselves are insufficient to establish FCA liability. *See Rostholder v. Omnicare, Inc.*, 745 F.3d 694 (4th Cir. 2014) and a discussion of the Ninth Circuit case here. *But see* a discussion about the Sixth Circuit case here, setting a lower threshold for materiality. In the Middle District of Florida, a district court vacated a verdict adverse to the nursing home defendant on the basis of the court's assessment of the materiality of defendant's allegedly non-compliant record-keeping practices. *Ruckh v. Salus Rehabilitation* (M.D. Fl. Jan. 11, 2018). In *Ruckh*, a $350 million verdict fell by the wayside because of evidence that the government continued paying defendant's claims despite knowing about its alleged record-keeping deficiencies. Most courts agree with the *Ruckh* court's reasoning that if the government continues paying a contractor after becoming aware of allegations of the contractor's non-compliance with statutory or contractual terms, the contractor's non-compliance was not material to the government's decision to continue payments. Brookdale Senior Living Communities, Inc., a major home health company, has petitioned the Supreme Court to resolve the circuit split.

Department of Justice Voluntary Dismissal of FCA Matters

The DOJ took a firm step towards greater transparency about its decision making process for dismissing *qui tam* matters over a relator's objection pursuant to 31 USC § 3730(c)(2)(A) and as further described in the Granston Memorandum. In a filing made by DOJ in the long-running federal FCA *qui tam, Gilead Sciences Inc. v. U.S. ex rel. Jeffrey*

Campie et al., case number 17-936, now before the Supreme Court, the DOJ asserted that it intends to file a motion to dismiss the declined *qui tam* matter if the Supreme Court lets stand the US Court of Appeals for the Ninth Circuit ruling that revived the relator's lawsuit, and subsequently remands the case back to the trial court for further proceedings. The case on the merits made its way to the Supreme Court on the basis of the parties' arguments regarding the application of the *Escobar* standards for adequately pleading False Claims. Gilead Sciences successfully argued to the district court on its motion to dismiss that relator's allegations were not material for FCA purposes. A Ninth Circuit panel reversed the district court's ruling, potentially opening the discovery floodgates for the pharmaceutical manufacturer and for the relevant US agencies responsible for regulating the approval and reimbursement of Gilead Sciences' products, specifically FDA.

Even while weighing in on the merits of the *Escobar* issue as the party in interest on relator's side, the DOJ included in its brief the following assertion: "[t]he government's authority to dismiss *qui tam* suits is not limited to circumstances where the defendant is entitled to dismissal on legal or factual grounds, but may be exercised whenever the government concludes that continued prosecution of the suit is not in the public interest." In particular, the DOJ cited concerns about the parties likely making "burdensome" requests for FDA documents and witness testimony during the ordinary course of discovery. "In addition, if this suit proceeded past the pleading stage, both parties might file burdensome discovery and *Touhy* requests for FDA documents and FDA employee discovery (and potentially trial testimony), in order to establish 'exactly what the government knew and when,' which would distract from the agency's public-health responsibilities . . . [b]ased on all those

considerations, the government has concluded that allowing this suit to proceed to discovery, and potentially a trial, would impinge on agency decision making and discretion and would disserve the interests of the United States."

Brand Memo

As discussed here, the DOJ announced a policy prohibiting the use of agency guidance documents as the basis for proving violations of applicable law in civil enforcement actions, including those brought under the FCA. The Brand Memo, issued by then-US Associate Attorney General Rachel Brand, defines "guidance documents" as "any agency statement of general applicability and future effect, whether styled as guidance or otherwise, that is designed to advise parties outside the federal executive branch about legal rights and obligations." It is unclear how this will affect the use of agency guidance in DOJ litigation, as DOJ and relators have historically relied on such documents to support their legal position concerning whether a particular practice violates the law. The basic premise of the Brand Memo is that most guidance documents are not subject to the Administrative Procedure Act's notice-and-comment rulemaking, and the DOJ "may not use its enforcement authority to effectively convert agency guidance documents into binding rules."

FDA is, however, unique among most agencies in promulgating guidance documents according to its own good guidance practices, under which "Level 1" guidance documents must undergo formal notice and comment. Level 1 documents are nonbinding guidance documents that set forth initial interpretations of statutory or regulatory requirements, set forth changes in interpretation or policy that are of more than a minor nature, include complex scientific issues, or cover highly controversial issues. *See* 21 CFR § 10.115. Although FDA's guidance documents are not binding on FDA or the public, it is unclear what impact, if any, this distinction could have on the application of the Brand Memo to disputes involving the application or interpretation of FDA's guidance documents. It is also unclear what impact Brand's resignation and Attorney General Jeff Sessions' resignation will have on the future of the Brand Memo and its precursor, the Sessions Memo.

THE YEAR AHEAD

FDA's activities and initiatives in 2018 suggest that 2019 will bring greater focus on data strategy; patient perspectives; and innovative ways to leverage data to influence product development, risk management and regulatory decisions. The agency's focus on data may lead to greater emphasis and renewed focus on data integrity and data quality issues throughout the product lifecycle, from clinical research to manufacturing. The continued focus on novel products and new expedited review processes for digital health, regenerative therapies and novel devices may mean fewer barriers to market entry for novel products, but it may also mean more significant post-market data collection and surveillance requirements. Policy and regulatory initiatives on cybersecurity and interoperability suggest the possibility of increased enforcement and scrutiny of these issues in standard quality and cGMP inspections. While warning letters and other FDA enforcement actions remain static, the agency appears to be leveraging procedural and administrative processes to influence broader policy objectives in areas such as drug pricing and generic competition. Life sciences companies may benefit from greater flexibility regarding the use of data from nontraditional sources to drive product development, advertising and promotion and quality. They may also benefit from the availability of a number of means to engage in pre-development and pre-submission discussions with the agency.

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