SPECIAL REPORT

2020 FDA YEAR IN REVIEW

January 2021

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OVERVIEW

The US Food and Drug Administration (FDA) became a central focus of US and global attention in 2020, since the agency regulates many of the therapies, treatments and interventions necessary to mitigate and combat the COVID-19 pandemic. The agency faced many challenges in light of the inevitable politicization of a public health emergency, exercising rarely used authorities to facilitate an expedient response to the pandemic in addition to pushing forward its traditional regulatory agenda.

This Special Report reviews notable actions that shaped FDA-regulated industries and products in 2020, and it offers insights into the agency's 2021 expected actions and priorities.

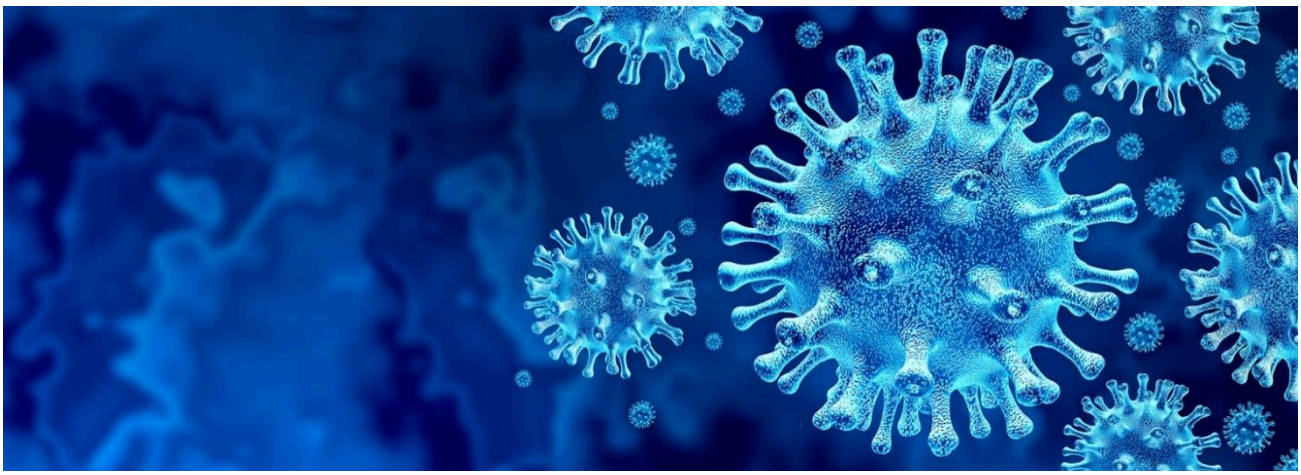
COVID-19

The COVID-19 pandemic has had a massive impact on the life sciences industry. Companies have pivoted entire production lines to manufacture critical products, such as personal protective equipment (PPE) and diagnostic tests. Many companies in the biotechnology and medical device sectors have shifted their resources to developing COVID-19 therapies and treatments. Still others have had to rethink approaches to marketing activities such as product demonstrations, trainings, and other interactions between clinicians and company sales representatives and medical science liaisons that often occur in person. We summarize here some of the key FDA actions and impacts on FDA-regulated industry.

CARES Act

As discussed in-depth here, on March 27, 2020, President Trump signed the Coronavirus Aid, Relief, and Economic Security (CARES) Act in response to the COVID-19 pandemic. The CARES Act amended section 506C of the Federal Food, Drug, and Cosmetic Act (FDCA) to require manufacturers of (1) any "drug that is critical to the public health during a public health emergency" and (2) active pharmaceutical ingredients (APIs) used in any such drug to notify FDA of a "permanent discontinuance of the manufacture" or "interruption in the manufacture" of the drug or API, respectively. FDA previously only required manufacturers of drugs characterized as "life-supporting," "life-sustaining" or "intended for use in the prevention or treatment of a debilitating disease or condition" to report drug shortages. FDA also issued a Notifying FDA of a Permanent Discontinuance or Interruption in Manufacturing Under Section 506C of the FD&C Act Guidance for Industry, describing how and when to notify FDA of a discontinuance or interruption in manufacturing and what information to include. The CARES Act also created a new section 506J of the FDCA, which requires medical device manufacturers to report potential shortages or supply chain disruptions.

The CARES Act established section 505G of the FDCA, which clarifies the FDA approval process for certain over-the-counter (OTC) drugs marketed without an approved drug application under section 505 of the FDCA. It also established an OTC Drug User Fee, subject to reauthorization in 2025. The new sections 744L to 744N apply to facilities identified as "OTC monograph drug facilit[ies]" and contract manufacturers of OTC drugs as well as to those that



submit an OTC monograph order request. Finally, the CARES Act gives manufacturers of OTC drugs the ability to obtain 18 months of market exclusivity for their products, which could spur OTC drug innovation.

Emergency Use Authorizations and Temporary Enforcement Policies

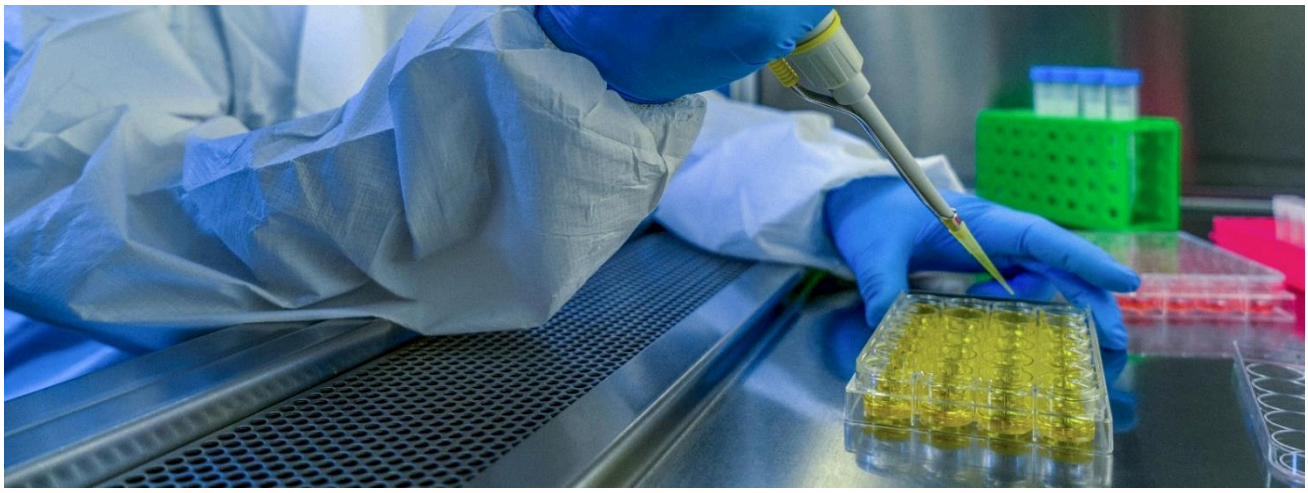
Section 564 of the FDCA allows the FDA Commissioner to allow unapproved medical products or unapproved uses of approved medical products to be used in an emergency under an emergency use authorization (EUA) to diagnose, treat or prevent serious or life-threatening disease or conditions by chemical, biological, radiological and nuclear (CBRN) threat agents when there are no adequate, approved and available alternatives. With the COVID-19 pandemic, we saw the most expansive use of this authority ever.

Under this authority, FDA has issued hundreds of EUAs for *in vitro* diagnostic products (primarily COVID-19 tests, discussed below), PPE and related devices, ventilators and other medical devices, and drugs and biologics (primarily for treatment of COVID-19 patients). As of the date of this writing, FDA has issued two EUAs for COVID-19 vaccines.

The Public Readiness and Emergency Preparedness (PREP) Act authorizes the US Department of Health and Human Services (HHS) to issue a PREP Act declaration, which provides immunity from liability—except for willful misconduct—for claims of loss arising out of, relating to, or resulting from administration or use of "countermeasures" to diseases, threats and conditions. The PREP Act requires that a "covered countermeasure" be a "qualified pandemic or epidemic product," which must be "approved, licensed, or cleared by the FDA" or otherwise authorized by an EUA, emergency use instructions, or used under an Investigational New Drug (IND) or Investigational Device Exemption (IDE). HHS issued a declaration under the PREP Act for medical countermeasures against COVID-19 on March 17, 2020 (most recently amended on December 9, 2020). As a result, manufacturers of COVID-19 products under an EUA have a valuable liability shield, which encourages them to produce critical medical products and supplies during a global pandemic. Relatively few court cases have been filed in the past year that test the boundaries and contours of PREP Act protections. Products liability actions arising from COVID-19 activities and products may increase in the aftermath of this unprecedented public health crisis.

Temporary Enforcement Policies

FDA has the authority under section 701(h)(1)(C) of the FDCA and 21 CFR § 10.115(g)(2) to issue guidance documents without prior public comment when it determines that prior public participation is not feasible or appropriate. On January 31, 2020, HHS issued a declaration of a public health emergency related to COVID-19 (Pandemic Declaration), renewed most recently on October 8, 2020, and on March 13, 2020, President Trump declared a national emergency in response to COVID-19. As a result of these actions and authorities, FDA has issued dozens of guidance documents and temporary enforcement policies in which the agency effectively waives or exercises enforcement discretion over many of the traditional legal and regulatory requirements for medical products during the COVID-19 public health emergency. Depending on the risk profile of the product, many of these guidance documents and temporary enforcement policies impose performance standard and labeling, registration and listing, or



adverse event reporting requirements on product manufacturers or distributors. The agency's plans for addressing the cessation of marketing of these products after the public health emergency ends are not entirely clear. Companies that market products under these enforcement policies should develop strategies to secure required marketing authorizations or implement contingency plans to ensure compliance with applicable requirements if and when FDA withdraws or amends these enforcement policies.

Clinical Trials

FDA issued guidance on the Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency in March 2020 (updated in December 2020) in response to the challenges presented by quarantines, site closures, travel limitations, interruptions to supply chain for investigational products, study staff and subject infections and various COVID-19 protocols limiting individuals' access to physical facilities. FDA's key objectives are to maintain the safety of trial participants, comply with good clinical practice (GCP) and minimize the risk to trial integrity.

Key elements of FDA's COVID-19 clinical trials guidance include provisions instructing sponsors and investigators on how to make protocol changes to minimize or eliminate immediate hazards or to protect the life and wellbeing of research participants without obtaining prior institutional review board approval. The guidance also provides recommendations on notifying FDA and institutional review boards, and documenting protocol deviations and amendments. It provides recommendations on alternative administration of investigational products, *e.g.*, through home nursing or use of non-study personnel, such as a subject's local healthcare provider (HCP). It also allows for modifications to study monitoring and consenting procedures.

Manufacturing

COVID-19 has also had an impact on medical product manufacturing activities, creating delays, supply reductions, reduced staff, site closures and other challenges. In many instances, the pandemic forced manufacturers to temporarily depart from current good manufacturing (cGMP) practices. FDA's 2011 Planning for the Effects of High Absenteeism to Ensure Availability of Medically Necessary Drug Products guidance recommends a risk-based approach to determine which products should be prioritized and which cGMP activities can be delayed, reduced or otherwise modified. In its September 2020 Resuming

Normal Drug and Biologics Manufacturing Operations During the COVID-19 Public Health Emergency: Guidance for Industry, FDA reiterates that cGMP requirements remain in effect during the COVID-19 pandemic and provides guidance on how manufacturers should return to normal operations using a quality risk-management approach. Specifically, the guidance addresses how manufacturers should identify and document deviations from cGMP and how to consider remediating products manufactured with unapproved changes to critical operations and materials. FDA also recommends that manufacturers implement a resumption plan specific to their operations and organizational needs, using a risk management approach that identifies, evaluates and mitigates factors that may affect product quality.

Enforcement

With many sellers advertising products that claim to prevent, treat, mitigate, diagnose or cure COVID-19, FDA and the Federal Trade Commission (FTC) have been actively coordinating to monitor and issue enforcement actions for fraudulent COVID-19 prevention and treatment claims. To date, FDA and FTC have issued more than 140 warning letters for fraudulent products. FDA's primary concern is that these deceptive and misleading products might cause Americans to delay or stop appropriate medical treatment, leading to serious and life-threatening harm. FDA is concerned that these products, in addition to simply not working or doing what they claim, could cause adverse effects or interact—and potentially interfere—with essential medications.

- Fraudulent products have included dietary supplements, such as vitamins, "essential oils," colloidal silver or other products with unproven health claims, including the prevention or treatment of COVID-19 or related symptoms.
- Some hand sanitizers have included lower amounts of alcohol than labeled or contain methanol, which is not approved as an OTC ingredient for hand sanitizers.
- Cannabis-derived products, including those with cannabidiol (CBD), have been mislabeled as preventing or treating COVID-19.

COVID-19 Diagnostic Tests

In 2020, the FDA spent considerable time evaluating *in vitro* diagnostic tests (IVDs) for use in the detection, care and management of patients with COVID-19, caused by the SARS-CoV-2 virus. FDA issued EUAs for more than 300 tests, including molecular tests, antibody tests and antigen tests; held weekly stakeholder town halls; and published multiple "template" EUA submission documents to facilitate the validation and review of novel COVID-19 tests, among other efforts to facilitate access to reliable testing.

Perhaps unsurprisingly given the novel nature of the virus and the nation's evolving demand for tests, FDA's requirements for COVID-19 testing evolved over the course of the year. Specifically, whether an EUA is required to offer a test primarily depends on two factors: the type of test (diagnostic or serology), and who is offering the test (test kit manufacturer or high complexity Clinical Laboratory Improvement Amendments of 1988 (CLIA)-certified clinical laboratory). The following table summarizes the FDA's premarket regulatory requirements with respect to each test type:

TYPE OF TEST	FDA PATHWAY
Diagnostic test kits	**Required to seek an EUA.** However, tests can be offered prior to receipt of an EUA if the manufacturer: Validates the test Notifies FDA of its intent to distribute the test and submits an EUA within 15 business days Provides instructions for use and posts performance data on its website Includes a disclaimer in labeling and test reports that the test has been validated but FDA's independent review of that validation is pending.
Serology test kits	**Required to seek an EUA.** Initially, FDA announced that serology test kits would not be required to seek an EUA. However, after stakeholders raised concerns about the quality of certain serology tests marketed under this enforcement discretion policy, FDA announced in May 2020 that it would begin requiring serology test kits to obtain EUAs. As with diagnostic test kits, however, validated serology test kits may be offered prior to receipt of an EUA if the manufacturer notifies FDA of its intent to do so and submits an EUA (among other requirements).
Diagnostic tests offered by laboratories as laboratory developed tests (LDTs)	**Not required to seek an EUA.** Initially, FDA required laboratories offering COVID-19 tests as LDTs to obtain an EUA. However, in August 2020, HHS announced that FDA would not require premarket review for any LDT (including COVID-19 LDTs) unless and until the agency goes through notice-and-comment rulemaking. As a result, high-complexity CLIA laboratories can now offer LDTs without an EUA. Such laboratories may, however, voluntarily seek an EUA.
Serology tests offered by laboratories as LDTs	**Not required to seek an EUA.** FDA has maintained this policy of enforcement discretion throughout the pandemic.

Looking Ahead to 2021

The public health emergency has necessitated the manufacture and distribution of several products that FDA has assessed to be safe and effective, but which may not be optimized for the end user. Manufacturers, particularly vaccine developers, likely will continue to refine their chemistry, manufacturing and controls (CMCs) to improve shelf-life, stability, and the conditions under which products can be stored and distributed. For example, some vaccine formulations have been improved to avoid the need for extreme cold storage, and others are being developed to only require one dose rather than two or more doses for full effectiveness.

When the COVID-19 public health emergency ends or the HHS rescinds its Pandemic Declaration, FDA will need to reinstitute the traditional legal and regulatory requirements for medical products that are currently subject to enforcement discretion. FDA likely will phase in its legal and regulatory requirements using a risk-based approach. It is also possible that some products may be "downregulated," at least with respect to some regulatory requirements, as appropriate. Once enforcement discretion ends under an EUA, some manufacturers might choose to discontinue marketing their products, whereas others may pursue permanent authorizations through 510(k) clearances, premarket approvals (PMAs), new drug applications (NDAs) and biologic license applications (BLAs). Some EUAs may provide a unique opportunity to use real world data (RWD) and real world evidence (RWE) to accelerate those permanent authorizations.

A substantial number of COVID-19 tests remain under review at the FDA. While FDA has taken steps to decrease its backlog (*e.g.*, limiting itself to one round of feedback on most EUA submissions), test developers

likely will continue to see substantial review times at least through the first half of 2021.

Tests currently offered under an EUA will eventually need to obtain a "full" marketing authorization from FDA to remain on the market. Initial tests are likely to be reviewed under the *de novo* classification process, while subsequent tests should be able to rely on the 510(k) pathway if the test developer can establish substantial equivalence to an authorized test. However, the timeline for this transition remains uncertain. The agency announced that it is developing guidance to help developers transfer out of an EUA-centric process, and has acknowledged that it will approach this issue with flexibility to avoid creating testing shortages. The exact parameters of the process are yet to be determined. Interested stakeholders should monitor FDA communications on this topic to facilitate their transition into a more traditional medical device regulatory framework.

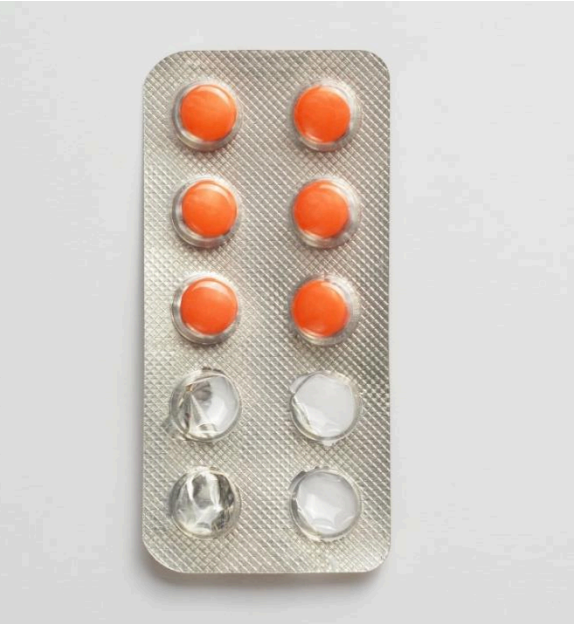
DRUGS AND BIOLOGICS

Drugs

FDA approved 50 new drugs in 2020, which is similar to the number FDA approved in 2019. FDA approved several drugs intended to treat various cancers, including lung cancer, breast cancer, multiple myeloma and lymphoma. For infectious diseases, FDA approved drugs for treatment of Human Immunodeficiency Virus (HIV), Ebola Virus Disease and COVID-19.

Indicating support for development of gene therapy products, FDA issued six final guidances in 2020, focused on gene therapy manufacturing and clinical development. In a January 2020 statement, FDA noted that more than 900 IND applications had been submitted for ongoing clinical studies involving gene therapies, and that FDA anticipates a significant number of forthcoming gene therapy approvals. This objective, however, may have been impacted by COVID-19. In January 2020, FDA also issued a draft guidance, Interpreting Sameness of Gene Therapy Products Under the Orphan Drug Regulations, to assist industry with orphan drug development of gene therapies.

In March 2020, FDA published its final Competitive Generic Therapies Guidance for Industry. This guidance tracks the draft guidance and clarifies the FDA process that companies can follow to request a designation of a drug as a competitive generic therapy (CGT), which is a drug with "inadequate generic competition." FDA also provides information on how FDA may expedite the development and review of abbreviated new drug applications (ANDAs) for CGTs and how the agency implements the 180-day exclusivity period for certain CGT ANDA applicants. In September 2020, FDA published ANDA Submissions – Amendments and Requests for Final Approval to Tentatively Approved ANDAs Guidance for Industry, which provides clarity for ANDA applicants in preparing and submitting amendments to tentatively approved ANDAs, including requests for final approval.



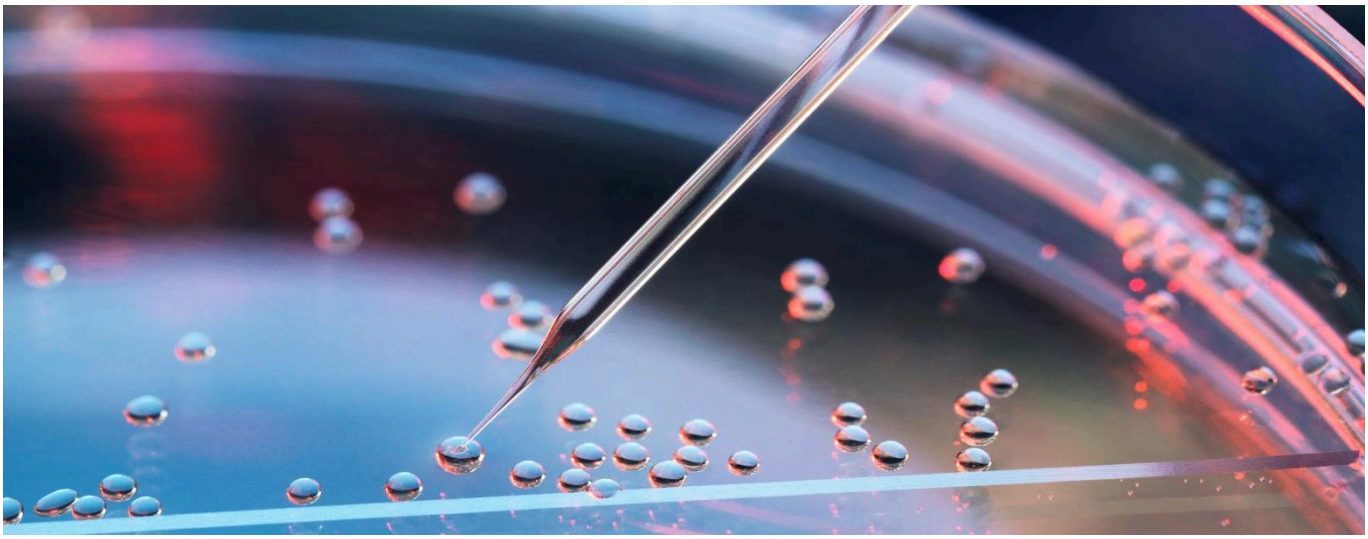
As discussed here, on August 6, 2020, President Trump issued an executive order that directs FDA and other federal agencies to take actions for ensuring that there is an adequate supply in the United States of essential medicines, medical countermeasures and critical inputs (*i.e.*, the ingredients and components used to make essential medicines and medical countermeasures) in the face of chemical, biological, radiological and nuclear threats and public health emergencies, such as infectious disease outbreaks. As part of the order, FDA issued a list of such products that are medically necessary to have available in an adequate amount in the United States at all times.

In November 2020, HHS announced through a Federal Register Notice the termination of FDA's Unapproved Drugs Initiative and withdrawal of FDA's "Marketed Unapproved Drugs – Compliance Policy Guide, Sec. 440.100, Marketed New Drugs Without Approved NDAs or ANDAs." As described in HHS FAQs, the Unapproved Drugs Initiative was established through FDA guidance to reduce the number of unapproved drugs on the market by requiring manufacturers of previously unapproved drugs to undergo the FDA approval process. According to HHS, a study conducted by the Yale School of Medicine and the University of Utah found that the Unapproved Drugs Initiative had the "unintended consequence of increasing drug prices and shortages" and did not achieve FDA's goal of obtaining more data on older, unapproved drugs. HHS also had concerns that the initiative was not established pursuant to legally appropriate notice-and-comment rulemaking procedures.

Biologics

In February 2020, FDA and FTC announced a collaboration agreement to deter anticompetitive practices for biological products, including biosimilars and interchangeable biologics, and to address false and misleading promotional activities by biologic manufacturers. The anticompetitive practices at issue include "anticompetitive reverse payment agreements, abusive repetitive regulatory filings, or misuse of restricted drug distribution programs."

In February 2020, FDA issued a final rule, in line with the requirements of the Biologics Price Competition and Innovation Act of 2009 (BPCI Act), revising the definition of the term "biological product" to include the term "protein," which means "any alpha amino acid polymer with a specific, defined sequence that is greater than 40 amino acids in size." This is a significant development for manufacturers of insulin and certain human growth hormone products, which now may be regulated as biological products. In March 2020, FDA published The "Deemed To Be a License" Provision of the BPCI Act Questions and Answers Guidance for Industry, clarifying FDA's implementation of the "transition" provision of the BPCI Act, under which an application for a biological product approved as a drug under the FDCA would be deemed a license for a biological product under Public Health Act as of March 23, 2020. In November 2020, FDA published Biosimilarity and Interchangeability: Additional Draft Q&As on Biosimilar Development and the BPCI Act Guidance for Industry, which provides information on the abbreviated pathway to market created by the BCPI Act for biologics shown to be biosimilar to, or interchangeable, with an FDA-licensed reference product. Insulin and certain hormone products can serve as FDA-licensed reference products for biosimilar or interchangeable products approved under this new abbreviated pathway. Ultimately, these efforts are aimed at potentially increasing market competition and patient access to more affordable medications. Manufacturers of these transitioning products should note that these products are no longer eligible for the exemptions for compounded drugs as of March 23, 2020.



Human Cells, Tissues, and Cellular and Tissue-Based Products

FDA regulates human cells, tissues, and cellular and tissue-based products (HCT/Ps) solely under 21 CFR Part 1271—*i.e.*, these items do not require a BLA if they meet all the requirements set forth in 21 CFR § 1271.3. HCT/Ps are articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion or transfer into a human recipient. In July 2020, FDA reissued its Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use: Guidance for Industry and Food and Drug Administration Staff, which supersedes the 2017 version of the guidance, to clarify its interpretation of "minimal manipulation" and "homologous use." For structural tissue, "minimal manipulation" is processing that does not alter the original relevant characteristics of the tissue, and for cells and nonstructural tissues, it is processing that does not alter the relevant biological characteristics of cells or tissues. FDA states that if information does not exist to show that processing of tissues meets the definition of "minimal manipulation," FDA will consider the processing to be "more than minimal manipulation" outside the scope of 21 CFR Part 1271. Similarly, homologous use means the repair, reconstruction, replacement or supplementation of a recipient's cells or tissues with an HCT/P that performs the same basic function or functions in the recipient as in the donor. FDA provides numerous examples of both minimal manipulation and homologous use, and provides a flowchart to demonstrate how manufacturers can determine whether their product is an HCT/P. Most critically, FDA extends the period of enforcement discretion for products that do not meet the definition of HCT/P to May 31, 2021, with respect to the IND and premarket approval requirements.

DRUG PRICING

Drug Importation

On October 1, 2020, HHS issued its Importation of Prescription Drugs final rule implementing sections 804(b) through (h) of the FDCA. This final rule allows states and Indian tribes to authorize commercial importation of certain prescription drugs from Canada through FDA-authorized, time-limited programs. The final rule went into effect on November 30, 2020. While the Centers for Medicare and Medicaid Services has determined that drugs imported under these "Section 804 Importation

Programs" would not meet the definition of a "covered outpatient drug" under the Medicare Drug Rebate Program, they may be eligible for Medicaid federal financial participation as prescribed drugs.

Industry groups have filed a complaint against HHS in the US District Court for the District of Columbia, seeking to permanently enjoin the final rule, arguing the Secretary of HHS' certification that implementation of Section 804 "poses no additional risk to the public's health and safety and will result in a significant reduction in the cost of covered products to the American consumer" is contrary to Section 804 and unsupported by the administrative record. The complaint also alleges the final rule infringes manufacturers' First and Fifth Amendment rights. Specifically, plaintiffs allege the final rule violates their First Amendment rights by compelling manufacturers to make certain statements about the drugs with which they may disagree and which involve disputed issues of fact and opinion, and by preventing them from adding statements to their labels explaining the differences between FDA-approved drugs and drugs imported under Section 804. They also allege the final rule violates the Fifth Amendment's Takings Clause by requiring manufacturers to disclose trade secrets and other confidential information and provide samples of analytical reference standards and FDA-approved drug to importers for free.

The final rule also authorizes the re-importation of insulin products made in the United States and creates a pathway for widespread use of personal importation waivers of the prohibition of importation of prescription drugs at authorized pharmacies.

Medicare Rebate Rule

On November 30, 2020, HHS issued its Fraud and Abuse; Removal of Safe Harbor Protection for Rebates Involving Prescription Pharmaceuticals and Creation of New Safe Harbor Protection for Certain Point-of-Sale Reductions in Price on Prescription Pharmaceuticals and Certain Pharmacy Benefit Manager Services final rule, which narrows the Anti-Kickback Statute's discount safe harbor protection for price reductions provided by manufacturers to Medicare Part D sponsors and pharmacy benefit managers (PBMs), unless the price reduction is required by law. The final rule retains the safe harbor for rebates to Medicaid managed care organizations and creates two new safe harbors. One of the new safe harbors applies to discounts, including rebates, offered at the point-of-sale that are passed through to the dispensing pharmacy and applied to the price charged to a beneficiary, and the other applies to fees charged by PBMs to manufacturers. This final rule will go into effect January 1, 2022, to allow affected entities to make changes to their business arrangements. See our detailed discussion here.

Looking Ahead to 2021

We expect to see more regenerative medicine and gene therapy development programs in 2021 with the advent of mRNA vaccines and the associated advantages of faster production capability than traditional vaccine development. We also expect more development of new biosimilar products as a result of the FDA and FTC collaboration agreement and BPCI Act changes resulting in an abbreviated pathway to market. We likely will see more proactive development of essential medicines, medical countermeasures and critical inputs as a result of lessons learned from the shortages that occurred during the COVID-19 pandemic.

MEDICAL DEVICES

Multiple Function Device Products

In July 2020, FDA issued its final Multiple Function Device Products: Policy and Considerations guidance. An analysis of the 2018 draft guidance is available here. FDA reiterated that while non-device functions or device functions subject to enforcement discretion will not be the focus of its review, FDA may assess the impact of "other functions" when assessing the safety and effectiveness of the device "functions-under-review." In their premarket submissions, manufacturers should provide information related to the impacts of "other functions" if those functions could negatively or positively affect the device function-under-review. Manufacturers also should document such impacts as part of design validation under 21 CFR § 820.30(g). FDA included a flowchart in the final guidance to help manufacturers assess whether these impacts should be documented, and included additional examples of ways in which the "other function" can affect the device function-under-review, such as impacts to memory requirements, shared programming pointers and privileges that can cause delays or interruptions. FDA also provided two additional examples of multiple function devices.

Medical Device Inspections

As part of the FDA Reauthorization Act of 2017, Congress directed FDA to issue guidance specifying how the agency will implement uniform processes and standards for routine device establishment inspections for both domestic and foreign establishments. On June 29, 2020, FDA issued its Review and Update of Device Establishment Inspection Processes and Standards: Guidance for Industry. Under the guidance, FDA aims to make reasonable efforts to make contact with firms to preannounce inspections. The agency also plans to maintain inspection timeframes of approximately three to six continuous business days, and make every reasonable effort to discuss all observations with the relevant responsible party or parties.

Unique Device Identifiers

In its July 2020 Unique Device Identification: Policy Regarding Compliance Dates for Class I and Unclassified Devices and Certain Devices Requiring Direct Marking: Immediately in Effect Guidance for Industry and Food and Drug Administration Staff, FDA announced that, in response to the COVID-19 pandemic, it will not enforce the Unique Device Identification (UDI) requirements for class I and unclassified devices, other than implantable, life-supporting or life-sustaining (I/LS/LS) devices before September 24, 2022, giving an additional two-year extension to manufacturers and labelers.

Combination Products

In December 2020, FDA issued its final Requesting FDA Feedback on Combination Products: Guidance for Industry and FDA Staff. FDA provided product developers additional guidance on Combination Product Agreement Meetings (CPAMs) as a mechanism for agency feedback. The guidance includes a structured process for managing pre-submission interactions between FDA and sponsors developing combination products, and FDA and sponsor best practices to ensure that FDA feedback

represents the agency's best advice based on information provided.

FDA also clarified what information sponsors should submit with a request for a CPAM and the form and content of CPAM agreements. FDA stated that any agreements made through the CPAM process will remain in effect except in the limited circumstances set forth in § 503(g)(2)(A)(iv) of the FDCA (*e.g.*, new information or updated scientific thinking) or if the sponsor changes the basis of the agreement (*e.g.*, fails to follow an agreed upon pre-clinical or clinical protocol, makes substantive changes to an endpoint, alters manufacturing process or controls, or changes the investigational plan).

DIGITAL HEALTH

Digital Health Center of Excellence

In September 2020, FDA launched the Digital Health Center of Excellence (DHCoE) as part of the agency's efforts to modernize digital health regulatory approaches and policies, and to provide access to specialized agency expertise, technological knowledge and tools to accelerate access to digital health technology. The DHCoE is focused on:

- Empowering digital health stakeholders to advance healthcare
- Innovating regulatory approaches to provide efficient and least burdensome oversight
- Connecting and building partnerships to accelerate digital health advancements
- Sharing knowledge to increase understanding and advance best practices.

In 2020, FDA focused on the first part of its three-phase approach to the DHCoE, *i.e.*, raising awareness and engaging stakeholders through listening sessions, resource development and beginning to operationalize outcome measurements.

Software Pre-Certification Program

In September 2020, FDA published its Developing the Software Precertification Program: Summary of Learnings and Ongoing Activities, concluding the following about the Software Pre-Certification (Pre-Cert) Program:

- A mock Excellence Appraisal, which is intended to identify the objective criteria and methodology that FDA will use to pre-certify a company and decide whether a company can keep its precertification status, that is reliant on remote pre-work and objective evidence, appears to be a viable alternative to a multi-day onsite visit.
- Additional exploration and testing is necessary to inform a Streamlined Review, which is intended to identify the type of information that a pre-certified company would include in its premarket submission for the FDA to review software products for safety and effectiveness before patients access them.
- Collection of real world performance data allowed for the observation of several important measures, including human factors usability engineering, and metrics that provide assurance that safety risks are managed and mitigated in a timely way.
- More testing is needed to understand how health benefits may be observed in real world performance data.

FDA will use these learnings and information to explore how the agency can develop a structured, objective and repeatable approach to assessing organizational excellence, which will help FDA identify and test parameters for ongoing monitoring of software as a medical device (SaMD) product performance. After FDA assesses and evaluates the readiness of the Pre-Cert Program, FDA will consider obtaining legislative authority to fully implement the Pre-Cert Program as a pathway for SaMD clearance or approval.

Looking Ahead to 2021

The Center for Devices and Radiological Health (CDRH) agenda for Fiscal Year 2021 includes publication of the final Clinical Decision Support Software guidance. More information on the 2019 draft Clinical Decision Support Software guidance is available here.

FDA will also launch the next phases of its three-phase approach to the DHCoE:

- Building strategic partnerships, developing resources for external stakeholders, creating a practice community, and assembling FDA and CDRH advisory groups (winter 2020 to winter 2021)
- Building and sustaining capacity, including by updating and implementing regulatory frameworks and continuing to harmonize with other regulators (winter 2021 and beyond).

CLINICAL LABORATORY IMPROVEMENT AMENDMENTS

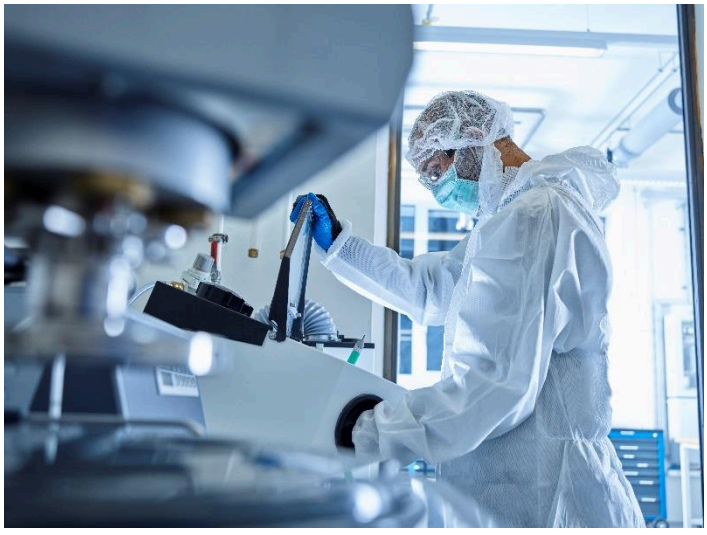
FDA has the authority to grant a test waived status under CLIA—and to therefore make the test eligible for performance in a laboratory operating under a CLIA Certificate of Waiver—if the test is simple and has an insignificant risk of producing an erroneous result. FDA assesses whether a test has an insignificant risk of producing an erroneous result in part by evaluating whether the test produces accurate results when used by a waived user. Historically, FDA evaluated accuracy by comparing the test's performance when used by a waived user to certain statistical guardrails that may or may not be clinically relevant based on the test's intended use. The 21st Century Cures Act required FDA to use a different, potentially less restrictive comparison when evaluating a test's accuracy—*i.e.*, the test's performance when performed by a moderate complexity user. In February 2020, FDA published a long-awaited update to its "waiver" guidance document, Recommendations for Clinical Laboratory Improvement Amendments of 1988 (CLIA) Waiver Applications for Manufacturers of In Vitro Diagnostic Devices, implementing this change.

LABORATORY-DEVELOPED TESTS AND PRECISION MEDICINE

On August 19, 2020, HHS announced that FDA will not require premarket review of LDTs without first outlining its plans for such review following formal notice-and-comment rulemaking.

The announcement clarified that clinical laboratories that develop and offer LDTs may voluntarily seek approval, clearance or an EUA from FDA, but that such laboratories are not required to do so. However, laboratories that chose to run LDTs for the SARS-CoV-2 virus without FDA premarket review or authorization will not be eligible for liability protections under the PREP Act.

The announcement also clarified that clinical laboratories remain subject to regulation under CLIA, regardless of whether they elect to seek premarket review of their LDTs. State laboratory licensure requirements are also unaffected by the notice.



Background

The FDA has long contended that it has the authority to regulate LDTs as medical devices. However, the FDA has historically exercised enforcement discretion with respect to most LDTs, which FDA defines as tests designed, manufactured and used within a single laboratory. However, with LDTs becoming increasingly complex, the FDA announced its intent to revisit its policy of enforcement discretion, and in July 2014 released draft guidance outlining its intent to regulate most LDTs as medical devices. In January 2017, the FDA announced that it would not finalize the 2014 guidance, and instead published a "discussion paper" that outlined a substantially revised approach to agency oversight of LDTs. Since then, the agency has primarily focused on responding to legislative efforts (*e.g.*, the Verifying Accurate Leading-edge IVCT Development (VALID) Act of 2020) as a mechanism to clarify its authority over LDTs.

Although the announcement was primarily positioned as relating to pandemic testing efforts, HHS's language regarding the requirement for notice-and-comment rulemaking is noticeably not limited to COVID-19 tests. Indeed, HHS intends for this announcement to apply to all tests offered as LDTs—not just tests for COVID-19. As such, this announcement appears to open the door for many types of LDTs that currently are not eligible for enforcement discretion (*e.g.*, companion diagnostics) to be offered without FDA clearance, approval or authorization. HHS has clarified that direct-to-consumer tests would not be considered LDTs under its policy.

Clinical laboratories would be prudent to consider the context in which this announcement was made before making wholesale changes to business plans. Notwithstanding the HHS announcement, FDA's LDT website remains unchanged, and the FDA website continues to link to previous guidance documents and informal statements, suggesting the agency intends to "stay the course" on its plans to regulate LDTs. The durability of this policy also remains in question, since a new Biden Administration may rescind this policy and take a position that makes it easier for FDA to exercise oversight of LDTs.

Moreover, any decisions by the executive branch concerning FDA regulation of LDTs may be short lived if Congress passes a bill to reform the regulation of laboratory tests. If enacted, the VALID Act would subject all diagnostic tests, including LDTs, to a novel risk-based oversight framework. In contrast, the Verified Innovative Testing in American Laboratories (VITAL) Act of 2020 would prohibit the FDA from regulating LDTs and confirm a CLIA-centric framework for FDA oversight.

Looking Ahead to 2021

While the HHS announcement is a notable development, the long-term impact of the announcement on LDTs is unclear at this time. Interested stakeholders should carefully monitor future statements from HHS and the FDA for clarifications on the applicability of this policy. Stakeholders should consult with their trusted advisors to determine whether to pursue premarket review and, if applications for such review are already submitted or in process, whether to withdraw such applications or stop such efforts pending formal rulemaking by the FDA on regulation of LDTs. More generally, stakeholders should consider the impact of the presidential election and congressional appetite to enact a new regulatory framework for diagnostics as they evaluate the ramifications of this announcement for their business plans and operations.

FOOD

FDA announced a joint initiative with the US Department of Agriculture and the Environmental Protection Agency in January 2020. The platform, called the Unified Website for Biotechnology Regulation, streamlines the information from all three regulatory bodies on agricultural biotechnology products.

In October 2020, FDA published its U.S. Agent Voluntary Identification System (VIS) for Food Facility Registration: Guidance for Industry. This guidance document provides notice of FDA's establishment of a VIS in conjunction with the food facility registration database, the Food Registration Module (FFRM). The VIS allows for a streamlined US agent verification process, whereby US agents can directly provide FDA with their contact information and the name of the facilities for which they agree to serve. FDA's VIS guidance outlines several benefits to US agents and foreign facilities, including use in facilitating verification for the purposes of compliance with regulations, automatic registration number assignment when a US agent adds facility information to the VIS profile and limits to the number of unauthorized or fraudulent US agent listings.

FDA also issued several guidance documents allowing for temporary flexibility during the COVID-19 pandemic regarding nutrition labeling of certain packaged food, menu labeling requirements for chain restaurants and similar retail food establishments, and certain labeling requirements for human foods.

Looking Ahead to 2021

On September 23, 2020, FDA published a proposed rule to establish additional traceability recordkeeping requirements for entities that manufacture, process, pack or hold foods that FDA has designated for inclusion on the Food Traceability List (FTL), which is a list of specific high-risk foods identified by FDA by a risk-ranking model for food tracing. Under the proposed rule, companies would need to establish records regarding critical tracking events in the supply chain, "such as growing, shipping, receiving, creating, and transforming the foods." Where there are outbreaks of foodborne illness or threats of serious adverse health consequences or death resulting from adulterated or misbranded food, this proposed rule is intended to help FDA quickly and accurately identify the recipients of the food. Comments on the proposed rule are due by January 21, 2021.

DIETARY SUPPLEMENTS

In response to COVID-19, FDA issued guidance in May 2020 to provide a convenient way for food producing facilities, including farms and manufacturers, to voluntarily report to FDA temporary closure or reduced production. The Reporting a Temporary Closure or Significantly Reduced Production by a Human Food Establishment and Requesting FDA Assistance During the COVID-19 Public Health Emergency guidance also describes ways for food producers to engage with FDA to discuss concerns or strategies for resuming operations or addressing other challenges posed by COVID-19. The policy is intended to remain in effect for the duration of the public health emergency.

In May 2016, FDA issued a final rule amending the conventional food and dietary supplement labeling regulations. The compliance dates were initially set for July 26, 2018, for food manufacturers with $10 million or more in annual sales, and July 26, 2019, for food manufacturers with less than $10 million in annual sales. These compliances dates were subsequently extended to July 1, 2020, and July 1, 2021, respectively. In February 2020, FDA issued its revised Food Labeling: Revision of the Nutrition and Supplement Facts Labels: Guidance for Industry

Small Entity Compliance Guide to provide guidance to small entities on the changes in the final rule. Topics include foods covered by the rule, nutrients that must be newly declared and changes to nutrients previously declared, recordkeeping requirements, updates to values of nutrients and formatting requirements.

Looking Ahead to 2021

Many US food producers have faced challenges in production and wrestled with the effects of COVID-19 on the health and safety of their workforce. The pandemic has also affected routine activities such as Foreign Supplier Verification Program (FSVP) requirements for food importers. FDA appears to be taking a flexible and risk-based approach to these and other programs affected by COVID-19, and seems to be actively encouraging companies to engage to address and resolve issues as they arise.

TOBACCO

Warning Statements and Plans

As discussed in our 2019 Year in Review, the US District Court for the District of Massachusetts ordered FDA to publish a new proposed rule in March 2020 establishing required warnings for cigarette packages and advertisements, and the court delayed the effective date of the proposed rule following FDA's issuance of such final rule for cigarette warnings. In March 2020, FDA published a final rule, codified at 21 CFR Part 1141. On April 3, 2020, industry challenged the final rule in the US District Court for the Eastern District of Texas, and on May 8, 2020, the court granted a joint motion to govern proceedings in that case and postpone the effective date of the final rule to October 16, 2021. Under Required Warnings for Cigarette Packages and Advertisements: Small Entity Compliance Guide (Revised): Guidance for Industry, FDA encourages entities to submit cigarette warning plans to FDA as soon as possible after publication of the final rule and, in any event, within five months or 120 days after the final rule's publication date. The agency also issued the Submission of Plans for Cigarette Packages and Cigarette Advertisements (Revised) and reissued the FDA Deems Certain Tobacco Products Subject to FDA Authority, Sales and Distribution Restrictions, and Health Warning Requirements for Packages and Advertisements: Guidance for Industry. In these guidances, FDA discussed the regulatory requirements to submit cigarette warning plans, including their scope, when to submit and what information to submit.

FDA's deeming rule requires that the packages and advertisements of all cigarette tobacco, roll-your-own tobacco and covered tobacco products bear an addictiveness warning label statement. The deeming rule also requires cigar packaging and advertising to include additional health warning label statements. On July 7, 2020, the US Court of Appeals for the DC Circuit found that FDA needed to examine more closely whether the health warnings would likely affect the number of users for cigars and pipe tobacco. Specifically, the DC Circuit found that FDA violated the Family Smoking Prevention and Tobacco Control Act and the Administrative Procedure Act by failing to study whether the extensive health warnings required on cigars would actually lower the number of smokers in promulgating the regulation. The DC Circuit remanded the case, and on September 11, 2020, the US District Court for the District of Columbia vacated and remanded the health warnings for cigars and pipe tobacco. As a result, FDA will not seek to enforce the warning requirements or the labeling requirements under sections 903(a)(2) and 920(a) of the FDCA for cigars and pipe tobacco at this time.

Premarket Submissions

In April 2020, FDA issued a revised Enforcement Priorities for Electronic Nicotine Delivery Systems (ENDS) and Other Deemed Products on the Market Without Premarket Authorization guidance. FDA reiterated that it intends to prioritize enforcement for the following ENDS products marketed without FDA authorization:

- Any flavored, cartridge-based ENDS products (other than tobacco- or menthol-flavored ENDS products)
- All other ENDS products for which the manufacturer has failed or is failing to take adequate measures to prevent minors' access
- Any ENDS product whose marketing is likely to promote use of ENDS to minors or that is targeted to minors

Consistent with the Further Consolidated Appropriations Act of 2020, for the purpose of this guidance, "minor" means individuals under the age of 21.

September 9, 2020 was the premarket submission deadline for certain deemed new tobacco products. FDA is reviewing submitted premarket tobacco product applications (PMTAs), substantial equivalence reports and exemption from substantial equivalence requests, and intends to prioritize enforcement of any products for which the manufacturer has not made the relevant submission.

Industry challenged the PMTA requirement for premium cigars when FDA denied requests to extend the filing deadline. The DC Circuit determined that FDA does not have the authority to change the grandfathering date for specific tobacco products, which applies once FDA deems a tobacco product subject to its regulation. The DC Circuit also determined that the PMTA deadline of September 9, 2020 was not arbitrarily or capriciously applied to substantial equivalence reports for cigar and pipe tobacco manufacturers. Industry has challenged these two holdings in ongoing litigation.

However, the DC Circuit held that FDA had not adequately considered or responded to industry concerns regarding the possibility of creating a separate, streamlined process for premium cigars, which do not appeal to minors. The Court remanded the issue to FDA to determine whether such a streamlined process is more appropriate for premium cigars and enjoined enforcement of premarket review requirements for premium cigars. FDA must specify when manufacturers will have to submit substantial equivalence reports once it makes a decision regarding the appropriate course for premium cigars, but industry has also requested clarification on whether the injunction vacates the deeming rule with regard to premium cigars, which would require FDA to engage in notice-and-comment rulemaking.

Looking Ahead to 2021

FDA likely will be met with ongoing litigation that seeks to define the limits of FDA's authority to regulate tobacco products that primarily appeal to adults, such as premium cigars. FDA retains the broad authority Congress granted it under the Family Smoking Prevention and Tobacco Control Act of 2009, however. FDA's efforts to establish warnings for cigars that withstand First Amendment scrutiny likely will mirror its multi-year effort to establish graphic warnings for cigarettes—a process that is still ongoing.

CANNABIS

In our 2019 Year in Review, we wrote about FDA's Scientific Data and Information about Products Containing Cannabis or Cannabis-Derived Compounds public hearing. FDA established a docket (FDA-2019-N-1482) for public comment on this hearing. In March

2020, FDA reopened the public hearing docket to facilitate information sharing indefinitely.

In March 2020, FDA also released a report to Congress summarizing the regulatory landscape surrounding CBD drugs, dietary supplements, foods, cosmetics and vape products. FDA's identified next steps included potentially adopting a risk-based enforcement policy. As discussed in detail here, in July, FDA issued its Cannabis and Cannabis-Derived Compounds: Quality Considerations for Clinical Research, Draft Guidance for Industry. Under this draft guidance, FDA clarified that clinical research involving cannabis over the 0.3% delta-9 tetrahydrocannabinol (THC) limit requires an approved IND with cannabis from a DEA-registered source, which historically has been only the National Institute on Drug Abuse (NIDA) Drug Supply Program, in contract with the University of Mississippi. However, for clinical research involving "hemp" products under the 0.3% delta-9 THC limit, researchers may obtain cannabis from other sources. FDA further recommends that, in an IND application, companies provide qualitative laboratory data and detailed testing methods, including testing methods to evaluate the level of delta-9 THC, in particular for phase 2 and 3 studies and marketing applications, which may differ depending on dosage form. FDA also cautioned NDA applicants to not rely on published literature in place of a full toxicology program to support development of a botanical drug product for phase 3 trials and beyond.

Looking Ahead to 2021

On July 22, 2020, FDA submitted its Cannabidiol Enforcement Policy; Draft Guidance for Industry to the White House Office of Management and Budget for review. FDA has yet to issue any official statements providing additional details regarding the draft guidance. For about two years, FDA has been considering potential regulatory pathways for lawful use of CBD and hemp-derived ingredients in food and supplements, but a lack of safety data has slowed progression. The cannabis industry is eagerly anticipating this guidance on FDA's enforcement position regarding CBD products.

Multiple federal legislative actions are pending that would increase flexibility for manufacturers of cannabis and cannabis-derived compounds and provide guidance in a space where FDA has been slow in issuing regulations. For example, HR 5587, introduced in the US House of Representatives on January 13, 2020, would amend the FDCA with respect to the regulation of hemp-derived CBD and hemp-derived-CBD-containing substances to allow them to be marketed as dietary supplements and in food. Similarly, HR 8179, the Hemp and Hemp-Derived CBD Consumer Protection and Market Stabilization Act of 2020, introduced in the House on September 4, 2020, would make hemp and hemp-derived CBD, and any other ingredient derived from hemp, "lawful for use under the [FDCA] as a dietary ingredient in a dietary supplement."

CLINICAL INVESTIGATIONS

Enhancing Diversity in Clinical Trials

On November 9, 2020, FDA issued its final guidance on Enhancing the Diversity of Clinical Trial Populations — Eligibility Criteria, Enrollment Practices, and Trial Designs Guidance for Industry, which Congress mandated under the FDA Reauthorization Act of 2017.

Pursuant to Congress' mandate, FDA addresses in the guidance:

- Broadening eligibility criteria, avoiding unnecessary exclusions for clinical trials, and applying these recommendations to trials of drugs intended to treat rare disease or conditions
- Developing eligibility criteria and improving recruitment so enrolled participants better reflect the populations most likely to use a drug.

While clinical research is critical to the development of safe and effective treatments and therapies, particularly for diseases and conditions that disproportionately affect certain groups of individuals, these same groups tend to be under-represented in clinical trials. These groups may share demographic characteristics (*e.g.*, sex, race, ethnicity, age, geographic location) or non-demographic characteristics (*e.g.*, patients with comorbidities or disabilities, pregnant women, children, or individuals with other medically complex circumstances). Lack of diversity in clinical trials limits the generalizability of a study's research findings; creates disparities in the safety, effectiveness and quality of treatments and therapies; exacerbates existing health disparities and inequalities; and decreases opportunities to deliver treatment and care to underserved populations. The COVID-19 pandemic has reinforced the need to develop medical products that are effective across multiple populations and healthcare disparities.

Eligibility

FDA recognizes that eligibility criteria exist primarily to exclude people for whom risk of an adverse event outweighs the potential benefit of participation and the resulting knowledge from the trial. Many sponsors have come to accept some common eligibility criteria without strong clinical or scientific justification, however. Many trial designs also lack reasonable accommodations for non-English speakers, patients who are unable to access transportation, or patients who work and must make site visits outside of normal business hours.

FDA's specific recommendations for inclusive enrollment include the following:

- Eliminating or modifying exclusions, such as by basing exclusions on appropriate specific measures (*e.g.*, setting a level of organ dysfunction that does not lead to unnecessary exclusion of those with milder dysfunction)
- Eliminating exclusion criteria from phase 2 studies in phase 3 protocols based on data available from completion of other relevant studies (*e.g.*, *in vitro* or *in vivo* drug-drug or drug-disease interaction studies)
- Enrolling participants who reflect characteristics of clinically relevant populations with respect to age, sex, race and ethnicity (*e.g.*, including, as appropriate, children and adolescents in confirmatory clinical trials involving adults; including women in adequate numbers to allow for analysis by sex; including racial and ethnic minorities and analyzing trial data by race and ethnicity, including differences in data attributable

to intrinsic factors, such as genetics, metabolism or elimination, or extrinsic factors, such as diet, environmental exposure or sociocultural issues)

- Using enrichment strategies to increase a trial's potential to show an effect, if one exists, by ensuring that participants have a particular severity or subset of a disease or genetic marker (*i.e.*, prognostic enrichment, which enrolls participants more likely to reach study endpoints, or predictive enrichment, which enrolls participants with a specific characteristic that makes them more likely to respond to an intervention) in conjunction with appropriate marker-negative participants
- Considering re-enrollment of early-phase participants into later-phase randomized trials when studying the effectiveness of rare diseases, when medically appropriate and scientifically sound
- Making available open-label extension studies with broader inclusion criteria after early-phase studies.

Enrollment

FDA also recommends that sponsors consider trial design and methodological approaches that will facilitate enrollment of broader populations, for example:

- Characterizing drug metabolism and clearance across populations that metabolize or clear the drug differently to avoid later exclusions and allow dose adjustments to optimize safety and efficacy across different populations
- Using adaptive clinical trial design to allow for pre-specified trial design changes, including altering the trial population, allowing expansion into broader populations based on interim safety data
- Considering a broader pediatric development program early, with staggered enrollment based on chronological age
- Including pharmacokinetic sampling to establish dosing in women who become pregnant during a trial to allow for continued participation and to provide information regarding drug metabolism during pregnancy
- Using data from expanded access programs to identify patients for subsequent studies.

Subject Recruitment and Retention

FDA recommends that sponsors address practical burdens during the study design phase by reducing the frequency of required subject visits, using electronic communication and remote monitoring to replace site visits, employing home visits and providing reasonable reimbursement for expenses associated with participation (*e.g.*, travel and lodging expenses).

The agency also recommends adopting enrollment and retention practices that enhance inclusiveness, including the following:

- Conducting public outreach and education with relevant community stakeholders, including patient advocacy groups
- Providing cultural competency and proficiency training to study staff to facilitate trust-building, decrease biased communication and behavioral practices and address patient reluctance to enroll
- Establishing sites in diverse geographic locations
- Holding recruitment events in accessible locations, during evening and weekend hours, and at trusted non-clinical locations or events (*e.g.*, places of worship, community centers, beauty salons, cultural festivals) or through social media.

With respect to patient records and consents, FDA recommends that sponsors explore agreements to facilitate exchange of medical records between sites to promote participant retention and to ease the burden on participants to gather and transfer their own

records. FDA also recommends providing resources and documents in multiple languages, employing multilingual research staff or interpreters and using electronic consents or holding consenting processes in locations more accessible to participants. Finally, the agency recommends using real world data to promote more efficient recruitment of diverse populations, if patients have provided relevant permissions and consents for access to and sharing of identifiable data from their records.

Looking Ahead to 2021

FDA has expressed a commitment to exploring the effects of bias in clinical trial design and the lack of diverse population representation in product development. The guidance is an important step in the right direction because it contains practical, common sense recommendations. It remains to be seen whether guidance alone, without additional or specific regulatory authority, will encourage changes in product development and clinical research. Initiatives such as the Pediatric Research Equity Act (PREA), which gave FDA the authority to require pediatric studies in certain drug and biologic products, have encouraged greater focus on innovative trial designs for pediatric populations. While these issues are not without challenges and complexities, they continue to be a focus for FDA and industry in 2021.

ADVERTISING AND PROMOTION

Enforcement

In 2020, FDA's Office of Prescription Drug Promotion (OPDP) issued only five warning letters and one untitled letter related to prescription drug promotion. The warning letters focused on failure to present any risk information, making false or misleading claims about risk or safety and effectiveness and making claims about unapproved new uses or indications. The untitled letter was for a direct-to-consumer television advertisement, which FDA alleged made false or misleading claims and representations about the drug product's associated risks and efficacy. As previously noted, FDA issued numerous warning letters related to fraudulent COVID-19 products. CDRH did not issue any non-COVID-19-related warning letters for medical device promotion. However, it is difficult to ascertain whether the downtrend is primarily a result of the pandemic, or if it is in line with the recent decline in FDA warning letters for advertising and promotion.

Intended Use Rule

As discussed in depth here, FDA published its Regulations Regarding "Intended Uses" Proposed Rule to amend its "intended use" regulations at 21 CFR §§ 201.128 and 801.4, and with the intent to clarify that the manner in which HCPs prescribe or use a product cannot be the sole basis for determining intended use. The comment period for this proposed rule closed October 23, 2020.

Social Media

Both FDA and the FTC remain focused on social media influencers. FDA announced that it plans to evaluate the influence of four types of endorsers (celebrity, physician, patient and influencer) in two separate studies examining whether the presence and type of disclosure language (one direct and consumer-friendly, and one less direct) influences participant reactions. FTC requests comments on its Guides Concerning the Use of Endorsements and Testimonials in Advertising.

FTC sent a warning letter to Teami stating that because Instagram users typically see only the first few lines of a post unless they click "more," endorsers should disclose any material connection above the "more" link. Teami responded by implementing a social media policy (given to influencers or included in their contracts) that instructed influencers to include effective disclosures above the "more" button. FTC alleged in its complaint that the new policy did not

result in effective disclosures. As part of its $15.2 million settlement with Teami, FTC required the company to maintain a system to monitor and review how endorsers disclose material connections. FTC noted that when it comes to social media influencers, "[a] contract provision is a fine start, but it's probably not enough," and "[a] written policy for influencers without effective monitoring and follow-through" "isn't worth the paper it's printed on."

FDA and FTC also issued joint warning letters to four companies manufacturing and marketing flavored e-liquid products. FDA determined that the e-liquids were misbranded because the social media posts at issue did not include FDA's required nicotine warning. FTC cited the companies for unfair or deceptive trade practices under the FTC Act, because the companies failed to disclose material health or safety risks in advertising.

Looking Ahead to 2021

Despite a historic low in advertising-and-promotion-related enforcement outside of COVID-19-related enforcement, the incoming Biden Administration's priorities likely will result in an uptick in warning letters and untitled letters.

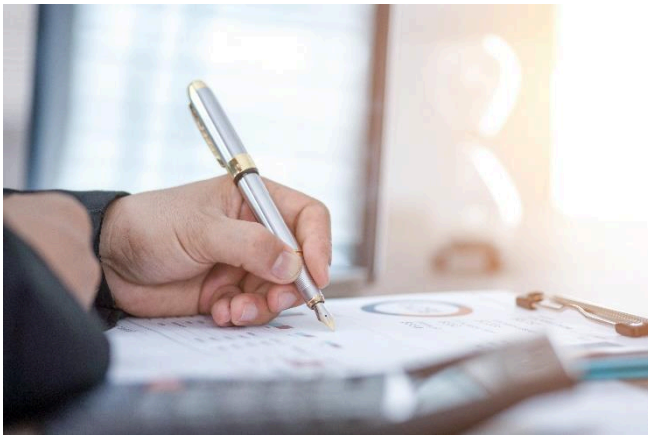
ENFORCEMENT

Inspections

In March 2020, FDA announced the postponement of all domestic and foreign routine surveillance facility inspections due to the health risk posed by the COVID-19 pandemic. In July 2020, FDA stated its plan for resuming prioritized onsite domestic inspections. In the interim, FDA had continued its "mission critical" inspections and had utilized other tools, including "remote assessments and import alerts." Under its stated plan, FDA determined that prioritized domestic inspections would be pre-announced for the foreseeable future (with the exception of retail tobacco inspections). In its August 2020 Manufacturing, Supply Chain, and Drug and Biological Product Inspections During COVID-19 Public Health Emergency Questions and Answers guidance, FDA reiterated that foreign pre-approval and for-cause inspections would remain temporarily postponed, while mission-critical inspections would continue. Mission-critical inspections are assessed based on multiple factors, including whether the product has a special designation, such as a breakthrough therapy or regenerative medicine advanced therapy, or whether the product is intended for a serious disease or condition with no adequate substitute.

Warning Letters

Despite the postponement of inspections, warning letter numbers (excluding tobacco retailer warning letters) in 2020 overall were higher than in 2019 or 2018, mainly attributed to the agency's focus on ensuring unapproved and misbranded products related to COVID-19 were kept off the market. Aside from the COVID-19-related warning letters, FDA continued to focus enforcement efforts on claims that go beyond the indication for use in existing clearances or approvals, and claims that suggest a product can diagnose, prevent, treat or cure a disease or condition without clearance or approval. For example, in July 2020, FDA issued seven warning letters to dietary supplement companies making unapproved claims that their products cure, treat, mitigate or prevent hangovers. In October 2020, FDA issued five warning letters to dietary supplement companies marketing products containing cesium chloride because of significant safety



concerns. These warning letters may indicate a continued agency focus on dietary supplement products.

With reference to medical devices, 2020 saw an uptick in warning letters issued by CDRH after a significant downturn in recent years. In 2015, CDRH issued 83 warning letters, a number that has decreased each year since, down to a total of 12 issued in 2019. In 2020, CDRH issued a total of 27 warning letters, but 16 of those letters were related to COVID-19, making a total of 11 non-COVID-19 warning letters.

For drugs, several warning letters issued by the Center for Drug Evaluation and Research (CDER) cited cGMP violations, suggesting a continued focus in this area. CDER also issued several warning letters to companies for the unlawful sale of opioids online to US consumers.

On November 16, 2020, the HHS Office of Inspector General (OIG) issued a special fraud alert, discussed in detail here, drawing attention to the potential fraud and abuse risks of speaker programs hosted by pharmaceutical companies. The alert encouraged pharmaceutical companies to reassess the need for in-person and virtual programs where remuneration may be paid to speakers and attendees, and encouraged HCPs to consider the risks of soliciting and receiving remuneration tied to speaker programs. OIG acknowledged that the risks posed by speaker programs depend on the facts, circumstances and intent of the parties, and provided a list of factors that may increase the enforcement risk of such programs.

Looking Ahead to 2021

Inspections will likely increase as FDA continues to adapt to the COVID-19 pandemic, whether by adopting more proactive remote inspections or resuming frequent in-person domestic and foreign inspections as COVID-19 vaccine distribution increases. FDA likely will issue more warning letters to companies claiming to prevent, treat, mitigate or cure COVID-19. We also anticipate more warning letters to e-commerce companies illegally selling products such as tramadol and oxycodone over the internet, as the opioid epidemic continues in the United States.

2021 OUTLOOK

At the close of 2020, the outgoing Trump Administration issued several last-minute executive orders and rulemakings. Because several of these rulemakings relied on exceptions from notice-and-comment requirements under the Administrative Procedure Act, industry groups and stakeholders have already challenged several Trump Administration rules (see, *e.g.*, the Drug Importation discussion above), and the incoming Biden Administration likely will spend much of 2021 assessing the impact of the Trump Administration's policies and deciding which, if any, it will carry forward.

As of this writing, President-Elect Biden has selected his picks for HHS secretary and director of the Centers for Disease Control and Prevention, but the FDA commissioner pick remains outstanding. It is unclear whether Biden will opt to retain Commissioner Hahn in the role for continuity during the early deployment of the COVID-19 vaccines, or whether he will opt for a leadership transition. The President-Elect's COVID-19 task force includes former FDA Commissioner David Kessler, who served under President George H.W. Bush and President Bill Clinton, and who remains a possible candidate. What is clear is that the national response to COVID-19 will remain a high priority for FDA, with additional vaccine authorizations likely and greater coordination with other agencies and international stakeholders.

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