SPECIAL REPORT

FDA 2019 YEAR IN REVIEW

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SPECIAL REPORT

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INTRODUCTION

The US Food and Drug Administration's (FDA's) 2019 regulatory agenda focused on digital health, streamlined product approvals, evolving evidentiary thresholds for product approvals and strategic enforcement. The agency continued to implement initiatives and mandates required by the 21st Century Cures Act (Cures Act) and it navigated leadership and staffing changes at many levels. Most notably, Commissioner Scott Gottlieb resigned on April 5. Norman Sharpless and Brett Giroir served as acting interim commissioners following Commissioner Gottlieb's resignation. On December 17, Congress swore in Commissioner Stephen Hahn, a radiation oncologist and former chief executive of MD Anderson Cancer Center.

This *Special Report* reviews notable actions that shaped FDA-regulated industries and products last year and it offers insight into the agency's 2020 priorities and expected actions.

DRUGS AND BIOLOGICS

DEVELOPMENTS IN 2019

Modernizing FDA's New Drugs Regulatory Program

As discussed in depth here, FDA made a series of announcements for a proposal to modernize new drug development consistent with the authorities Congress granted the agency under the Cures Act. The program is a major agency focus. Highlights of FDA's initial proposal included:

- Focusing on recruiting talent across disciplines
- Building multidisciplinary teams for more efficient collaboration
- Prioritizing operational excellence through a single and consistent review process
- Improving knowledge management through enhancements to information technology and honed expertise within review divisions
- Emphasizing safety and risk-benefit analysis before and after approval
- Incorporating the patient voice into product development.

The Center for Drug Evaluation and Research's (CDER's) other oversight priorities include overseeing 503B outsourcing facilities' drug compounding activities and other multi-state, large-volume distribution of compounded drugs; continuing to develop opioid policies that support substance use-disorder prevention; and continuing to develop its biosimilars program.

Drugs and Biologics Guidance

FDA issued its Qualification Process for Drug Development Tools Guidance for Industry and FDA Staff, as required under section 3011 of the Cures Act. The guidance describes FDA's current thinking on taxonomy for biomarkers and other drug development tools (DDTs) and the voluntary process for qualifying DDTs to support product approval or licensure. DDTs can include biomarkers used for clinical trial

development; clinical outcome assessments used to assess the clinical benefit of a product; or other analytical methods, animal models or measures that can aid in drug development or regulatory review. The Cures Act added new provisions in section 507 of the Federal Food, Drug and Cosmetic Act (FDCA) with respect to the processes for using and qualifying DDTs. FDA believes that having qualified DDTs that are available for use by many different sponsors in different drug development contexts will help optimize and in some cases expedite product development and FDA's review.

"Qualifying" a DDT means that, within the stated context of use (COU), FDA can rely upon the DDT to have a specific interpretation and application in drug development and regulatory review.

Requestors seeking qualification must follow a three-stage process by submitting a letter of intent, a qualification plan and a full qualification package. However, drug makers may use unqualified DDTs (or DDTs qualified for a different COU), when appropriate, after seeking the agreement of the appropriate drug review division.

In its Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products draft guidance, FDA complemented and expanded on the May 1998 guidance, Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products. The guidance describes, among other things, the evidence necessary to satisfy the substantial evidence standard in different circumstances, including for products that address life-threatening or severely debilitating diseases, rare disease or instances where human clinical trials are not ethical or feasible. The guidance also reflects the agency's ongoing efforts to be flexible in the amount and type of evidence necessary where it does not adversely affect patient safety.

The Patient-Focused Drug Development: Methods to Identify What Is Important to Patients Guidance for Industry, Food and Drug Administration Staff and Other Stakeholders draft guidance describes how to collect and submit patient experience data to support product approval and FDA review. This is the second of four in a series of patient-focused drug development guidance documents required under the Cures Act. In this guidance, FDA focused on approaches to identify what is most important to patients with respect to their experience as it relates to burden of disease and burden of treatment. The agency described three research methods to characterize these endpoints: qualitative research (*e.g.*, interviews and focus groups), quantitative research (*e.g.*, surveys) and mixed-method research (*i.e.*, those that combine qualitative and quantitative research). The previously released guidance in this series, entitled Patient-Focused Drug Development: Collecting Comprehensive and Representative Input draft guidance, was published in June 2018 and addressed methods to collect patient experience data that are accurate and representative of the intended patient population. The two forthcoming guidance documents will focus on:

- Approaches to identify and develop methods to measure impacts in clinical trials

- Methods, standards and technologies to collect and analyze clinical outcome assessment data for regulatory decision-making.

The Development of Therapeutic Protein Biosimilars: Comparative Analytical Assessment and Other Quality-Related Considerations Guidance for Industry draft guidance replaced a 2015 guidance on quality considerations for demonstrating biosimilarity as well as a 2017 draft guidance on statistical approaches to evaluating biosimilarity. FDA discussed its recommendations on the design and evaluation of comparative analytical studies intended to support biosimilarity and recommendations on the scientific and technical information for the chemistry, manufacturing and controls (CMC) portion of a biosimilar marketing application. Factors sponsors should consider in performing comparative analytical assessments include the expression system, manufacturing process, physiochemical properties, functional activities, target binding, impurities, the reference product and reference standards, the finished drug product and product stability.

In May, FDA issued its long-awaited Considerations in Demonstrating Interchangeability With a Reference Product Guidance for Industry to provide clarity for developers that want to demonstrate that their biological product meets the statutory standard for "interchangeability." "Interchangeability" means that the product is suitable for substitution without the involvement of the prescriber (*e.g.*, automatic substitution by a pharmacy would be permissible) because it can be expected to produce the same clinical result as the reference product in any given product, similar to how generic drugs may be substituted for name brand drugs. Patients must also be able to switch between the interchangeable product and reference product without additional risks with respect to safety or diminished efficacy. The guidance outlines scientific considerations in demonstrating interchangeability with a reference product (*e.g.*, product complexity, product-specific risks) and explains scientific recommendations for an application or supplement for such a product (*e.g.*, considerations for switching studies to assess the risk of alternating or switching between the reference product and the proposed interchangeable product).

To date, none of the agency's 26 biosimilars approvals have been for an "interchangeable" biosimilar. Acting Commissioner Sharpless issued a statement in May highlighting the importance of providing an approval pathway for interchangeable products in order to increase patient access to treatments and potentially lowering healthcare costs through competition.

Priority Review Vouchers

In 2019, FDA issued a record 10 priority review vouchers (PRVs): five for rare pediatric diseases, four for neglected tropical diseases and one for a material threat medical countermeasure. PRVs can be used to accelerate approval of drug products, as FDA has six months to review and come to a decision on an application for which the sponsor uses a PRV. A PRV may be used by the sponsor that receives it or may be sold to another sponsor that can use it for an application for *any* drug product. The sale of a PRV can generate significant revenues (typically millions of dollars) for a PRV holder. Despite public misgivings about the use or "abuse" of PRVs, it appears that the PRV program has promoted significant research and development of drugs for rare and neglected diseases as originally conceived. In order to obtain a PRV, the original sponsor must develop a drug that fits within the criteria for that particular type of PRV (rare pediatric disease, neglected tropical disease or material threat medical countermeasure). The incentive appears to

have accelerated the availability of new treatments for neglected tropical diseases in particular—including malaria, Chagas disease, leishmaniasis, onchocerciasis (river blindness) and pulmonary multi-drug resistant tuberculosis—and coupled with post-marketing access plans, these treatments are becoming increasingly affordable.

In July, FDA released a revised draft guidance, entitled Rare Pediatric Disease Priority Review Vouchers: Guidance for Industry, which provides a description of the eligibility requirements for a rare pediatric disease priority review voucher, the rare pediatric disease designation process and examples to illustrate how the agency makes determinations. The draft guidance explains that the rare pediatric disease PRV sunsets on September 30, 2020. After that date, FDA may not award any vouchers, "unless the application is for a drug that was designated as a drug for a rare pediatric disease by September 30, 2020." Additionally, in September FDA announced the 2020 fee rate for all three priority review programs. This fee rate, paid in addition to the normal Prescription Drug User Fee Act fees, will be $2,167,116 for FY 2020.

Drug Pricing

FDA has taken several steps to address drug competition and pricing. The agency's Drug Competition Action Plan aims to:

- Streamline the review of abbreviated new drug applications (ANDAs) to increase efficiency, effectiveness and output of generic drug approvals in order to foster competition with expensive brand name products
- Maximize scientific and regulatory clarity with respect to the pathway for generics of complex products
- Close loopholes that allow brand name drug makers to "thwart" generic competition.

On May 10, the US Department of Health and Human Services (HHS) published a final rule requiring direct-to-consumer television advertisements (including broadcast, cable, streaming and satellite) of prescription drugs and biologics covered by Medicare or Medicaid to include the wholesale acquisition cost (WAC) or "list price" for a 30-day supply of any product that costs more than $35 a month. The rule was to go into effect on July 9, but on July 8, the US District Court for the District of Columbia issued an order granting Amgen Inc., Merck & Co. and Eli Lilly & Co.'s motion to stay the rule. Plaintiffs argued that the rule exceeded HHS's authority because Congress neither expressly nor impliedly granted HHS power to regulate drug marketing and that the rule is compelled speech that violates the First Amendment. The court found that HHS lacked the statutory authority to adopt the rule and did not reach the First Amendment question. On August 21, HHS filed a notice of appeal

in response to the district court's July 8 order granting plaintiffs' motion to stay the final rule. The US Court of Appeals for the District of Columbia Circuit will review the case.

On December 23, FDA issued a proposed rule and draft guidance to implement and facilitate two pathways for the legal importation of certain drugs. The proposed rule, Importation of Prescription Drugs, 84 Fed. Reg. 70,796, would allow importation of certain prescription drugs from Canada. If finalized as proposed, states or other non-federal governmental entities could submit importation program proposals to FDA for review and authorization. Such programs could be co-sponsored by a pharmacist, wholesaler or other state or non-federal governmental entity and would require applicants to explain why the program would be expected to result in a significant reduction in the cost of covered drug products to the US consumer. The draft guidance, entitled Importation of Certain FDA-Approved Human Prescription Drugs, Including Biological Products, under Section 801(d)(1)(B) of the Federal Food, Drug and Cosmetic Act, describes procedures to obtain a National Drug Code (NDC) for a multi-market approved (MMA) drug product—a product that is FDA-approved but authorized for sale in a foreign country in which the drugs were originally intended to the marketed—that is imported into the United States in compliance with the FDCA. The guidance also describes recommended labeling changes and the process of registering and listing the drugs in the United States. The guidance is intended to provide an additional avenue through which drugs could be sold at a lower cost in the United States.

Homeopathic Drug

Under FDA's Drug Products Labeled as Homeopathic: Guidance for FDA Staff and Industry draft guidance, the agency intends to prioritize enforcement and regulatory actions with respect to premarket approval requirements involving homeopathic drug products that are marketed without the required FDA approval and fall within the following categories:

- With reported safety concerns
- That contain or purport to contain ingredients associated with potentially significant safety concerns
- For routes of administration other than oral or topical, *e.g.*, for use as an injection or taken nasally
- That claim to treat or prevent serious and/or life-threatening diseases and conditions, such as cancer
- That are marketed to vulnerable populations, including children, pregnant women and the elderly
- With significant quality issues.

Until the draft guidance is finalized, FDA intends to apply its general approach to prioritizing risk-based regulatory and enforcement action. The draft guidance suggests that FDA will enforce new drug approval requirements for injectable or oral drugs that present safety issues, target vulnerable populations or include population health management data. FDA may continue to exercise enforcement discretion for other homeopathic drugs that implicate some but not all of the criteria set forth in the agency's draft guidance.

FDA withdrew its 1988 Compliance Policy Guide (CPG) 400.40, Conditions Under Which Homeopathic Drugs May be Marketed, on October 24. The CPG provided guidance on the regulation of over-the-counter and prescription homeopathic drugs and

described conditions under which homeopathic drugs could be marketed in the United States.

The CPG reflected FDA's intent to prioritize enforcement where products raised significant quality concerns or other health risks.

The withdrawal of the CPG and issuance of the new draft guidance followed an apparent uptick in the number of inspections of homeopathic drug manufacturers and related Warning Letters involving alleged current Good Manufacturing Practice (cGMP) violations for homeopathic drugs.

LOOKING AHEAD TO 2020

FDA's activities in 2019 suggest that the agency may renew its focus on safety and quality issues for homeopathic drugs and other OTC products.

Further, the changes to the PRV user fee rates may spur an increase in the number of PRVs and increased availability of PRVs on the market. The new fee rate for the priority review programs represents a significant drop from the FY 2019 fee of $2,457,140 and is the lowest since FY 2011. As FDA issues more PRVs and they become more readily available, we also may see sponsors selling these vouchers to other sponsors at lower prices than in previous years.

The finalized Considerations in Demonstrating Interchangeability With a Reference Product guidance may yield the first biologic product approved as interchangeable with its reference product. In light of the national drug pricing discussion, FDA may face pressure to prioritize review and approval of such product applications. Additionally, effective March 23, 2020, the Biologics Price Competition and Innovation Act of 2009 (BPCIA) requires that a marketing application for a "biological product" that previously could have been submitted under section 505 of the FDCA must be submitted as a biologics license application (BLA) under section 351 of the Public Health Service Act (PHS Act) and thus be subject to BPCIA biosimilar competition.

COMBINATION PRODUCTS

DEVELOPMENTS IN 2019

On February 5, the agency released a Principles of Premarket Pathways for Combination Products draft guidance, which provides FDA's current thinking on principles for premarket review of combination products. The draft guidance is part of FDA's efforts to implement section 3038 of the Cures Act, which amended section 503(g) of the FDCA, the principal section of the FDCA addressing combination products, to address their development and premarket review.

The guidance aims to address the complexities of developing products that combine a drug or a biologic with a device by providing clarity regarding the premarket review process for combination products, including how to determine which type of application is appropriate for the products.

While the draft guidance does not contain any departures from the agency's guidance on combination products following the enactment of the Cures Act, it aggregates much of the guidance into a single document. For example, FDA emphasized that a single premarket application containing enough data and information to enable a robust evaluation of each constituent part is generally appropriate for a combination product. However, the agency also emphasized the fact that the data and information necessary to address safety and effectiveness questions related to the non-lead constituent part may differ from that required to obtain marketing authorization for that article as a standalone product. Further, although the draft guidance does not explicitly reference digital products, former Commissioner Gottlieb acknowledged the particular challenges of developing combination products containing digital health technologies and the need to enhance clarity, predictability, efficiency and consistency of premarket review for these and other combination products.

FDA intends to streamline the submission process through the single application process, providing a clearer and more efficient process for the review of combination products consistent with the goals of section 3038 of the Cures Act. In some cases, premarket review can be streamlined when the sponsor is legally authorized to rely on FDA's prior findings of safety or effectiveness or substantial equivalence with respect to an approved or cleared constituent part or the sponsor has a right of reference for another sponsor's data. In those cases, FDA generally should only require additional data and information that is required to address additional questions of safety and effectiveness that arise from the proposed use or function of the constituent parts in the combination product. Occasionally, a single application will not be appropriate and may require consultation and alignment between the lead and non-lead centers. Separate applications may be necessary when:

- The sponsor is applying for Hatch-Waxman exclusivities.
- The constituent parts of the combination product are separate and complex (such as drugs and implantable delivery pumps).
- The constituent parts have uses beyond the combination products (such as single-dose drugs and reusable delivery devices used in the delivery of other drugs).
- Labeling revisions are required for a constituent part that is already approved for a use that does not include the combination product indication.

On December 18, FDA issued the Bridging for Drug-Device and Biologic-Device Combination Products draft guidance. Bridging is the process of establishing

the scientific relevance of information developed in an earlier phase of the development program or another development program to support the combination product for which an applicant is seeking approval. The guidance describes the agency's thinking on how to approach bridging, using a stepwise framework, in new drug applications (NDAs) or BLAs for drug-device and biologic-device single entity or co-packaged combination products. Once the applicant establishes the relevance of earlier information (*i.e.*, bridges the information) to its product, it can leverage the information to streamline its development program. For certain types of applications, bridging may require that the applicant own the information or have a right of reference.

In July, FDA issued the Postmarketing Safety Reporting for Combination Products: Guidance for Industry and FDA Staff, which clarifies how to comply with the 2016 final rule, Postmarketing Safety Reporting for Combination Products. In the final rule, FDA described the postmarketing safety reporting requirements that apply when two or more different types of regulated medical products (drugs, devices or biological products, which are referred to as "constituent parts" of a combination product) comprise a combination product and the combination product or its constituent parts have received FDA marketing authorization. The guidance outlines how to submit reports and avoid duplication and explains recordkeeping requirements. FDA also indicated that it will enforce the additional constituent part-based requirements in July 2020 for most combination products, except vaccine combination products, for which it will enforce the requirements in January 2021.

LOOKING AHEAD TO 2020

As mentioned, starting July 31, 2020, FDA intends to enforce additional constituent part-based postmarket safety reporting requirements and recordkeeping requirements for combination product applicants using the FDA Adverse Event Reporting System (FAERS) and Electronic Medical Device Reporting System (eMDR) to report Individual Case Safety Reports (ICSRs). Comments to the Bridging for Drug-Device and Biologic-Device Combination Products draft guidance should be submitted to the agency by February 18, 2020, to ensure that FDA considers the comments before it starts the process to finalize the guidance.

DRUG QUALITY SECURITY ACT IMPLEMENTATION

DEVELOPMENTS IN 2019

Compounding

In February, FDA finalized its list of bulk drug substances that can be used to compound drugs under section 503A of the FDCA (503A bulks list), including six bulk drug substances and expressly excluding four bulk drug substances. The agency issued a Section 503A Bulks List Final Rule Questions and Answers; Small Entity Compliance Guide, which contains a question-and-answer format addressing common questions about the 503A bulks list. FDA clarified that it is evaluating drug substances for addition to the 503A bulks list on a rolling basis and that it intends to publish additional notice and comment rulemaking to address whether additional substances should be included on the list. FDA also

noted that compounders who wish to use one of the four bulk drug substances that it excluded should submit a citizen petition explaining how their use of the substance differs from the use the agency previously evaluated when considering the substance for the 503A bulks list.

FDA also finalized its list of bulk substances that can be used to compound drugs under section 503B of the FDCA (503B bulks list), excluding three nominated substances. In its correspondence guidance, Evaluation of Bulk Drug Substances Nominated for Use in Compounding Under Section 503B of the Federal Food, Drug and Cosmetic Act, FDA explained its thinking regarding the meaning of the phrase "bulk drug substances for which there is a clinical need" as it is used in section 503B. Specifically, a substance may be included on the 503B bulks list if (1) there is a clinical need for an outsourcing facility to compound a drug product and (2) the drug product must be compounded using the bulk drug substance.

If the bulk drug is a part of an FDA-approved drug product, FDA's Part 1 analysis asks:

- Whether there is basis to conclude, for each FDA-approved product that includes the nominated bulk drug substance, that (1) an attribute of the FDA-approved drug product makes it medically unsuitable to treat certain patients for a condition that FDA has identified for evaluation and (2) the drug product proposed to be compounded is intended to address that attribute
- Whether there is a basis to conclude that the drug product proposed to be compounded must be produced from a bulk drug substance rather than from an FDA-approved drug product.

If the answer to both of the above questions is "no" (or the bulk drug is *not* part of an FDA-approved drug product), FDA intends to apply a balancing test of four factors for Part 2 to assess whether a product should be included on the 503B bulks list:

- The physical and chemical characterization of the substance
- Any safety issues raised by the use of the substance in compounding
- The available evidence of effectiveness or lack of effectiveness of a drug product compounded with the substance, if any such evidence exists
- Current and historical use of the substance in compounded drug products, including information about the medical condition(s) that the substance has been used to treat and any references in peer-reviewed medical literature.

On April 3, former Commissioner Gottlieb stated that FDA would revise the current Hospital and Health System Compounding Under the Federal Food, Drug and Cosmetic Act: Guidance for Industry draft guidance "to provide further clarification on how the FDA intends to apply section 503A of the [FDCA] to drugs compounded at these facilities." He stated that the revisions would "provide guidance for hospital or health system pharmacies that might be considering registering as an outsourcing facility under section 503B," given the unique considerations for hospitals and health systems, both in terms of sophistication and supply needs. In its 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 for Industry guidance, FDA noted that it "is considering the applicability of the policies described in this guidance to hospitals and health systems and intends to address

these issues in separate guidance or rulemaking. FDA regards a health system as collection of hospitals that are owned and operated by the same entity and that share access to databases with drug order information for their patients." There does not seem to have been any movement on this issue since April, however.

On November 19, FDA issued a new draft guidance, entitled Compounding Animal Drugs from Bulk Drug Substances: Guidance for Industry, intended to provide guidance for the limited circumstances in which an animal drug may be compounded from bulk drug substances. On the same day, FDA also announced that it is accepting nominations to List of Bulk Drug Substances for Compounding Office Stock Drugs for Use in Nonfood-Producing Animals or Antidotes for Food-Producing Animals. FDA stated that once it finalizes the draft guidance, it does not intend to take enforcement action against a state-licensed pharmacy or state-licensed veterinarian using the bulk drug substances on the list to compound the certain drug preparations for office stock or antidotes.

In June, the United States Pharmacopeia (USP) published new and revised standards updating USP General Chapters on compounding nonsterile medicines (USP <795> Pharmaceutical Compounding – Nonsterile Preparations), compounding sterile medicines (USP <797> Pharmaceutical Compounding – Sterile Preparations) and new standards for compounding radiopharmaceutical drugs (USP <825> Radiopharmaceuticals – Preparations, Compounding, Dispensing, Repackaging). The effective date for the new and revised standards, as well as the USP General Chapter <800> Hazardous Drugs – Handling in Healthcare Settings, was December 1, 2019.

LOOKING AHEAD TO 2020

The comment period for the draft guidance entitled Compounding Animal Drugs from Bulk Drug Substances: Guidance for Industry closes on February 18, 2020. Additionally, FDA's Compounding Quality Center of Excellence, which is focused on improving the quality of compounded drugs, will host a conference in September 2020 in Dallas, Texas, to

bring the compounding industry, state and federal regulators and other stakeholders together to discuss compounding topics. The Center of Excellence also will provide in-person and online trainings for outsourcing facility staff related to cGMP requirements and policies in 2020. The FY 2020 budget includes $13.5 million to "catalyze development of policies and regulations for outsourcing facilities, including advancement of the list of bulk drug substances that outsourcing facilities may use in compounding and CGMP guidance and regulation specific to outsourcing facilities." We can expect to see developments from FDA on these matters.

THE DRUG SUPPLY CHAIN SECURITY ACT

DEVELOPMENTS IN 2019

On July 3, FDA issued a notice in the *Federal Register* reopening the comment period for the notices published therein on April 15, 2016 and April 28, 2017, requesting comments regarding "issues related to utilizing the product identifier for product tracing, improving the technical capabilities of the supply chain and identifying system attributes that are necessary to implement the requirements established under the Drug Supply Chain Security Act (DSCSA)."

In September, FDA issued a final guidance document, entitled Wholesale Distributor Verification Requirement for Saleable Returned Drug Product—Compliance Policy. This guidance document clarified that, under section 582(c)(4)(D) of the FDCA, wholesalers are required to verify the product identifier, including the standardized numerical identifier, on each sealed homogeneous case of saleable returned product or, if such product is not in a sealed homogeneous case, on each package of saleable returned product, prior to further distributing such returned product. FDA further delayed implementation of this compliance requirement for one year, until November 27, 2020.

LOOKING AHEAD TO 2020

Starting November 27, 2020, wholesale distributors must verify the product identifier prior to further distributing returned packages or sealed homogenous case of product. Also starting in November, dispensers must also only accept products that contain the required product identifier.

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.

DIGITAL HEALTH

DEVELOPMENTS IN 2019

As discussed in depth here, FDA recently released six guidance documents—five final guidance documents and a re-issued draft guidance document—as part of the agency's continued focus on updating the regulatory stance on software as a medical device and other digital health products. The updated guidance documents reflect the need for a more flexible, risk-based approach to regulation that accommodates a rapidly evolving technological landscape.

In April, FDA issued a white paper, Proposed Regulatory Framework for Modifications to Artificial Intelligence/Machine Learning (AI/ML)-Based Software as a Medical Device, announcing steps FDA will take to consider a new regulatory framework to promote the development of safe and effective medical devices that use advanced AI algorithms. AI and specifically ML, are "techniques used to design and train software algorithms to learn from and act on data."

FDA's proposed approach would allow modifications to algorithms to be made from real-world learning and adaptation that accommodates the iterative nature of AI products while ensuring FDA's standards for safety and effectiveness are maintained.

The white paper is discussed in detail here.

As part of its digital health software precertification (Pre-Cert) program, further described here, FDA sought test cases from software organizations planning to submit a *de novo* request or 510(k) submission for software as a medical device (SaMD) in 2019 or shortly thereafter to meet the goals of its 2019 Test Plan.

LOOKING AHEAD TO 2020

FDA likely will continue to focus on digital health initiatives in 2020. In terms of the digital health software Pre-Cert program, FDA intends to select test case participants that best match particular selection qualities. One of these qualities is that the company plans "to submit a De Novo Request or 510(k) submission for a software product that meets the definition of a device . . . prior to June 2020."

FDA also provided lists of prioritized guidance documents that the Center for Devices and Radiological Health (CDRH) intends to publish in FY 2020 and guidance documents that CDRH intends to publish as guidance development resources permit in FY 2020. Of the prioritized guidance documents, digital health related final guidance topics include:

- Safer Technologies Program for Medical Devices
- Clinical Decision Support Software
- Multiple Function Device Products: Policy and Considerations.

Draft guidance topics include:

- Content of Premarket Submissions for Management of Cybersecurity in Medical Devices
- Computer Software Assurance for Manufacturing, Operations and Quality System Software.

The agency has also planned a public workshop, Evolving Role of Artificial Intelligence in Radiological Imaging, to take place on February 25 to 26, 2020, focused on discussing emerging applications of "AI in radiological imaging, including devices intended to automate the diagnostic radiology workflow as well as guided image acquisition."

MEDICAL DEVICES

DEVELOPMENTS IN 2019

FDA continued to focus on optimizing and adapting device regulatory process to keep pace with the speed of innovation while balancing associated safety and performance risk. In so doing, the agency considered several factors, including greater input and collaboration with industry stakeholders and the impact of regulatory "uncertainty" in characterizing risks and benefits of medical devices.

In August, the agency issued its final guidance, Consideration of Uncertainty in Making Benefit-Risk Determinations in Medical Device Premarket Approvals, De Novo Classifications and Humanitarian Device Exemptions. The guidance describes a methodical approach for the consideration of "uncertainty" when evaluating the benefits and risks of a medical device. This consideration of uncertainty will help the agency to determine when it may be appropriate to shift certain data collection requirements from the premarket to the postmarket phase for premarket approval, *de novo* and humanitarian device exemption (HDE) devices. In some ways, the guidance addresses long-standing criticisms regarding the statutory framework for premarket review of medical devices, most recently highlighted in documentaries and related media commentaries criticizing the alleged lack of robust safety and effectiveness data for certain devices. The agency acknowledged that it is not possible to have all the information regarding the long-term safety and performance of a medical device during the initial premarket review. Prior FDA guidance documents listed "uncertainty" as a factor in benefit-risk decisions, but this guidance reflects the agency's attempt to clarify how it will determine what level of uncertainty is appropriate or acceptable for a given device.

FDA will consider several factors in benefit-risk decisions, including but not limited to:

- Whether the probable benefits are greater than those of the standard of care or approved or cleared alternative treatments or diagnostics
- The extent of the probable risks of the device, taking into account the severity, type, number, rates, probability and duration of those risks
- The extent of uncertainty regarding the benefit-risk profile of approved or cleared alternative treatments or diagnostics or the standard of care (*e.g.*, the strength of the evidence supporting the alternative treatment or diagnostic)
- Patients' perspectives on appropriate uncertainty about the probable benefits and risks of the device, if available

> The guidance states that FDA's consideration of these factors will be "pragmatic, context-dependent (considered in the context of the relevant non-clinical and/or clinical information about the device, e.g., information about the device's mechanism of action and modes of failure) and consistent with FDA's statutory and regulatory authorities and requirements."

The guidance signals the continued importance of real world evidence and patient input in medical device development and FDA's continued efforts to adopt practical regulatory strategies.

FDA is collaborating with stakeholders to build the National Evaluation System for health Technology (NEST) to "more efficiently generate better evidence for medical device evaluation and regulatory decision-making" across the total product lifecycle of devices. According to CDRH Director Jeffrey Shuren, NEST "should serve as a catalyst to support the timely and reliable development of [real world evidence]" through partnerships with a range of stakeholders that provide data and analytics solutions, setting data quality and methods standards and offering value."

The agency also continued to focus on streamlining pathways to market for new devices. The Safety and Performance Based Pathway: Guidance for Industry and Food and Drug Administration describes the Safety and Performance Based Pathway, an optional pathway for certain, well-understood device types, through which a submitter may demonstrate that a new device meets FDA-identified performance criteria to show the device is as safe and effective as a legally marketed device. The guidance builds on the Abbreviated 510(k) (described in our FDA 2018 Year in Review), explaining how substantial equivalence may be demonstrated in a less burdensome way for certain device types. The amount and type of information necessary to support a finding of substantial equivalence from the guidance is below:

TYPE OF PERFORMANCE CRITERIA AND METHODOLOGY		SUBMISSION SHOULD INCLUDE
Performance Criteria	*Testing Methodology*	
FDA-recognized consensus standard	FDA-recognized consensus standard	Declaration of Conformity
FDA-established	FDA-recognized consensus standard	Results Summary and Declaration of Conformity
FDA-established	FDA-recommended or specified	Results Summary and Testing Protocol
FDA-established	None recommended or specified or alternative to FDA-specified methodology used	Complete Test Report

In the future, FDA intends to maintain a list of device types appropriate for the Safety and Performance Based Pathway on the FDA website. FDA expects to operationalize this pathway once the first device types and applicable performance criteria have been identified and final guidance documents have been published.

The five types of devices FDA has preliminarily proposed for this pathway include spinal plating systems, cutaneous electrodes for recording purposes, conventional Foley catheters, orthopedic non-spinal metallic bone screws and washers and magnetic resonance coils.

FDA issued a number of guidance documents regarding premarket approval applications, most notably:

- 30-Day Notices, 135-Day Premarket Approval (PMA) Supplements and 75-Day Humanitarian Device Exemption (HDE) Supplements for Manufacturing Method or Process Changes: Guidance for Industry and FDA Staff, which provides guidance on the changes FDA believes may qualify for the 30-day notice (when altering a manufacturing procedure or method). For example, changes to sterilization process parameters within the same facility, automating existing procedures, joining processes, updates to cleaning methods, changes to manufacturing materials, changes to a facility's environmental conditions, changes in suppliers, changes in quality control testing or changes to the type of manufacturing process may qualify for a 30-day notice. Changes that do not qualify for a 30-day notice may include changes in the manufacturing or sterilization site of a finished device, device design or performance specifications, material specifications or device operating software.
- Acceptance and Filing Reviews for Premarket Approval Applications (PMAs): Guidance for Industry and Food and Drug Administration Staff, in which the agency clarified that submitters seeking action on a combination product must identify the product as such and per amended section 503(g)(5) of the FDCA under the Cures Act, device-led and device-drug combination products must include the following:
  - A patent certification or the statement described in section 505(b)(2) of the FDCA (*i.e.*, a certification that, in the opinion of the applicant and to the best of the applicant's knowledge, there is no patent that claims the drug, such patent has expired, that such patent is invalid or the existing patent is not for the same method of use for which the applicant is seeking approval)
  - Notice as described in section 505(b)(3) of the FDCA (*i.e.*, that an applicant has submitted an application before the expiration of the patent referred to in the prior certification and a detailed statement of the factual and legal basis for why the patient is invalid or will not be infringed) if the combination product contains an approved drug as a constituent part.

- A corresponding Refuse to Accept Policy for 510(k)s guidance document.
- Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications: Guidance for Industry and Food and Drug Administration Staff, which describes the process FDA follows for considering acceptable levels of uncertainty about a device in making benefit-risk determinations for premarket applications, *de novo* classification requests or humanitarian device exemption applications. In addition to assessing the extent of probable benefit(s) (*e.g.*, type, magnitude, probability, duration) and the probable risk(s) or harm(s) (*e.g.*, severity, types, number, rates of harmful events, probability, duration, risk from false-positive or false-negative results for diagnostics), FDA considers other facts, such as degree of certainty regarding risks and benefits, patient-centric assessments and patient-reported outcomes, the characterization of the disease (*i.e.*, the condition, its clinical manifestation, how it affects patients, the history and progression of the disease), patient perspectives, the availability of alternative treatments or diagnostics, risk mitigations, postmarket data and the presence of novel technology addressing unmet medical need.

Under the Medical Device User Fee Amendments of 2012 (MDUFA III), FDA committed to identifying low-risk medical devices to exempt from premarket notification requirements. Congress also gave FDA authority under the Cures Act to exempt certain class I and II reserved medical devices from premarket notification on a periodic basis. Thus, FDA identified and formally exempted certain unclassified medical devices, which it intends to classify into class I or II, from premarket notification requirements under its Intent to Exempt Certain Unclassified Medical Devices from Premarket Notification Requirements: Guidance for Industry and Food and Drug Administration Staff. These devices remain subject to other requirements, such as registration and listing, labeling, Quality System Regulation and Medical Device Reporting. Note that a pre-amendments device is a device that was on the market prior to the enactment of the Medical Device Amendments to the FDCA on May 28, 1976. An "unclassified device" is a pre-amendments device for which a classification regulation has not been promulgated. Unclassified devices generally require submission of a 510(k) premarket notification to CDRH. A "not-classified" device, on the other hand, is a post-amendments device for which the agency has not yet reviewed or made a final decision on a marketing application.

LOOKING AHEAD TO 2020

FDA's regulatory priorities for medical devices in 2020 reflect a continued focus on updating various older guidance documents and implementing remaining Cures Act mandates across program areas. Below is a complete list of prioritized guidance documents that CDRH intends to publish in FY 2020:

Final Guidance Topics

- Select Updates for Recommendations for Clinical Laboratory Improvement Amendments of 1988 (CLIA) Waiver Applications for Manufacturers of In Vitro Diagnostic Devices
- Recommendations for Dual 510(k) and Clinical Laboratory Improvement Amendments Waiver by Application Studies
- 510(k) Third Party Review Program
- Safer Technologies Program for Medical Devices

- Process to Request a Review of FDA's Decision Not to Issue Certain Export Certificates for Devices
- Labeling Recommendations for Surgical Staplers
- Nonbinding Feedback After Certain Food and Drug Administration Inspections of Device Establishments
- The Accreditation Scheme for Conformity Assessment (ASCA) Pilot Program
- Recognition and Withdrawal of Voluntary Consensus Standards
- Clinical Decision Support Software
- Multiple Function Device Products: Policy and Considerations
- Device-Specific Criteria Guidance(s) for Safety and Performance Based Pathway Implementation

Draft Guidance Topics

- Labeling and Informed Decision Checklist for Breast Implants
- Content of Premarket Submissions for Management of Cybersecurity in Medical Devices
- Distinguishing between Medical Device Servicing and Remanufacturing
- Computer Software Assurance for Manufacturing, Operations and Quality System Software
- Procedures for Handling Post-Approval Studies Imposed by PMA Order (revision)
- Postmarket Surveillance Under Section 522 of the Federal Food, Drug and Cosmetic Act (revision)
- Unique Device Identification: Policy on Enforcement of GUDID Submission Requirements for Certain Class I Devices
- Pragmatic Generation of Validity Evidence for Patient-Reported Outcome Measures Used in Medical Device Submissions

Revised AdvaMed Code

Effective January 1, 2020, the revised Advanced Medical Technology Association Code of Ethics on Interactions with U.S. Health Care Professionals (AdvaMed Code) contains new provisions and revisions to existing language that touch on many common industry activities. Changes include express reference to digital health and software technologies as covered by the Code, clarifications on topics such as "legitimate need" for consulting services, development of fair market value methodologies and guardrails around research grants and charitable donations. Changes in the 2020 AdvaMed Code are discussed in detail here.

LABORATORY-DEVELOPED TESTS AND PRECISION MEDICINE

DEVELOPMENTS IN 2019

FDA continued to chip away at its longstanding enforcement discretion for laboratory-developed tests (LDTs) when it informed certain laboratories offering pharmacogenomic tests (*i.e.*, genetic tests that claim to predict a patient's response to specific medications) that such tests may be subject to FDA regulation as medical devices. To date, the agency has not articulated a clear standard regarding the type(s) of claims that will cause a test to fall outside of the agency's enforcement discretion. As a result, laboratories offering pharmacogenomic tests took a variety of approaches—including modifying test

reports to remove references to specific medications or classes of medications, removing references to drugs altogether or ceasing testing operations—to reduce the risk of agency enforcement action.

LOOKING AHEAD TO 2020

As in 2019, Congress is actively drafting legislation, currently called the Verifying Accurate Leading-edge IVCT Development (VALID) Act, that would clarify and substantially revise FDA's role in the oversight of *in vitro* diagnostics (including LDTs). While FDA and most stakeholders agree on the need for changes to the regulatory framework for diagnostics, considerable substantive work remains regarding the details of such a framework. Interested observers should expect to see updated draft legislative text—if not legislation officially introduced in Congress—as early as the first quarter of 2020.

FOOD AND DIETARY SUPPLEMENTS

DEVELOPMENTS IN 2019

The Voluntary Qualified Importer Program (VQIP) is a voluntary, fee-based program required under the Food Safety Modernization Act (FSMA) (Pub. L. 111-353). The VQIP provides expedited review and import entry of human and animal foods into the United States for participating importers who have demonstrated a high level of control over the safety and security of their supply chains. The Guidance for Industry: FDA's Voluntary Qualified Importer Program outlines the benefits VQIP importers can expect to receive, eligibility criteria for participation, instructions for completing a VQIP application, conditions that may result in revocation of participation and criteria for reinstatement following

revocation. 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.

TOBACCO

DEVELOPMENTS IN 2019

In March, FDA issued a Modifications to Compliance Policy for Certain Deemed Tobacco Products Draft Guidance. The guidance described FDA's plans to prioritize enforcement actions for electronic nicotine delivery systems (ENDS) products that are offered for sale in ways that pose a greater risk for minors or those marketed without an approved premarket tobacco product application (PMTA). In November, the Trump Administration appeared to abruptly reverse course, abandoning its advanced notice of proposed rulemaking for the Regulation of Flavors in Tobacco Products and declining to issue a ban on candy, fruit and mint flavored tobacco products. However, on January 2, 2020, FDA issued its Enforcement Priorities for Electronic Nicotine Delivery System (ENDS) and Other Deemed Products on the Market Without Premarket Authorization guidance, announcing that the agency intends to ban any flavored, cartridge-based ENDS product other than tobacco or menthol flavored ENDS products beginning 30 days after FDA issued the guidance (on or around February 1, 2020). The policy mirrors the statutory prohibition against flavored cigarettes other than tobacco or menthol and it appears to be a compromise with industry advocates who maintain that menthol-flavored ENDS products do not have the same youth appeal as, for example, fruit and candy flavors. The agency also intends to prioritize enforcement of any ENDS product that is offered for sale after May 12, 2020, for which the manufacturer has not submitted a PMTA.

A number of states and municipalities have also placed temporary or permanent bans on the sale of flavored or all ENDS products, such as e-cigarettes. On December 20, the president signed the "Tobacco 21" law into immediate effect as part of the Further Consolidated Appropriations Act, 2020. The law raises the minimum purchase age for tobacco products, including vaping products, to 21. The agency has six months to update its regulations to reflect the change.

FDA issued the Premarket Tobacco Product Applications and Recordkeeping Requirements proposed rule, which would require manufacturers to maintain records establishing that their tobacco products are legally marketed.

> The rule would require tobacco product manufacturers to maintain records regarding the legal marketing of grandfathered tobacco products and products that are exempt from the requirements of demonstrating substantial equivalence.

In addition, the rule proposes to require that PMTAs contain sufficient documentation to enable FDA to find whether:

- There is a showing that marketing of the new tobacco product would be appropriate for the protection of the public health
- The methods used in or the facilities and controls used for, the manufacture, processing or packing of the product conform to the requirements of section 906(e) of the FDCA
- The product labeling is not false or misleading in any particular.

FDA also issued a new proposed rule, Tobacco Products; Required Warnings for Cigarette Packages and Advertisements. FDA previously published a final rule in 2011 requiring health warnings with color graphics to accompany the required health warnings with text statements under the Family Smoking Prevention and Tobacco Control Act. However, several tobacco companies challenged the final rule, which the US Court of Appeals for the District of Columbia ultimately vacated in August 2012, holding it in violation of the First Amendment. In response, FDA undertook an extensive scientific, legal and regulatory analysis in support of the proposed health warnings. Following a lawsuit by several public health advocates, the US District Court for the District of Massachusetts ordered FDA to publish a new proposed rule and to issue a final rule in March 2020. However, the proposed effective date of the proposed rule is 15 months after the agency issues a final rule.

On December 17, FDA approved its first PMTAs on two cigarette products that contained a reduced amount of nicotine compared to typical commercial cigarettes. The agency has not completed its evaluation of the company's separate modified risk tobacco product (MRTP) applications or issued an MRTP order allowing the company to market the products as having reduced nicotine content. In October, FDA authorized its first modified risk orders for eight smokeless tobacco products, authorizing the manufacturer to market its smokeless tobacco products (specifically, snus) as presenting a "lower risk of mouth cancer, heart disease, lung cancer, stroke, emphysema and chronic bronchitis."

LOOKING AHEAD TO 2020

The agency will continue to face pressure from the public to regulate the vaping industry and, in particular, to address concerns regarding underage vaping. Manufacturers of all new tobacco products—products not commercially marketed in the United States prior to February 15, 2007—are required to submit PMTAs by May 11, 2020. FDA's decisions on these applications may significantly affect products deemed to be under FDA's authority in 2016 (*i.e.*, cigars, ENDS products, pipe tobacco and hookah tobacco). However, with the approval of the first MRTP orders, the industry may also see greater clarity regarding the "continuum of risk" and which products FDA regards as being less harmful or presenting lower risk to individual users and benefitting the population as a whole.

CANNABIS

DEVELOPMENTS IN 2019

In 2019, FDA worked to clarify and update its position regarding the use of cannabis and cannabis-derived compounds, such as cannabidiol (CBD), in FDA-regulated products after the passage of the Agricultural Improvement Act of 2018, Pub. Law 115-334 (2018 Farm Bill) (described in our FDA 2018 Year in Review).

FDA's regulatory responsibility with regard to these products includes scientific and regulatory support for research on potential uses of cannabis, the regulation of products (*e.g.* drugs, foods, dietary supplements and cosmetics) containing cannabis and cannabis-derived compounds and enforcement actions, as necessary, against cannabis related products that may pose health risks. Because the 2018 Farm Bill explicitly preserved FDA's regulatory authority under the FDCA and section 351 of the PHS Act over hemp and hemp-derived products, the FDA has steadily maintained that it will regulate these products like any other FDA-regulated product. However, to begin a dialogue with stakeholders and gather information regarding both the potential use and risks associated with cannabis products (most notably hemp-based CBD), FDA held a public hearing in May, entitled Scientific Data and Information about Products Containing Cannabis or Cannabis-Derived Compounds, "to obtain scientific data and information about the safety, manufacturing, product quality, marketing, labeling and sale of products containing cannabis or cannabis-derived compounds."

Use of Cannabis in FDA-Regulated Products

FDA has determined that it is illegal to sell a food in interstate commerce to which tetrahydrocannabinol (THC) or CBD, even hemp-based CBD, has been added. Under the relevant provision of the FDCA, it is unlawful to introduce any food into interstate commerce that contains a substance (such as THC or CBD) that is an active ingredient in an FDA-approved drug product or is the subject of an investigational new drug (IND) application that has gone into effect. Because FDA approved the prescription drugs that contain synthetic THC or CBD prior to the passage of the 2018 Farm Bill, FDA maintains that both THC and CBD meet this definition. In contrast, ingredients derived from parts of a cannabis plant that do not contain THC or CBD might be able to be added to food, such the hemp-seed-derived food ingredients FDA has determined to be generally recognized as safe (GRAS) (*i.e.*, hulled hemp seed, hemp seed protein powder and hemp seed oil). No health claims can be made for hemp-containing food products regardless of their source unless and until the proposed health claims undergo review by FDA through a petition process.

FDA has also determined that THC and CBD cannot be marketed as dietary supplements because these compounds are active ingredients in FDA-approved drugs. However, a chemical compound other than THC and CBD contained in cannabis (there are more than 78 other compounds) could be a viable dietary supplement. If approved, the dietary supplement could be marketed with "structure/function" claims about affecting or maintaining the normal structure or function of the body, general well-being claims and claims related to a nutrient deficiency disease (like vitamin C and scurvy). These claims must be accompanied by a disclaimer that FDA has not evaluated the claim and that the dietary supplement is not intended to "diagnose, treat, cure or prevent any disease."

Although cosmetics are not subject to premarket approval by FDA, they cannot not contain any ingredients that FDA has specifically prohibited for use in cosmetics. FDA has made clear that it has not identified cannabis or any cannabis-derived ingredient, including hemp-based CBD, as a prohibited or restricted cosmetic ingredient at this time. However, as with dietary supplements, cosmetics cannot be marketed with any health claims or impermissible "structure/function" claims (*e.g.*, changing skin at a cellular level, reducing swelling).

In addition to federal regulators, the states play a vital role in cannabis and cannabis-derived product regulation.

State and local departments of health, state cannabis commissions and state departments of agriculture all play a role in making and enforcing regulations regarding these products.

Research and Drug Approval Process

In December, FDA updated its website to include detailed information on the research and drug approval process for cannabis and cannabis-derived products. FDA outlined the steps for cannabis study drugs controlled under Schedule I of the Controlled Substances Act (CSA) (greater than 0.3% THC on a dry weight basis) as well as for cannabis study drugs containing hemp (no more than 0.3% THC on a dry weight basis).

Enforcement

FDA issued 22 Warning Letters to companies selling CBD-containing products. Most recently, on November 25, FDA issued 15 Warning Letters to companies illegally marketing CBD-containing dietary supplements or foods with claims that the products prevent, diagnose, mitigate, treat or cure serious diseases, such as cancer, Alzheimer's or Parkinson's. FDA relies on promotional statements and labeling claims to establish that CBD-containing products are either marketed with false or misleading claims or are marketed as unapproved new drugs.

Jurisdictional Lines

There are various potential regulators for cannabis and cannabis-containing products. Among the most relevant are FDA, the Federal Trade Commission (FTC), the Drug Enforcement Administration (DEA), the US Department of Agriculture (USDA) and the states.

In addition to FDA, FTC reviews advertising for food, drugs, cosmetics and devices to ensure there is no false advertising or any unfair or deceptive practices.

Under the 2018 Farm Bill, the DEA will continue to play a role in hemp not controlled under the USDA, state or tribal plans. DEA will need to conduct chemical analysis of Schedule I substances because it could potentially test cannabis with THC concentration above 0.3% on a dry weight basis. Disposal will need to comply with the CSA and product tested at above 0.3% THC concentration will need to be destroyed by a DEA-registered reverse distributor or a federal, state or local law enforcement officer. Additionally, researchers who wish to conduct clinical trials with marijuana must obtain it through DEA-registered sources. In August, DEA issued a press release stating that it is moving forward with its review of pending applications from entities applying to be registered to manufacturer marijuana for research purposes.

On October 31, USDA issued interim new rules effective through November 1, 2021, regarding the implementation of the 2018 Farm Bill. These rules, among other provisions, addressed USDA approval of state and tribal plans, states and territories that do not have USDA-approved plans, information on testing of

THC levels, disposal of plants and hemp protection record-keeping.

LOOKING AHEAD TO 2020

The recent uptick in FDA Warning Letters may indicate the agency's intent to focus enforcement efforts in 2020 on companies marketing CBD-containing products with unproven disease or health related claims and those potentially producing products with unsafe manufacturing practices. Companies should closely examine their marketing claims and manufacturing processes to ensure compliance with FDA regulations.

As reflected in the agency's November consumer update, FDA will likely continue to work "to answer questions about science, safety and quality of products containing cannabis and cannabis-derived compounds, particularly CBD." To answer these questions, FDA will use resources such as feedback from the Scientific Data and Information about Products Containing Cannabis or Cannabis-Derived Compounds public hearing and the information and data gathered through the public docket.

FDA also intends to continue to update the public as it learns more about CBD products. The agency will examine CBD-related questions around cumulative exposure, special populations and CBD use in animal products, among other topics. FDA also plans to evaluate the regulatory frameworks that apply to cannabis-derived products intended for non-drug uses and may issue further guidance on potentials pathways for products this year.

CLINICAL INVESTIGATIONS

DEVELOPMENTS IN 2019

Section 3024 of the Cures Act allows for a waiver or alteration of informed consent when a clinical investigation poses no more than minimal risk to the human subject and includes appropriate safeguards to protect the rights, safety and welfare of human subjects. FDA's Proposed Rule: Institutional Review Board Waiver or Alteration of Informed Consent for Minimal Risk Clinical Investigations would amend FDA's current institutional review board (IRB) regulation to allow IRBs responsible for the review, approval and continuing review of clinical investigations to approve an informed consent procedure that waives or alters certain informed consent elements or that waives the requirement to obtain informed consent. This exception from the requirement to obtain informed consent would apply

only when a clinical investigation poses no more than minimal risk to the human subject and includes appropriate safeguards to protect the rights, safety and welfare of human subjects. Because of technical issues with the Federal eRulemaking Portal, FDA extended its comment period for the proposed rule to February 2020.

While largely the same as the draft version, the finalized Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program guidance includes a table on processes by Q-Submission (Q-Sub) types, detailing the method of feedback and timeframes for submissions. The agency also included cybersecurity in its list of possible pre-submission questions (*i.e.*, when requesting feedback from FDA prior to submitting a marketing application). Of note, FDA removed its previous advice recommending pre-submissions for clinical studies conducted outside the United States.

Certain populations and groups continue to be underrepresented in many clinical trials. Section 610(a)(3) of the FDA Reauthorization Act of 2017 (FDARA) required FDA to issue a draft guidance regarding eligibility criteria for clinical trials. FDARA specifically required FDA to provide guidance on methodological approaches to broaden eligibility criteria for trials, eligibility criteria to ensure that trial participants more accurately reflect the like population of users and appropriate use of these approaches and criteria for drugs intended for the treatment of rare diseases or conditions. Accordingly, FDA issued the Enhancing the Diversity of Clinical Trial Populations — Eligibility Criteria, Enrollment Practices and Trial Designs Guidance for Industry draft guidance, which discourages sponsors from excluding subjects without a strong clinical or scientific justification. FDA's suggested inclusive trial practices include:

- Examining each exclusion criterion to determine if it is necessary to help ensure subject safety or to achieve the study objectives when developing trial protocols
- Considering whether exclusion criteria from Phase II studies—which may be more restrictive and are often automatically transferred to Phase III protocols—can be eliminated or modified
- Basing exclusions on an appropriate measure of organ dysfunction that does not lead to unnecessary exclusion
- Considering including children and adolescents (ages two through 17) in confirmatory clinical trials with adults, when appropriate.

FDA also suggests a number of trial design and methodological approaches to enroll broader populations as well as overall study design and conduct considerations to reduce burdens, enhance diversity and inclusiveness and expand access to trials.

Section 3021 of the Cures Act mandated that FDA issue guidance on addressing the use of complex adaptive and other novel trial design in the development and marketing applications for drugs and biological products. The Interacting with the FDA on Complex Innovative Trial Designs for Drugs and

Biological Products: Draft Guidance for Industry provides agency guidance to sponsors on how to obtain feedback on technical issues related to modeling and simulation and the types of quantitative and qualitative information that should be submitted to the agency for review. FDA also encourages sponsors of complex innovative trial design proposals to seek early interaction with FDA using existing pathways, such as Type A, Type B and Type C meetings as well as pre-IND meetings or IND amendment reviews.

The Patient Engagement in the Design and Conduct of Medical Device Clinical Investigations draft guidance is intended to help sponsors improve design and conduct of device investigations by using patient experience, perspectives and other relevant information to address common challenges, such as study recruitment issues, loss to follow-up and protocol deviations and violations. For purposes of the draft guidance, FDA defines "patient advisors" as individuals with experience living with a disease or condition who are not study subjects in the trial at hand.

FDA frames the guidance with four key questions:

- What approaches might sponsors use to engage patient advisors to inform the design and conduct of device clinical investigations? The agency specifically recommends working with patient advisors to:
  - Improve the informed consent document
  - Obtain input on how to conduct follow-up visits and data collection techniques to reduce unnecessary burdens on subjects
  - Discuss which potential endpoints are most clinically meaningful for those with the disease or condition
  - Develop patient reported outcome measures to better reflect outcomes that are important to patients
  - Inform the design of patient preference studies to understand the benefit-risk tradeoffs for proposed treatments.
- When can input be gathered from patient advisors and incorporated into the clinical investigation?
- What are the roles of IRBs and other institutional groups in patient engagement?
- How can a sponsor receive feedback on its patient engagement plan or patient-centered study design from FDA?

The Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug and Cosmetic Act Guidance for Industry provides guidance on implementation of FDA's statutory authority to require post-approval studies and post-approval clinical trials for drugs and biological products. Under the Substance Use-Disorder Prevention that Promotes Opioid Recovery and Treatment for Patients and Communities Act (SUPPORT Act), Congress required FDA to issue guidance describing the use of postmarket studies or clinical trials to assess the safety and effectiveness of a drug over the product's lifecycle. Specifically, Congress directed FDA to consider the circumstances under which it could use postmarket data to assess the potential reduction in effectiveness of a drug and how such reduction could change the benefit-risk profile of a product. Spurred, in part, by FDA's postmarket experience with opioid drug products, the guidance attempts to clarify when postmarket study data may help to predict or assess when a potential failure of expected pharmacological action could result in a serious adverse drug experience (*e.g.*, addiction and drug overdoses). The draft guidance does not apply to

non-prescription drugs approved under a new drug application or generic drugs approved under section 505(j) of the FDCA. The draft guidance will replace the April 2011 guidance when finalized.

ADVERTISING AND PROMOTION

DEVELOPMENTS IN 2019

CDER's Office of Prescription Drug Promotion (OPDP) issued a total of six Untitled Letters and three Warning Letters in 2019, a slight increase over 2018. Two of the Untitled Letters focused on the pre-approval promotion of investigational products as safe and effective. Two of the Untitled Letters and one of the Warning Letters included allegations for false or misleading claims about the efficacy of the respective products. Four of the Untitled Letters and two of the Warning Letters included allegations regarding failure to provide adequate risk information or false or misleading risk presentations. Only one of the Warning Letters alleged lack of adequate directions for safe and effective use because the manufacturer allegedly advertised its product for a new use for which it lacks approval and none expressly addressed alleged off-label promotion. OPDP may continue a more targeted approach to advertising and promotion enforcement in light of ongoing First Amendment concerns.

Of note, three of the Untitled Letters cited claims on the drug makers' websites and three cited claims in direct-to-consumer videos or broadcast advertisements, reflecting the agency's continued focus on digital marketing. Additionally, in June, FDA and FTC jointly sent Warning Letters to four sellers of e-cigarette liquid for social media postings made on their behalf by paid social media influencers. The Warning Letters explain that, from FDA's perspective, social media posts are "labeling and/or advertising," and consequently the postings failed to include the required nicotine warning statement for the e-liquid products. FTC charged the sellers with unfair or deceptive marketing, as "failure to disclose the presence of and risks associated with nicotine raises concerns that the social media postings could be unfair or likely to mislead consumers." Furthermore, FTC's Guides Concerning Use of Endorsements and Testimonials in Advertising (Endorsement Guides) require that any "material connection" between the marketer of a product and the endorser (*e.g.*, paid social media influencers) should be "clearly and conspicuously" disclosed, unless the connection is already clear from the context of the communication containing the endorsement.

ENFORCEMENT

DEVELOPMENTS IN 2019

Overview

FDA's enforcement actions—including Warning Letters, Civil Monetary Penalties, No-Tobacco-Sale Orders, Import Alerts, Seizures, Injunctions and Criminal Prosecutions—decreased slightly from 2018, a continued indication of the agency's current focus on more targeted risk-based enforcement in the wake of high-profile court cases. Overall, Warning Letter numbers also decreased slightly, including in key areas of historical focus, such as prescription drug marketing and promotion.

FTC, the US Department of Justice (DOJ) and states are using their authorities to fill perceived gaps in FDA enforcement.

These regulators are focusing on claims that go beyond the indication for use in existing clearances or approvals; claims that suggest a product can diagnose, prevent, treat or cure a disease or condition without clearance or approval; comparative claims of superior safety or effectiveness in the absence of clinical evidence; use of survey and registry data (*e.g.*, selective use of data, older or incomplete data) in a false or misleading manner and the use of healthcare professional or patient testimonials in a false or misleading manner. Recent False Claims Act (FCA) settlements involving sales and promotion activities for medical device products suggest continued focus on FDA-related violations as a basis for liability under related laws.

Stem Cell Products

FDA continued its enforcement efforts against unapproved and unproven stem cell technologies, as articulated by former Commissioner Gottlieb. In November, FDA issued two Untitled Letters to companies for marketing unapproved stem cell products, as the products do not appear qualify for an exception under 21 CFR § 1271.15 for homologous use human cell, tissue or cellular or tissue-based products (HCT/Ps). In December, FDA also issued a Warning Letter to two companies for processing and distributing unapproved umbilical cord blood stem cell products. As in its 2018 enforcement actions, discussed in our FDA 2018 Year in Review, FDA focused on significant deviations from current good tissue practice (cGTP) and cGMP requirements.

Dietary Supplements

FDA posted five Advisory Letters and issued 12 Warning Letters in July to dietary supplement marketers that made claims that their products prevent, treat or cure serious diseases and health conditions. The Warning Letters cited active ingredients that are either "new dietary ingredients," are unsafe as a food additive or do not meet the definition of a dietary ingredient under the FDCA.

FDA issued the Initiation of Voluntary Recalls Under 21 CFR Part 7, Subpart C Guidance for Industry and FDA Staff draft guidance clarifying FDA's recommendations regarding the timely initiation of voluntary recalls. Specifically, the agency detailed:

- The preparatory steps a firm in the product's supply chain should take to facilitate a timely recall
- How to identify and investigate a problem and make a decision and take action
- How to initiate the voluntary recall
- How FDA works with a recalling firm.

THE YEAR AHEAD

It remains to be seen whether Commissioner Hahn will advance a number of the initiatives that former Commission Gottlieb began, including those focused on youth vaping, stem cell therapies and tighter regulations on dietary supplement manufacturers and drug compounders. Many industry stakeholders have embraced and applauded FDA's pragmatic approaches for creating new and expedited market pathways for digital health and innovative technologies. Others, however, have signaled the need for new legislation or additional medical device authorities to justify certain aspects of the agency's digital health framework. FDA's role in regulating products containing cannabis and cannabis-derived compounds, including CBD, will continue to evolve as FDA actively works to learn more about the safety of these products and publishes additional guidance on their use in drugs, dietary supplements, foods or cosmetics. In an election year, issues such as drug pricing and youth vaping are likely to remain at the forefront and to be highly politicized by congressional and presidential candidates alike.

McDermott
Will & Emery