SPECIAL REPORT

2022 FDA YEAR IN REVIEW

FEBRUARY 2023

McDermott Will & Emery

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OVERVIEW

As the United States' primary public health and consumer protection agency, the US Food and Drug Administration (FDA) regulates at least one quarter of the nation's economy and exerts significant influence over global economies. The agency's reach continues to expand with the proliferation of outsourced and offshore manufacturing, clinical trials and global supply chains. The past year was notable for FDA's continued efforts to align and scale its regulatory processes to keep pace with growing innovation in drug and device development and food production, and the rise and market dominance of *in vitro* diagnostics (IVDs), including laboratory-developed tests (LDTs), in the wake of the COVID-19 pandemic. Congress's failure to enact the long-awaited and hotly contested Verifying Accurate Leading-edge IVCT Development (VALID) Act, which would have expanded FDA's authority over LDTs, increases the likelihood that VALID will be on the legislative agenda in 2023. The drive toward modernization has also prompted a reexamination of established regulatory programs such as expedited review pathways for drugs and devices. As the number and corresponding financial import of breakthrough designations increase, the agency is under greater pressure to assess whether these programs have fulfilled their original goals of improving patient outcomes in areas of unmet need and clearing the path for innovative products.

FDA continues to tussle with industry and courts regarding the scope of its discretion to interpret decades-old statutory provisions. As it has in the past, the agency seeks to expand the bounds of its interpretative authority, and courts continue to chip away at the degree of deference afforded to the agency. In the areas of drug and device regulation and digital health (*i.e.*, the Software Pre-Certification Pilot Program), FDA has conceded the need for affirmative legislative authority and congressional intervention to respond to judicial pushback and regulatory complexities inherent in its responses to innovation. While FDA's various user-fee-related bills were for the most part passed without any revisions to the Federal Food, Drug, and Cosmetic Act (FDCA), legislative intervention came in the form of the Consolidated Appropriations Act, 2023 (2023 Omnibus), which contained the Food and Drug Omnibus Reform Act (FDORA), signed by President Biden on December 29, 2022. The 2023 Omnibus enacted a subset of the provisions contemplated in various user fee acts that enhance FDA's authority to address public health emergencies (PHEs), protect the drug supply chain, impose stricter cybersecurity requirements on medical devices and support greater access to generic drugs.

While enforcement declined in 2022, the steady march toward normalization of factory inspections and post-market surveillance activities may signal an increase in enforcement as FDA and the world emerges from the global pandemic. The finalization of key guidance documents for clinical decision support (CDS) and food labeling may also signal increased scrutiny in those sectors in 2023.

The FDA regulatory environment will be as complex and dynamic as ever in 2023. FDA will continue to implement new policies, reexamine old programs and normalize processes to encourage greater engagement with industry-significant policy issues. It remains to be seen how much the agency will accomplish and what it will prioritize before the start of the 2024 presidential election cycle, where healthcare will undoubtedly drive the agenda in a post-pandemic environment.

DRUGS AND BIOLOGICS

When Robert M. Califf, MD, became commissioner in February 2022, he made certain promises to Congress regarding his priorities for drugs and biologics regulation at FDA. First, Dr. Califf said that he would address Congress's perception that companies were taking advantage of accelerated approval and other expedited approval pathways, such as "breakthrough" therapy or fast track designations and priority reviews, without delivering on the promises of the potential benefits of their products. Dr. Califf also said that he would address the opioid drug crisis, in part by proposing that new opioids must demonstrate superior safety to existing products (*e.g.*, less abuse potential) for approval. Finally, Dr. Califf hoped to use generic user fees to fund research to facilitate the development and approval of complex generic drugs and maximize the number of generic drug applications approved to improve competition and lower drug prices.

Under Dr. Califf's leadership, FDA made some progress with guidance regarding expectations for drugs receiving expedited approvals. Toward the end of 2022, FDA began to address several components of the opioid drug crisis. FDA also took substantive steps to provide guidance for complex generics, resulting in several first-time complex generic approvals.

Novel Product Approvals

Overall, FDA experienced a decline in novel product approvals. The Center for Drug Evaluation and Research (CDER) posting only 37 new molecular entities and novel biologics in 2022—a marked drop off after five consecutive years of novel agent counts above 45, including 50 in 2021, and a high mark of 59 in 2018. FDA's Center for Biologics Evaluation and Research (CBER), with a significantly narrower remit than CDER, approved eight novel biologics in 2022, somewhat more consistent with its 15-year average of 7.6 novel biologics per year. Of note, CBER ushered in five new gene therapies along with the first fecal microbiota product approval and increased product development in the regenerative medicine space. So, while FDA received fewer novel drug approvals, perhaps in part due to reduced COVID-19 restrictions, novel biologics and in particular gene therapies are on the rise.

Orphan Products

Orphan drug and biologics[1] approvals continue to be a regulatory focus for FDA and industry due in part to advancements in the detection and characterization of rare diseases and the generous seven years of market exclusivity FDA grants to innovators. About 50% to 60% of the novel drug therapies approved by FDA each year have been designated as orphan drugs. However, recent litigation challenging FDA's historic "indication-specific" interpretation for orphan drug exclusivity may affect future approvals and incentives for additional research and development.

In September 2021, the US Court of Appeals for the Eleventh Circuit issued an opinion in *Catalyst Pharms., Inc. v. Becerra* that appeared to limit FDA's prior indication-specific interpretation of orphan drug exclusivity. Under FDA's historical approach, which was codified in the agency's 2013 regulations, a drug product approved for an "indication or use" that is narrower than the "rare disease or condition" for which the orphan designation was granted would obtain exclusivity only for the approved indication or use. Under this interpretation, drug companies could continue to study and seek approval for other uses of the drug for that disease or condition, such as a pediatric indication for a product that had been approved for adults. FDA developed this interpretation to encourage sponsors to conduct additional studies to capture data on the full rare disease or condition rather than the narrow indication for use. Now, given that the exclusivity extends to the full use or condition even if the product was only studied and labeled for the narrower indication, FDA believes the exclusivity will discourage research and development to better understand the orphan disease. This potential disincentive to conduct broader studies is heightened by the fact that orphan populations are by definition smaller and more difficult to study.

From FDA's own orphan drug exclusivity database and other reports, moreover, it appears that FDA's Office of Orphan Products Development has deferred most or all of its pending orphan exclusivity determinations since the Eleventh Circuit's decision. In particular, the office does not appear to have publicly noted orphan drug exclusivity for any product since November 2021. From most accounts, FDA had hoped that a retroactive legislative "fix" would be added to the Prescription Drug User Fee Act (PDUFA) to conform to FDA's historical interpretation. While this proposal appeared at one time in both House and Senate draft versions of PDUFA, it was removed in the version of PDUFA enacted and was not included in FDORA. FDORA included several provisions related to orphan drugs, including reauthorization for orphan drug grants (2023 Omnibus § 3107) to help encourage the development of orphan drugs. The Rare Disease Endpoint Advancement Pilot Program established in PDUFA VII requires FDA to create procedures to provide increased interaction with sponsors of rare diseases for the purpose of advancing the development of efficacy endpoints, including public workshops and a report to Congress for the program that sunsets on October 1, 2027.

Testing

Section 3209 of the 2023 Omnibus includes a provision on animal testing alternatives, clarifying that drug application sponsors can use alternative testing methods to animal testing in evaluating the safety and effectiveness of human drugs, *e.g.*, *in vitro*, *in silico*, *in chemico* or other non-human *in vitro* tests (such as organ on a chip). Section 3209 also clarifies that sponsors of biosimilar applications can demonstrate biosimilarity to a reference product using alternative testing methods to animal studies. Taken together, these provisions are significant, because FDA's statute required preclinical tests in animals, posing ethical

[1] Orphan products are drugs or biologics indicated for diseases or conditions that affect 200,000 or fewer people in the United States per year.

issues regarding needless testing in animals when there were equal or better alternatives.

Drugs

Pandemic Response

FDORA included several provisions related to enhancing FDA's authority to be nimbler during future PHEs, including pandemic situations, such as the following:

- Accelerating Countermeasure Development and Review (2023 Omnibus § 2501) codifies FDA's ability to conduct rolling and expedited review, increasing engagement with sponsors and building "senior" and "experienced" review teams. It also codifies FDA's ability to issue new, expedited guidance or policies to develop countermeasures during certain emergencies, such as a PHE.
- Third-Party Test Evaluation During Emergencies (2023 Omnibus § 2502) codifies FDA's ability to "consult with persons with appropriate expertise . . . or enter into cooperative agreements or contracts with such persons" to assist in the evaluation and review of emergency use authorization (EUA) submissions, including developing guidance on such arrangements, such as considerations related to conflicts of interest, compensation and information sharing.
- Increasing EUA Decision Transparency (2023 Omnibus § 2504) modifies statutory EUA provisions to direct FDA to publish information about EUAs in places other than the *Federal Register* and permits the publication of information about an authorization, termination or revocation of an EUA based on an expanded number of market access submissions to the FDA, "even if such summary may reveal the existence of such an application, request, or submission, or data contained in an application, request, or submission."
- Facilitating the Use of Real-World Evidence (2023 Omnibus § 3629) directs FDA to issue updated guidance and policies on the use of real-world evidence (RWE) to support regulatory decision-making with a focus on how RWE can be used to convert EUAs into formal market access decisions for drugs, biologics and medical devices.

While the agency had already advanced most of these provisions during the COVID-19 pandemic, making these changes statutory further enhances FDA's ability to continue to use these measures in the event of a future PHE.

Expedited Review Pathways

Each of FDA's expedited review programs is meant to speed development and approval of drugs to treat serious or life-threatening diseases without current approved therapies for treatment. As noted above, however, the FDA is reassessing the long-term benefits, risks and implications of these programs on patient safety and agency resources. FDA's breakthrough therapy designation (BTD)[2] for drugs is a recent example.

In June 2022, FDA took preliminary steps to be more proactive by issuing its draft Considerations for Rescinding Breakthrough Therapy Designation guidance. FDA clarified that it intends to periodically reassesses whether designated products continue to meet the criteria for BTD. FDA stated that periodic reassessments may be prudent because scientific evidence regarding the safety and effectiveness of

[2] A drug is eligible for a BTD "if the drug is intended, alone or in combination with one or more other drugs, to treat a serious or life-threatening disease or condition and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development."

drugs may evolve over time. In light of the resource-intensive nature of the BTD program, FDA may rescind the designation if it determines that a previously designated drug no longer meets the criteria. Factors FDA considers in rescinding the BTD include the following:

- A different drug is approved to treat the previously unmet need (unless that different drug received an accelerated approval).
- Emerging data shows that the drug may no longer demonstrate substantial improvement over existing therapies.
- The applicant is no longer pursuing the drug development program.
- The trials have a high quality of evidence (*e.g.*, conduct in larger populations; use of a well-understood, widely accepted and well-construed clinical endpoint; incorporation of certain design features, such as randomization and blinding).

A case that may signal whether Dr. Califf will make good on his promises to take a tougher stance on drugs that receive accelerated approval relates to the pre-term pregnancy drug Makena® (hydroxyprogesterone caproate injection). FDA approved Makena® in 2011 through an accelerated approval pathway to reduce the risk of preterm birth in women who previously had a spontaneous (*i.e.*, unexplained) preterm birth (*i.e.*, delivery of a baby before 37 weeks). FDA required Makena's sponsor to conduct an additional clinical trial to confirm that the drug provided its purported clinical benefit to newborns. The confirmatory clinical trial allegedly failed to show that the drug provided benefit to this intended patient population or that it reduced the risk of preterm birth. In October 2020, FDA proposed to withdraw Makena® from the market. FDA issued a notice of opportunity for a hearing to the application holder of Makena® and approved generics so they could provide comments. After a three-day hearing in October 2022, an FDA advisory panel voted 14-1 that Makena and its generic versions should be withdrawn. The current manufacturer of Makena® is vigorously contesting FDA action, and it is unclear at this point whether FDA will agree with the findings of its advisory panel. Prior to Makena®, FDA has only once before withdrawn an accelerated approval indication against a company's wishes—Avastin® (bevacizumab), which had been approved for use in the treatment of breast cancer.

As an alternative to a more aggressive FDA, Congress proposed a bill earlier in 2022, House Bill (passed in the House but not Senate) Accelerated Approval Integrity Act of 2022, HR 6963, 117th Congress (2022), which would have required an accelerated approval to automatically expire after a defined period of time unless the FDA confirmed that the approval was warranted based on sponsor-provided evidence. FDORA incorporates HR 6963 in 2023 Omnibus § 3210 (Modernizing Accelerated Approval).

These provisions now include the following:

- FDA must specify the conditions for required post-approval studies for products approved under accelerated approval, including enrollment targets, the study protocol and milestones, including the target date of completion. FDA is permitted to require post-approval studies to be underway prior to approval or within a specified time period after approval. FDA must publish on FDA's website an explanation when it does not require a sponsor to conduct a post-approval study.
- FDA must follow certain procedures to withdraw a product's accelerated approval on an expedited basis, including the following:
  - » Providing the sponsor with due notice, an explanation for the proposed withdrawal, an opportunity to meet with the commissioner or the commissioner's designee, and an opportunity for written appeal to the

commissioner or a designee of the commissioner

  - » Providing an opportunity for public comment
  - » Responding to such comments and providing the comments and agency responses on the FDA's website
  - » Convening an advisory committee relating to the proposed withdrawal if the sponsor requests one and no such advisory committee has previously advised FDA on the proposed withdrawal.

- FDA must provide reports on post-approval study progress no later than 180 days after approval and every 180 days thereafter until any required post-approval studies are completed or terminated.
- Failure to conduct required post-approval studies with due diligence and failure to submit the required reports are now prohibited acts that can result in a criminal prosecution.
- FDA must issue guidance on "how sponsor questions related to the identification of novel surrogate or intermediate clinical endpoints may be addressed in early stage development meetings with [FDA]," the use of novel clinical trial designs to conduct post-approval studies, the expedited withdrawal procedures, and "considerations related to the use of surrogate or intermediate endpoints that may support the accelerated approval of an application . . . , including considerations in evaluating evidence related to any such endpoints." FDA must also, within one year of the bill's enactment, create an intra-agency coordinating council within the FDA to ensure that FDA appropriately and consistently uses the accelerated approval process. This council must publish annual reports of its activities on FDA's website.

Companies should continue to monitor whether these new provisions allow FDA to meet this issue more directly in the coming year, and they should be mindful of the requirements to avoid enforcement actions.

Despite the increased scrutiny of the BTD program, the agency is set to explore a new expedited review pathway for "platform technologies." Section 2503 of the 2023 Omnibus requires FDA to create a platform technologies designation program. Platform technologies are technologies that have the potential to be incorporated in or used by more than one drug or biological product and are reasonably likely to make the drug development or manufacturing process and the review process more efficient. For example, mRNA is a platform technology used in COVID-19 vaccines with other applications. A platform technology is eligible for such designation if the following criteria are met:

- The technology is incorporated or used in an approved drug or biologic.
- Preliminary evidence demonstrates that the platform technology has the potential to be incorporated or used in more than one drug without adverse effect on quality, manufacturing or safety.
- Data indicates a "reasonable likelihood" that the technology would bring significant efficiencies to the drug development, manufacturing or review process by such designation.

Once FDA designates a platform technology as such, FDA "may expedite the development and review of any subsequent application submitted under § 505(b) of [the Food, Drug, and Cosmetic] Act or § 351(a) of the Public Health Service Act for a drug that uses or incorporates the platform technology." Sponsors may also "reference or rely upon data and information" from a previous application for a drug or biological product that incorporates or uses the same platform technology—as long as the data was submitted by the

same sponsor or the sponsor relying on the data received permission from the sponsor that originally submitted the data. FDA is required to issue draft guidance relating to the program within one year of enactment of FDORA.

Opioid Drugs

Opioid drug misuse and drug substance abuse reach new record levels during the COVID-19 pandemic, including in the number of drug overdose fatalities. In February 2022, FDA issued draft guidance to help develop more non-addiction medications for pain, Development of Non-Opioid Analgesics for Acute Pain.

In September 2022, FDA introduced the its Overdose Prevention Framework and started taking other public measures to address the opioid misuse epidemic. The framework has four main prongs: primary prevention, harm reduction, evidence-based treatments for substance use disorders, and protecting the public from unapproved, diverted or counterfeit drugs.

In March 2022, FDA held a public meeting to consider access to naloxone to help combat opioid addiction. In September 2022, FDA issued related guidance, Exemption and Exclusion from Certain Requirements of the Drug Supply Chain Security Act (DSCSA) for the Distribution of FDA-Approved Naloxone Products During the Opioid Public Health Emergency.

FDA considered issues related to prescriber education for opioids by holding two public workshops, Reconsidering Mandatory Opioid Prescriber Education Through a Risk Evaluation and Mitigation Strategy (REMS) in an Evolving Opioid Crisis and Identifying Key Competencies for Opioid Prescriber Education. In September 2022, FDA commissioned an external expert review to take a closer look at the labeling for FDA's marketed or approved opioids. FDA is reportedly considering asking Congress for authority to require that any new opioid be safer that those already on the market.

Other Drug-Related Guidance

In April 2022, FDA issued its final guidance Bioavailability Studies Submitted in NDAs or INDs – General Considerations, which finalized the February 2019 draft guidance of the same title. The final guidance provides recommendations on submitting bioavailability information for drug products in investigational new drug applications (INDs), new drug applications (NDAs) and NDA supplements to meet requirements in 21 C.F.R. Part 320 as they apply to oral administration dosage forms.

FDA's June 2022 Patient-Focused Drug Development: Selecting, Developing, or Modifying Fit-for-Purpose Clinical Outcome Assessments is the third in a series of four methodological patient-focused drug development guidance documents that describe how stakeholders (patients, caregivers, researchers, medical product developers and others) can collect and submit patient experience data and other relevant information from patients and caregivers to be used for medical product development and regulatory decision-making. This guidance is intended to help sponsors use high-quality measures of patients' health in medical product development programs. Ensuring high-quality measurement is important for measuring what matters to patients; being clear about what was measured; appropriately evaluating the effectiveness, tolerability and safety of treatments; and avoiding misleading claims.

The August 2022 Charging for Investigational Drugs Under an IND: Questions and Answers provides information for industry, researchers, physicians, institutional review boards (IRBs) and patients about the implementation of FDA's regulations at 21 C.F.R. § 312.8 on charging for investigational drugs under an IND for the purpose of either clinical trials or expanded access for treatment use, which went into effect on October 13, 2009. In general, sponsors cannot charge study subjects for investigational products. However, if the sponsor does all of the

following, FDA may permit reasonable charges to cover the cost of the experimental therapy:

- Provide evidence to FDA that the drug has a potential clinical benefit that, if demonstrated in clinical investigations, would provide a significant advantage over available products in the diagnosis, treatment, mitigation or prevention of a disease or condition (21 C.F.R. § 312.8(b)(1)(i))
- Demonstrate that the data to be obtained from the clinical trial would be essential to establishing that the drug is effective or safe for the purpose of obtaining initial approval, or would support a significant change in the labeling of an approved drug (*e.g.*, a new indication, inclusion of comparative safety information) (21 C.F.R. § 312.8(b)(1)(ii))
- Demonstrate that the clinical trial could not be conducted without charging because the cost of the drug is extraordinary to the sponsor (21 C.F.R. § 312.8(b)(1)(iii)) (see also Q5 regarding extraordinary cost)
- Provide documentation to support its calculation for cost recovery, to the extent applicable, to show that the calculation is consistent with the requirements of § 312.8(d)(1), along with a statement that an independent certified public accountant has reviewed and approved the calculation.

In December 2022, FDA issued its Homeopathic Drug Products: Guidance for FDA Staff and Industry, reiterating its October 2019 Drug Products Labeled as Homeopathic draft guidance, which states that the agency will prioritize enforcement for the following categories of homeopathic drug products:

- Products with reports of injury that, after evaluation, raise potential safety concerns
- Products that contain or purport to contain ingredients associated with potentially significant safety concerns
- Products for routes of administration other than oral and topical
- Products intended to be used for the prevention or treatment of serious or life-threatening diseases or conditions
- Products for vulnerable populations
- Products with significant quality issues

In December 2022, FDA issued its Investigational New Drug Applications; Exemptions for Clinical Investigations To Evaluate a Drug Use of a Product Lawfully Marketed as a Conventional Food, Dietary Supplement, or Cosmetic proposed rule. If finalized, the rule would exempt clinical investigations involving lawfully marketed foods for human consumption (conventional foods and dietary supplements) and cosmetics from the IND application requirements when the product is to be studied to evaluate its use as a drug. To satisfy the criteria for a "self-determined exemption," such studies must not present a significant risk to the health, safety or welfare of subjects, and they must not be intended to support a drug development plan or a labeling change that would cause a lawfully marketed food or cosmetic to become an unlawfully marketed drug. Additionally, where the sponsor determines that a study could present risk to human subjects, the sponsor would have the option of seeking an "FDA-determined exemption." In either case, these studies would remain subject to other good clinical practice requirements, such as informed consent and IRB oversight.

Over-the-Counter Drugs

FDA issued its proposed rule Nonprescription Drug Product with an Additional Condition for Nonprescription Use on June 28, 2022. Currently, nonprescription drugs, also known as over-the-counter (OTC) drugs, are limited to those that can be labeled

with adequate information for the patient to appropriately self-select and use the product, in accordance with 21 C.F.R. § 201.5 (Drugs; adequate directions for use). The proposed rule contemplates creating a class of drugs that are "nonprescription" with an "additional condition for nonprescription use (ACNU)." An ACNU would be a condition or conditions, approved by FDA, that a patient must fulfill to obtain the nonprescription drug product, such as a self-selection test (*i.e.*, a specific set of questions, potentially administered through a mobile application or automated telephone response system) or other requirements (*e.g.*, requiring the patient to view labeling and respond to questions to confirm the patient's understanding). This self-selection test may include elements about the patient's personal medical history (including prior medication history). The proposed rule would establish 21 C.F.R. § 314.56, which would create additional application requirements for a "nonprescription drug product with an ACNU" under an NDA or abbreviated new drug application (ANDA). FDA could approve—and the applicant could simultaneously market—nonprescription and prescription versions of a product with the same active ingredient (and potentially, but not necessarily, identical formulations) if the ACNU conditions were sufficient to ensure that a patient could appropriately self-select or use the nonprescription version of the product. The proposed rule would create 21 C.F.R. § 201.67(c) (general labeling requirements) and 21 C.F.R. § 201.130 (exemption from adequate directions for use). Nonprescription drugs with an ACNU would have separate post-market reporting requirements (proposed 21 C.F.R. § 314.81(b)(3)(v)). If this rule is finalized, applicants and sponsors could available themselves of this pathway by submitting a separate application for approval of a nonprescription drug with an ACNU alongside a new, or as a supplement to an existing, NDA or ANDA. Following approval of the nonprescription drug with an ACNU, it could be made available to the patient after the patient followed the approved of safe use (*e.g.*, self-selection tests administered through a mobile app or knowledge comprehension checks after the patient reviews labeling).

Generic and Other Therapeutically Equivalent Drugs

Throughout 2022, FDA published new product-specific guidance documents (PSGs), including 43 draft PSGs in February 2022, 37 draft PSGs in May 2022 and 48 draft PSGs in August 2022. Notable complex generic approvals included a first generic of Symbicort® (budesonide and formoterol fumarate dihydrate) inhalation aerosol, a first generic of Apokyn® (apomorphine hydrochloride) injection, 30 mg/3 mL (10 mg/mL), and a first generic of Restasis® (cyclosporine ophthalmic emulsion) 0.05% single-use vials.

FDORA includes several provisions related to generic drugs, most notably in 2023 Omnibus § 3222, which removes FDA's prior requirement for a citizen petition to consider therapeutic equivalence (TE) for 505(b)(2) NDAs with different active ingredients than the referenced drug. For applications approved prior to passage of the 2023 Omnibus, the applicant may submit an amendment or supplement to the application requesting a TE rating, and FDA will assign a TE rating within 180 days. For applications submitted after passage of FDORA, applicants may request a TE rating as part of the application, and FDA may assign a TE rating at the time of approval or not later than 180 days after approval. Section 3224 of the 2023 Omnibus allows certain generic drugs to be labeled temporarily with different labeling compared to the reference product, if the reference listed drug (RLD) has been changed within the last 90 days and the difference is not contained in the "warnings" section of the drug labeling. In such instances, the sponsor of the generic drug application "agrees to submit revised labeling for the drug that is the subject of the application" within 60 days of approval.

To help facilitate the development of generic drugs, including complex generic drugs, to compete with their innovator counterparts, FDA issued several

generic-focused guidance documents to help with product development including:

- Revising ANDA Labeling Following Revision of the RLD Labeling Guidance for Industry (January 2022) proposes to revise the April 2000 guidance of the same title and provide updates to outdated details about how to obtain information on changes to RLD labeling and how to submit revised ANDA labeling to FDA.
- Good ANDA Submission Practices (January 2022) highlights common recurring deficiencies that may lead to a delay in the approval of an ANDA and makes recommendations to applicants on how to avoid these deficiencies to help minimize the number of FDA review cycles for approval.
- Evaluation of Therapeutic Equivalence (July 2022) explains how FDA makes therapeutic evaluations for multisource prescription drug products that are listed in FDA's Orange Book. FDORA updated some of the recommendations, most notably that NDAs submitted under § 505(b)(2) of the FDCA may include a request for a TE determination without the need for a separate citizen petition request following approval, which was the prior procedure.
- Orange Book Questions and Answers: Guidance for Industry (July 2022) provides answers to questions that FDA has received on the Orange Book, including inquiries on the content and format of the Orange Book, petitioned ANDAs, the movement of drug products between the active and discontinued sections of the Orange Book, and patent listings.
- Sameness Evaluations in an ANDA — Active Ingredients (November 2022) provides recommendations for demonstrating sameness of active ingredients between a proposed generic drug product and its RLD in an ANDA.
- Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA Guidance for Industry (October 2022) describes an enhanced pathway for discussions between FDA and applicants preparing to submit or that have submitted a complex product as defined in the guidance. Complex products generally include products with complex active ingredients, complex drug-device combinations, or other products where complexity or uncertainty concerning the approval pathway or possible alternative approach would benefit from early scientific engagement.

Drug Supply Security and Related Policies

FDA also enhanced its monitoring and enforcement of the national drug supply by issuing several related guidance documents and a proposed rule:

- In February 2022, FDA announced a proposed rule, National Standards for the Licensure of Wholesale Drug Distributors and Third-Party Logistics Providers, which is discussed in depth here.
- Importation of Prescription Drugs Final Rule Questions and Answers; Small Entity Compliance Guide (May 2022) provides an explanation for small entities to better understand the final rule *Importation of Prescription Drugs*, published October 1, 2020, to allow importation of certain prescription drugs from Canada to achieve a significant cost reduction of covered products without posing additional risk to the public's health and safety.
- Identifying Trading Partners Under the Drug Supply Chain Security Act (July 2022) revises the agency's August 2017 draft guidance of the same title. It assists industry and state and local

governments in understanding how to categorize the entities in the drug supply chain in accordance with the DSCSA, including the status of some entities as trading partners (*e.g.*, private-label distributors, salvagers, and returns processors and reverse logistics providers), and provides clarification on certain drug distribution scenarios. It also addresses the interpretation of § 582(a)(7) of the FDCA, which discusses third-party logistics provider (3PL) licensure status prior to the effective date of the forthcoming regulations establishing licensure standards.

Section 2512 of the 2023 Omnibus also directs FDA to issue guidance with recommendations to ensure that "the longest feasible expiration date supported by . . . data" is included in a drug's labeling to maximize the availability of supply. It also directs FDA report to Congress "the number of drugs for which the Secretary has requested the manufacturer make a labeling change regarding the expiration date," and whether those drugs were at risk of shortage.

Looking Ahead to 2023

In general, FDA will be busy implementing FDORA, which entails drafting and promulgating several new regulations and guidance documents. FDA is likely to take a harder look at expedited drug approval now that the agency has been given additional authority to remove drugs from this category without confirmatory clinical evidence.

FDA will likely push Congress for its *Catalyst* legislative "fix," arguing that it cannot move forward with orphan exclusivity decisions without it. FDA is likely to look for ways to increase competition with new 505(b)(2) NDAs and ANDAs and to continue to engage with the US Patent and Trademark Office on how to collaborate on patent prosecution and patent listings in the Orange Book.

On the opioid front, FDA will receive information from its commissioned study regarding its opioid drug approvals, which will likely inform FDA that it must provide more narrowly tailored pain indications for opioids. FDA will also likely provide guidance or seek congressional change that would require new opioid sponsors to demonstrate a safety or efficacy benefit to prior-approved opioid drugs.

Finally, FDA likely will look to increase and tighten its inspections and increase its scrutiny for counterfeit drugs and violations of the DSCSA now that most of its provisions are effective.

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

In addition to the issues discussed above that affect biological products, such as expedited review and orphan drugs, FDORA added several new provisions affecting biologics:

- Biologics Marketing Status Transparency (2023 Omnibus § 3201) requires biologics manufacturers to notify FDA in advance of withdrawing a product from sale and provide a one-time notification to FDA regarding whether their products are still available for sale. FDA must update the Purple Book accordingly.
- Interchangeable Biosimilar Biologics (2023 Omnibus § 3206) clarifies FDA's authority to tentatively approve a subsequent interchangeable biosimilar biological product while a first interchangeable product's period of exclusivity is pending. It also clarifies that multiple interchangeable biosimilar biological products can share a period of first interchangeable exclusivity if they are approved on the same day and otherwise qualify for exclusivity.
- Advancing Qualified Infectious Disease Product Innovation (2023 Omnibus § 3212) allows for biological products to qualify as qualified infectious disease products (QIDPs) and allows

for priority review of innovative biological antifungal products if such products require clinical data to demonstrate safety or effectiveness. This provision, however, does not extend QIDP exclusivity to biological products.

- Public Workshop on Cell Therapies (2023 Omnibus § 3205) requires FDA to convene a public workshop on best practices for generating scientific data necessary to facilitate development of human cells, tissues, and cellular and tissue-based products (HCT/Ps) and the latest scientific information about such products.

FDA also published several notable guidance documents related to biologics:

- Investigational COVID-19 Convalescent Plasma; Guidance for Industry (January 2022) provides recommendations to healthcare providers and investigators on the use of COVID-19 convalescent plasma or investigational convalescent plasma during the PHE as well as recommendations to blood establishments on collection. This document supersedes previous guidance documents of the same title. In particular, the revised guidance reflects that the EUA authorizes COVID-19 convalescent plasma with high titers of anti-SARS-CoV-2 antibodies for the treatment of COVID-19 in patients with immunosuppressive disease or receiving immunosuppressive treatment in either the outpatient or inpatient setting. The guidance also revises certain recommendations pertaining to COVID-19 convalescent plasma donors.
- Emergency Use Authorization for Vaccines to Prevent COVID-19 (updated) (March 2022) indicates that new variant-directed COVID-19 vaccines should demonstrate superior, rather than merely noninferior, antibody response against the targeted variant relative to the original prototype vaccine. With these new, more stringent recommendations for demonstrating immunogenicity of modified vaccines, both for the primary series and booster doses, the agency is setting a higher bar that must be met before making the switch from the prototype COVID-19 vaccines to new formulations directed at specific variants. The FDA previously recommended an immunogenicity comparison based on noninferiority of seroresponse rates and geometric mean titers between the variant-directed vaccine and the original vaccine.
- An Acceptable Circular of Information for the Use of Human Blood and Blood Components (March 2022) affirms that a December 2021 circular with the same title prepared jointly by the Association for the Advancement of Blood and Biotherapies, the American Red Cross, America's Blood Centers and the Armed Services Blood Program remains acceptable for use. The FDA circular is periodically updated to address changes in regulations, technology, testing, and product indications.
- Considerations for the Development of Human Gene Therapy Products Incorporating Genome Editing; Draft Guidance for Industry (March 2022) provides recommendations to sponsors developing human gene therapy products incorporating genome editing of human somatic cells. Specifically, this draft guidance provides recommendations regarding information that should be included in an IND application to allow FDA to assess the safety and quality of the investigational genome edited product, as required in 21 C.F.R. § 312.23. This includes information on product design, product manufacturing, product testing, preclinical safety assessment and clinical trial design.

- Considerations for the Development of Chimeric Antigen Receptor (CAR) T Cell Therapies (March 2022) addresses CAR T cell products, *i.e.*, human gene therapy products in which the T cell specificity is genetically modified to enable recognition of a desired target antigen for therapeutic purposes. This draft guidance is intended to assist sponsors, including industry and academic sponsors, in developing CAR T cell products.
- Enforcement Policy Regarding Investigational New Drug Requirements for Use of Fecal Microbiota for Transplantation to Treat *Clostridioides difficile* Infection Not Responsive to Standard Therapies (November 2022) finalizes the draft guidance of the same name to inform members of the medical and scientific community and other interested persons of FDA's policy regarding the IND requirements for the use of fecal microbiota for transplantation to treat *Clostridioides difficile* (*C. difficile*) infection not responding to standard therapies. FDA stated that it intends to exercise enforcement discretion with respect to such requirements under limited circumstances as described in section II of this guidance, but this policy does not apply to fecal microbiota for transplantation that is obtained from a stool bank.

Looking Ahead to 2023

Outside of the expedited review and orphan products issues that affect biologics as well as drugs, FDA will likely push vaccine manufacturers to continue to attempt to develop longer-lasting vaccines for COVID-19 and other viral infections rather than continuing to approve boosters, if such efforts prove to be viable. FDA will likely expand its review and approval of antivirals, gene therapies, regenerative medicine and other novel biologics, and it will likely approve more biosimilars, including interchangeable biosimilars, which may now receive tentative approvals if not ready for a final approval. As with drugs, FDA is likely to enhance its inspections of biologics and HCT/P product manufacturers, the latter of which no longer have enforcement discretion for products that do not comply with the HCT/P requirements.

COMBINATION PRODUCTS

In January 2022, FDA issued its Principles of Premarket Pathways for Combination Products guidance, which serves as a high-level primer for developers and manufacturers of combination products, with information on principles and mechanics of premarket review and related agency interactions. The guidance also advises on how to determine which type of premarket submissions may be appropriate for combination products.

In September 2022, FDA published a notice on Alternative or Streamlined Mechanisms for Complying with CGMP Requirements for Combination Products, as required by the 21st Century Cures Act (Cures Act). The notice provides recommendations for complying with multiple product quality and current good manufacturing practices (cGMP), including testing and release, stability testing, reserve samples and design controls. The guidance also includes suggestions for interacting with various components within FDA.

Looking Ahead to 2023

FDA is likely to provide additional guidance for generic and therapeutically equivalent products to make combination products as FDA strengthens its complex generic-type guidance documents and support. FDA is also likely to provide additional support to combination product sponsors to help them comply with FDA's regulations, which may include increased inspectional oversight.

MEDICAL DEVICES

Device regulation continues to be an active and dynamic area for FDA, with significant investments in learning, promulgating standards and scaling existing processes to respond to rapid innovation. However, recent court decisions are forcing FDA to reexamine historical interpretations of medical device laws to align with the practical realities of product development today.

One area of continuing interest is the US Court of Appeals for the District of Columbia Circuit's decision in *Genus Med. Techs., LLC v. FDA*, 994 F.3d 631 (D.C. Cir. 2021), which held that the FDCA does not grant FDA discretion to classify any product a "drug" that also meets the statutory definition of a "device," except for combination products. *Genus* highlighted concerns regarding FDA's historical practice of classifying certain products as drugs because they are used in connection with diagnostic procedures, even though they also satisfy the legal criteria to be considered devices. This case underlines the complexity that manufacturers and FDA face in determining whether a product is a medical device and who gets to decide.

Several noteworthy developments followed the DC Circuit's ruling. Shortly after the *Genus* decision, FDA announced in a *Federal Register* notice that the agency would begin transitioning certain products regulated as drugs to device status and would publish in a future *Federal Register* notice a list of approved drug products that it determines should transition to device status. Although FDA has yet to publish a list of these products, it did issue an immediately in effect guidance in March 2022, Certain Ophthalmic Products: Policy Regarding Compliance with 21 CFR Part 4: Guidance for Industry. In the guidance, FDA states that it will regulate eye cups, eye droppers and other dispensers intended for ophthalmic use (collectively, referred to as ophthalmic dispensers) that are packaged together with the ophthalmic drug as "drug-led combination products" rather than simply as drugs. This reclassification affects all products with approvals, pending applications and OTC monograph drugs. FDA also will exercise enforcement discretion for the next 12 months with respect to noncompliance with 21 C.F.R. Part 820 (cGMP/quality system regulation (QSR)) and 21 C.F.R. Part 4, Subpart B (recalls). For products subject to a pending application, FDA intends to request that firms provide additional documentation and information, including an updated Form FDA-356h, and FDA may determine that a pre-approval inspection of combination product manufacturing facilities may be warranted before application approval.

Notably, FDORA partially reverses the *Genus* decision for some products. Section 3621 of the 2023 Omnibus amends § 503 of the FDCA to define contrast agents, radioactive drugs and OTC monograph drugs as drugs rather than devices.

Other FDORA highlights for medical devices include the following:

- Certificates to Foreign Governments (CFGs) (2023 Omnibus § 3304) states that FDA may issue CFGs for devices manufactured outside the United States provided that the manufacturer is registered, the device is listed, and the device is lawfully sold and imported or offered for import in the United States.
- Bans of Devices for One or More Intended Uses (2023 Omnibus § 3306) authorizes FDA to ban a device "for one or more intended uses." This section is a response to *Judge Rotenberg Educ. Ctr., Inc. v. FDA*, which held that FDA could not proscribe a particular intended use of a device. Such a limitation violates 21 U.S.C. § 396, which prohibits FDA from regulating the practice of medicine. The legislative fix clarifies that when FDA bans one or more intended uses, the devices are not legally marketed when intended for such uses.

In January 2022, FDA issued its Notifying FDA of a Permanent Discontinuance or Interruption in Manufacturing of a Device Under Section 506J of the FD&C Act draft guidance, which is intended to address implementation of § 506J of the FDCA outside the COVID-19 PHE. Section 506J requires manufacturers to notify FDA of a permanent discontinuance or interruption in the manufacture of certain devices that is likely to lead to a meaningful disruption in supply of that device. FDA defines "permanent discontinuance" as being "when the manufacturer ceases manufacturing and distributing a product indefinitely for business or other reasons," and defines "interruptions in manufacturing" as being those "that occur as a result of a decrease in manufacturing capability or an increase in demand due to the current or potential public health emergency." FDA states that device manufacturers should report based on their own capacity, supply and orders. They should not base reporting on their perception of market demand for the device or the capacity of other device manufacturers. Section 2514 of the 2023 Omnibus also codifies FDA's authority to receive voluntary notifications from manufacturers of certain medical devices regarding a discontinuance in the manufacture of the device or an interruption of manufacture likely to lead to a "meaningful disruption" in supply.

In January 2022, FDA issued its Principles for Selecting, Developing, Modifying, and Adapting Patient-Reported Outcome Instruments for Use in Medical Device Evaluation: Guidance for Industry and Food and Drug Administration Staff, And Other Stakeholders. A patient-report outcome (PRO) instrument facilitates the systematic collection of how patients feel, function and survive to support the regulatory and healthcare decision-making processes (*e.g.*, patient journals, rating scales, symptom measures, questionnaires) and may be considered valid scientific evidence to measure the effects of an investigational product or changes in health status. The guidance addresses selection of PRO instruments, including the importance of ensuring they are fit for purpose, and details best practices to ensure that PRO instruments are relevant, reliable and sufficiently robust. The key principles when incorporating a PRO instrument are as follows:

- Establishing or defining the concept of interest that the PRO instrument is designed to capture
- Identifying the role of the PRO instrument (*e.g.*, safety, effectiveness, primary, secondary, ancillary) in the study protocol and statistical analysis plan
- Providing or documenting evidence of the PRO instrument's reliability in assessing the concept of interest
- Appropriately and effectively communicating the PRO-related results in labeling.

In evaluating whether a PRO instrument is fit for purpose, sponsors should consider whether the concept of interest being measured is meaningful to patients, the role the PRO instrument will play in the study protocol and statistical analysis plan, and whether the evidence supports the instrument's use in measuring the concept of interest.

In February 2022, FDA published its Medical Devices; Quality System Regulation Amendments proposed rule, discussed in depth here. While FDA generally framed the proposal as an effort to incorporate International Organization for Standardization (ISO) 13485 (2016) by reference, the proposal includes several key changes that medical device manufacturers should consider for potential comment. These include requirements relating to risk management within quality management systems (QMS), clarification and revisions to certain defined terms, recordkeeping requirements, current cGMP requirements for combination products, and changes

to FDA's long-standing Quality System Inspection Technique (QSIT) procedures.

As part of the 510(k) process, FDA assesses the completeness of a 510(k) during what is known as the acceptance review, and it assesses the quality of the submitted information during the substantive review. In April 2022, FDA issued its Refuse to Accept Policy for 510(k)s guidance, which provides detailed information on how FDA will assess whether a submission is administratively complete and includes all information necessary to proceed to substantive review. Applicants can use the guidance's appendices to conduct a self-review prior to submitting a 510(k).

FDA's Voluntary Improvement Program (VIP) is a voluntary public-private partnership program facilitated by the nonprofit Medical Device Innovation Consortium (MDIC). The VIP is a quality maturity appraisal and continuous improvement program that uses third-party appraisals to evaluate the capability and performance of device manufacturers' practices that have undergone FDA marketing review (*i.e.*, manufacturers of devices exempt from premarket review or approval are not eligible). In May 2022, FDA issued its Fostering Medical Device Improvement: FDA Activities and Engagement with the Voluntary Improvement Program draft guidance to discuss potential benefits of, and expectations for, VIP participation. VIP participants that demonstrate sustained performance for improvements may benefit from consideration in FDA's risk-based inspection planning and the opportunity to use a modified submission format for various submissions related to modifications to manufacturing, site changes or manufacturing modules. Participating manufacturing sites must undergo initial and annual appraisals, perform check-ins and submit certain quality performance measures. Manufacturers must also have a history of compliance with applicable FDCA requirements, and participants can either voluntarily withdraw or be recommended for removal by FDA if they do not continue to comply with requirements of participation.

In its October 2022 draft Select Updates for the Breakthrough Devices Program Guidance: Reducing Disparities in Health and Health Care, FDA made select updates to its still-in-effect December 2018 Breakthrough Devices Program guidance. FDA clarified that the Breakthrough Devices program may be available to devices that benefit populations impacted by health or healthcare disparities. FDA also clarified that certain non-addictive medical products to treat pain or addiction may be eligible under the Breakthrough Device program, consistent with § 3001 of the Substance Use-Disorder Prevention that Promotes Opioid Recovery and Treatment for Patients and Communities Act (SUPPORT Act).

In July 2022, FDA issued its Unique Device Identification: Policy Regarding Compliance Dates for Class I and Unclassified Devices, Direct Marking, and Global Unique Device Identification Database Requirements for Certain Devices guidance, replacing its July 2020 Unique Device Identification: Policy Regarding Compliance Dates for Class I and Unclassified Devices and Certain Devices Requiring Direct Marking guidance. FDA indicated that it does not intend to enforce the Global Unique Device Identification Database (GUDID) submission requirements under 21 CFR § 830.300 for consumer health products. While FDA did not define consumer health products, it indicated that it does not consider Class I devices typically used in healthcare settings and Class I devices that require a 510(k) to be under this categorization. FDA extended the existing compliance policy regarding GUDID submission requirements for all class I and unclassified devices, other than implantable, life-supporting or life-sustaining devices, for an additional 75 calendar days to December 8, 2022.

In advance of its October 2022 Medical Devices; Ear, Nose, and Throat Devices; Establishing Over-the Counter Hearing Aids final rule, in August 2022 FDA issued its Regulatory Requirements for Hearing Aid Devices and Personal Sound Amplification Products guidance, which summarizes the applicable FDCA

requirements for hearing aids and personal sound amplification products (PSAPs). While PSAPs are subject to FDA's regulatory requirements for electronic products and radiation-emitting products, because PSAPs are not intended for use by non-hearing-impaired users and are used to accentuate sounds in specific listening environments (*e.g.*, listening for prey while hunting), they do not meet the medical device definition and are not required to comply with medical device regulations. FDA provides examples of intended uses or claims for PSAPs that would suggest they are intended for use as a medical device (*i.e.*, hearing aid). The October 2022 final rule, which preempts state and local laws to the contrary, establishes an OTC category of hearing aids for adults with perceived mild to moderate hearing impairment. OTC hearing aids must be manufactured under the QSR and must be accompanied by user-friendly labeling. The final rules limit the maximum sound output and insertion depth of OTC hearing aids and requires that they include user-adjustable volume control to allow the user to make high-level customizations to the output characteristics most significant to the user's hearing perception. "Self-fitting," on the other hand, is a process that instills frequency-dependent output settings that is intended to correspond to the user's audiogram. Self-fitting hearing aids remain subject to the 510(k) requirement.

FDA issued its October 2022 Procedures for Handling Post-Approval Studies Imposed by PMA Order guidance to provide information regarding format, content and review of post-approval studies and their protocols and study timelines (*e.g.*, enrollment milestones and completion).

The Voluntary Malfunction Summary Reporting (VMSR) program allows manufacturers of devices within eligible product codes to submit certain device malfunction medical device reports (MDRs) in summary form quarterly, as an alternative to submitting individual 30-day malfunction reports. The program excludes deaths, serious injuries and malfunctions subject to the five-day malfunction report. FDA periodically evaluates the eligible product codes, and manufacturers can submit eligibility requests to FDA. In its December 2022 Voluntary Malfunction Summary Reporting (VMSR) Program for Manufacturers: Draft Guidance for Industry and Food and Drug Administration Staff, FDA provided additional information on how manufacturers may submit eligibility requests and the mechanics of quarterly reporting.

In its December 2022 Content of Human Factors Information in Medical Device Marketing Submissions: Draft Guidance for Industry and Food and Drug Administration Staff, FDA provided recommendations on the content of human factors (HF) or usability engineering information applicants should include in marketing submissions. FDA introduced risk-based HF submission categories 1 to 3 and a flow chart to determine the HF submission category.

- For Category 1, which presents the lowest risk, applicants should submit a conclusion and high-level summary of the HF evaluation.
- For Category 2, applicants should provide a rationale in submission for why, for new devices, there are no critical tasks (*i.e.*, a task that, if performed incorrectly or not performed at all by the user, would or could cause serious harm to the patient or user, where harm is defined to include compromised medical care) or, for modified devices, there are no new critical tasks introduced or no changes that impact critical tasks.
- For Category 3, which presents the highest risk, applicants should provide an HF engineering report that includes validation testing addressing, for new devices, critical tasks or, for modified devices, new critical tasks introduced or existing critical tasks impacted by change.

Looking Ahead to 2023

In 2023, FDA will continue to focus resources and investment in the development and harmonization of technical and performance standards for medical devices. The implementation of the EU Medical Device Regulation and the growing complexity of medical device supply chains will likely spur increased focus on harmonizing and updating quality standards to align with global requirements. Innovations in device design and increased complexity of premarket submissions for novel devices may prompt greater focus on design controls, engineering and HF testing.

DIGITAL HEALTH

In April 2022, FDA issued its draft Cybersecurity in Medical Devices: Quality System Considerations and Content of Premarket Submissions guidance, replacing its 2018 draft version discussed here. When final, the guidance will supersede the October 2014 Content of Premarket Submissions for Management of Cybersecurity in Medical Devices – Final Guidance. FDA removed the concept of Tier 1 and Tier 2 cybersecurity risk levels introduced in the 2018 draft guidance. FDA also introduced the concept of a secure product development framework (SPDF), or a set of processes to reduce the number and severity of vulnerabilities throughout the total product lifecycle. Elements of such an SPDF include the following:

- Threat modeling (*i.e.*, identifying security objectives, risks and vulnerabilities)
- Assessing third-party software components for cybersecurity risk and addressing identified risks
- Having a robust software bill of materials (SBOM) (*i.e.*, a complete inventory of codebase)
- Providing FDA with a list of software anomalies (*e.g.*, bugs, defects) and the impact of each anomaly on the device's safety or effectiveness
- Documenting outputs of the security risk management processes
- Ensuring resources and processes to identify, assess and mitigate vulnerabilities as they are identified throughout the total product lifecycle.

The updated guidance also includes recommendations related to communication and documentation.

The increased importance of cybersecurity is also apparent in FDORA, which codifies FDA's authority to establish cybersecurity requirements for medical devices. As part of FDORA, FDA defines "cyber devices" as devices that (1) include software validated, installed or authorized by the sponsor as a device or in a device; (2) have the ability to connect to the internet; and (3) contain any such technological characteristics validated, installed or authorized by the sponsor that could be vulnerable to cybersecurity threats. Manufacturers of these devices must submit a plan to FDA to monitor, identify and address cybersecurity vulnerabilities, and they must implement processes and procedures to provide a reasonable assurance that such devices are cybersecure. *See* 2023 Omnibus § 3305.

In September 2022, FDA concluded its five-year Software Pre-Certification Pilot Program and issued its Report: The Software Precertification (Pre-Cert) Pilot Program: Tailored Total Product Lifecycle Approaches and Key Findings. The pilot involved FDA conducting ongoing "excellence appraisals" of the pilot's nine participants, *i.e.*, assessments of the culture of quality and organizational excellence, ability to develop safe and effective devices, and capacity to monitor and improve products during the product's lifecycle. The objective was to streamline FDA's medical device review process for pre-certified organizations. In the report, FDA described the current framework as "rigid" and therefore unable to adapt to new information, including device improvements and emerging medical technology such as software devices. FDA concluded that a new regulatory paradigm through legislative change could

optimize FDA's ability to regulate medical device software and improve public health outcomes. FDA also concluded that the limited participation combined with the need to limit products to those subject to a *de novo* classification resulted in few devices being available for consideration. Relatedly, FDA acknowledged that the pilot program created regulatory complexities for follow-on devices seeking to rely on Pre-Cert pilot program devices as predicates. Because devices in the Pre-Cert program received their clearance through a streamlined review process for general and special controls, new market entrants that did not undergo the same excellence appraisal as their pilot program predicates may be unable to demonstrate substantial equivalence in the same way. The inability to apply the same review process and standards for new market entrants is not only inconsistent with substantial equivalence requirements, it also would lead to inevitable questions of fairness and potentially meaningful differences in product quality and performance. Finally, FDA was not able to require pilot participants to provide information that was not otherwise already required under the FDCA, although many participants provided additional information on a voluntary basis.

As discussed in depth here, in September 2022, FDA issued its final CDS software guidance. FDA also reissued its Policy for Device Software Functions and Mobile Medical Applications and its Medical Device Data Systems, Medical Image Storage Devices, and Medical Image Communications Devices guidance documents to reflect the changes to the CDS software guidance.

In September 2022, FDA issued its Computer Software Assurance for Production and Quality System Software draft guidance, which provides recommendations on "computer software assurance"—a risk-based approach to establish confidence in the automation used for quality or production systems or implement improvements thereto—and automated data processing systems used as part of device quality or production systems. FDA provided guidance on testing methods and activities that may be used to validate computer software and establishing appropriate records for assurance activities.

FDA's 2019 Proposed Regulatory Framework for Modifications to Artificial Intelligence/Machine Learning-Based Software as a Medical Device discussion paper introduced the concept of a "predetermined change control plan," which would include the types of anticipated modifications based on an algorithm's retraining and model update strategy. Section 3308 of the 2023 Omnibus codifies this concept by establishing § 515C of the FDCA. The new section authorizes FDA to approve a predetermined change control plan submitted in a premarket approval or 510(k) that would describe planned changes that may be made without impacting the device's safety or effectiveness. Changed versions of a device implemented in accordance with an established predetermined change control plan cannot be used as a predicate device; only the originally cleared or approved version may be used as a predicate.

Looking Ahead to 2023

FDA's focus on refining and harmonizing standards for digital health will continue in 2023. The growth of entities such as the Office of Science and Engineering Laboratories within the Center for Devices and Radiological Health (CDRH), which conducts testing and research to inform regulatory decisions and standards for innovative medical devices including additive manufacturing and artificial intelligence/machine learning, signals a move toward new consensus standards for digital health and software as a medical device (SaMD). Cybersecurity will continue to be a focus for FDA with a likely increase in cybersecurity "observations" in routine inspections as FDA ramps up device inspections post-pandemic. It is also possible that legislative efforts will focus on clarifying FDA's authority to regulate certain types of CDS in wake of concerns regarding the expanded scope of authority in the final CDS

software guidance. It is also possible that legislation will be introduced to give FDA greater flexibility to implement the software Pre-Cert program or similar expedited pathways for SaMD.

LABORATORY DEVELOPED TESTS AND PRECISION MEDICINE

Legislative Proposals

For several years, members of Congress, industry stakeholders and the FDA itself have been actively engaged in the development of legislation that, if enacted, would fundamentally alter FDA's oversight of IVDs, including LDTs. Congress did not enact the latest iteration of this legislation—the VALID Act—as part of the medical device user fee reauthorization bill in September 2022 or as part of the 2023 Omnibus in December 2022. However, as it appears likely that VALID will be reintroduced in some form in 2023, we offer the following summary of the bill's key provisions.

If eventually enacted, VALID would represent a significant turning point in FDA's oversight of IVDs, as it would settle a longstanding legal debate regarding FDA's authority to regulate tests offered as LDTs, most of which have historically been offered under the agency's enforcement discretion. Under FDA's exercise of enforcement discretion, clinical laboratories that developed LDTs were not subject to certain requirements that typically apply to medical device manufacturers, such as premarket review (depending on complexity), registration and listing requirements, medical device reporting, the QSR and post-market controls.

The version of the legislation that came so close to passing last term would have created a new category of regulated product—*in vitro* clinical tests (IVCTs)—comprising test kits, systems, protocols, instruments, specimen receptacles and software meeting certain criteria. IVCTs would be regulated pursuant to a tiered, risk-based framework based on their respective classification, *i.e.*, as "high-risk," "moderate-risk" or "low-risk" tests:

- An IVCT would be considered high-risk when an undetected inaccurate result from the respective test or test category is "reasonably likely" to result in serious or irreversible harm to patients or serious harm to the public health, or the test is "reasonably likely to result in the absence, significant delay, or discontinuation of life-supporting or life-sustaining medical treatment" when used as intended, and mitigating measures are not available to sufficiently protect against such results.
- An IVCT would be considered moderate-risk when the test or test category does not meet the criteria for a high-risk or a low-risk test. A moderate-risk IVCT includes tests that would otherwise be considered high-risk, but for which mitigating measures can be established and provided to sufficiently protect against the harmful results.
- An IVCT would be considered low-risk when an undetected or inaccurate result from the respective test or test category causes only "minimal or immediately reversible harm" to patients and would lead only to a remote risk of adverse patient or public health impact when used as intended, or sufficient mitigating measures are applied to ensure the test meets this standard.

Other key aspects of the VALID Act include the following:

Premarket Review

In general, IVCTs would not be permitted to enter interstate commerce unless they undergo premarket or abbreviated premarket review, are offered under a

technology certification order or meet the requirements of an applicable exemption. The appropriate premarket review pathway would depend on an IVCT's risk classification. High-risk IVCTs must undergo full premarket review, moderate-risk tests must undergo either abbreviated premarket review or be offered pursuant to a technology certification order, and low-risk IVCTs are generally exempt from premarket review. For all tests subject to premarket review requirements, VALID would require test developers to provide "valid scientific evidence" that the test is analytically valid and clinically valid for its intended use.

Technology Certification

In a notable addition to a framework that otherwise largely follows FDA's approach to the regulation of medical devices, VALID would create a new "technology certification" program under which a test developer that adequately demonstrates it has implemented necessary validation and quality procedures (among other requirements) may offer certain moderate-risk tests (or modifications to such tests) falling within the scope of an order from FDA without submitting a test-specific request for premarket approval. High-risk tests, as well as first-of-a-kind tests without appropriate mitigating measures, would not be eligible for technology certification. For eligible tests, the technology order would provide a potentially streamlined approach to IVCT development.

Exemptions from Premarket Review

Certain IVCTs would be exempt from premarket review, including low-risk tests, humanitarian tests (*i.e.*, those that are used to diagnose contagious and non-contagious diseases are limited to a certain number of individuals and meet criteria set forth in the VALID Act), custom tests and low-volume tests, and manual tests.

The most recent version of the VALID Act also added a narrow exemption for academic medical center (AMC) laboratories if certain criteria are met, including the following:

- The laboratory is part of an AMC that has a medical residency or fellowship program related to IVCT development.
- The test is performed solely on the order of licensed provider who is on the staff of the AMC.
- The test is performed solely for patients receiving care at the same physical location as the AMC lab.
- The test serves a purpose that would not be met by an available approved test.
- The test is not advertised or promoted outside the AMC, unless it conspicuously discloses the specified patient limitations.

Considering these conditions, this exemption would appear to have limited applicability to AMC labs, including those operating as more traditional reference laboratories.

Grandfathered and Transitional IVCTs

Many tests historically offered as LDTs in high-complexity Clinical Laboratory Improvement Amendments (CLIA) labs would be eligible for grandfathering—and therefore would generally not be subject to premarket review, labeling requirements, or design and quality requirements—if they are first offered for clinical use within 45 days of the enactment of the VALID Act and were not intended solely for investigational use. Grandfathered tests would, however, remain subject to other FDA regulatory obligations, such as registration and listing, and adverse event reporting.

In a notable deviation from previous proposals, LDTs incorporating at-home specimen collection would not be eligible for grandfathered status unless the specimen is collected with a container that has been approved or cleared by FDA (or is otherwise legally marketed for use) for home specimen collection, and

the collection procedure is performed consistent with the product's directions for use. This limitation may significantly restrict many at-home testing companies' ability to leverage grandfathered status for tests previously offered as LDTs.

VALID would allow FDA to "claw back" grandfathered status for a test upon determining, for example, that there is insufficient evidence to support clinical validity or analytical validity of the test, or false or misleading analytical or clinical claims have been made about the test. Any claw back would be made following a public process that affords the opportunity for labs to respond to FDA's allegations.

Transition Period and Effective Date

The VALID Act would also provide a transition period for IVCTs first offered between the cutoff for grandfathering and the effective date of the law (October 1, 2028). Such tests may remain on the market after the VALID Act's effective date, provided the developer submits an application within a specified time period (*i.e.*, within 90 days of the effective date for high-risk tests, or lists the test within 10 days and submits an application for the test within one year of the effective date for moderate-risk tests). Additional extensions would apply to IVCTs that have been approved by the New York State Department of Health. The VALID Act allows an extension of five years after the date of enactment (to October 1, 2033) for an application for a genetic testing molecular test, a microbiology molecular test, an oncology molecular test or any other type of molecular test, and two years (to October 1, 2030) for other IVCTs approved by the New York State Department of Health.

Modifications

Under VALID, modified tests meeting certain criteria (*i.e.*, tests that have gone through premarket review, but for which modifications do not constitute significant changes to the indications for use, cause the test to no longer comply with mitigating measures, or significantly change performance claims or significantly and adversely change performance requirements) would not be required to undergo premarket review. Furthermore, VALID explicitly recognizes the concept of a change protocol, under which FDA and a test developer would pre-negotiate the requirements to validate certain modifications to a test, and it would allow a developer to incorporate such modifications without receiving prior FDA approval provided the developer follows such protocol.

Additional Regulatory Requirements

Borrowing heavily from the existing medical device framework, the VALID Act would subject IVCT developers—unless exempt—to establishment registration, device listing, quality systems (including design controls), adverse event reporting, labeling restrictions, inspection, corrections and removal, and user fees for premarket applications.

Looking Ahead to 2023

If enacted next term in substantially the same form, the VALID Act would go into effect on October 1, 2028, bringing with it a sweeping change to the regulatory landscape for diagnostic testing services. While it is unclear whether the law will be enacted, IVCT developers—particularly clinical laboratories that have not historically been subject to the FDA regulatory scheme—should begin reviewing the previous term's text and planning for compliance with the new regulatory regime. Stakeholders also would have a substantial opportunity to influence FDA's thinking on the implementation of VALID by participating in the notice and comment rulemaking process contemplated by the law.

It is also possible that the agency will take regulatory action to increase its oversight of LDTs, independent of VALID. LDT developers should monitor agency announcements on this topic as well.

FOOD AND DIETARY SUPPLEMENTS

In 2022, FDA continued to balance its priorities to address the global pandemic while simultaneously redirecting resources to other regulated industries. FDA resumed its focus on critical issues for the food and dietary supplement industries, such as implementation of food safety and compliance under the Food Safety Modernization Act (FSMA), label claims and novel food ingredients.

In January 2022, FDA issued a proposed rule, Food Additives: Food Contact Substance Notification That Is No Longer Effective, which proposes to amend the regulations related to the procedures by which FDA determines that a premarket notification for a food contact substance (FCN) is no longer effective. The proposed rule, if finalized, would ensure that manufacturers or suppliers have the opportunity to provide input before FDA can determine that an FCN is no longer effective. FDA likely issued this proposed rule in response to requests from public interest groups to remove certain substances from the food additive regulations because of environmental and other concerns (*see, e.g.*, *National Resources Defense Council et al.*, a petition to remove three perfluoroalkyl-ethyl-containing food-contact substances (filed January 7, 2015, denied January 26, 2022) (FDA Docket No. FDA-2015-F-0714)).

In April 2022, FDA issued its guidance Compliance with Providing an Acceptable Unique Facility Identifier for the Foreign Supplier Verification Programs for Food Importers Regulation, which replaces its March 2018 guidance of the same name. The 2022 guidance removes the temporary policy of permitting the use of the entity role code "UNK" (unknown) in lieu of a Data Universal Numbering System (DUNS) number. As of July 24, 2022, Foreign Supply Verification Program (FSVP) importers must comply with the requirement in 21 C.F.R. § 1.509(a) by providing a unique facility identifier recognized as acceptable by FDA when filing entry with US Customs and Border Protection (CBP). CBP will reject an entry line of a food subject to the FSVP regulation when the importer's DUNS number is not provided in the entity number field.

In April 2022, FDA issued its draft guidance The Accredited Third-Party Certification Program: Questions and Answers, which answers frequently asked questions relating to the requirements of the Accredited Third-Party Certification Program (also referred to as the Third-Party Program or TPP) established in 21 C.F.R. Part 1, Subpart M (21 C.F.R. §§ 1.600-1.695, 21 C.F.R. §§ 1.700-1.725). This guidance intends to assist accreditation bodies, third-party certification bodies and eligible entities in understanding the TPP regulation and program requirements for conducting food safety audits and certifying that eligible foreign food entities and food produced by such entities meet applicable FDA requirements.

In March 2022, FDA denied two citizen petitions requesting that the agency render a decision regarding the status of N-acetyl-L-cysteine (NAC) as a dietary supplement. FDA followed this action by issuing the April 2022 draft guidance Policy Regarding N-acetyl-L-cysteine, in which the agency indicated that it will exercise enforcement discretion for products containing NAC and labeled as a dietary supplement. FDA issued a final version of the guidance in August 2022. Also relevant to the dietary supplement industry, in May 2022, FDA issued its draft guidance Policy Regarding Certain New Dietary Ingredients and Dietary Supplements Subject to the Requirement for Pre-market Notification, which outlines FDA's intent to exercise enforcement discretion over companies that fail to submitted a premarket safety notification to FDA at least 75 days before introducing a product that contains a new dietary ingredient into the food supply, in accordance with § 413(a)(2) of the FDCA.

In June 2022, FDA issued FDA Oversight of Food Covered by Systems Recognition Arrangements,

which provides guidance related to FDA's regulatory oversight activities for food covered by a Systems Recognition Arrangement between another country's food safety authority and FDA. Such an arrangement establishes a regulatory partnership between FDA and the foreign country's food regulatory counterpart. To the extent practicable, FDA will leverage the work done by foreign competent authorities to help ensure the safety of imported foods.

In September 2022, FDA published the long-awaited proposed rule Food Labeling: Nutrient Content Claims; Definition of Term "Healthy," which proposes to update the definition for the implied nutrient content claim "healthy" to be consistent with current nutrition science and federal dietary guidance. This action, if finalized, will revise the requirements for when the term "healthy" can be used as an implied claim in the labeling of human food products to indicate that a food's level of nutrients may help consumers maintain healthy dietary practices by helping them achieve a total diet that conforms to dietary recommendations. The requirements associated with the term "healthy" impact many food companies and other stakeholders. It is anticipated that numerous comments will be submitted, which will likely extend the rulemaking process and finalization of the rule.

In November 2022, FDA issued a press release, FDA Completes First Pre-Market Consultation for Human Food Made Using Animal Cell Culture Technology. FDA evaluated information submitted by UPSIDE Foods regarding its use of animal cell culture technology to take living cells from chickens and grow the cells in a controlled environment to make the cultured animal cell food. FDA had no further questions about the safety conclusions. This is an important step in the advancement of cell-based food technology and encouraging for other companies considering pursuing FDA review.

In November 2022, FDA issued its Draft Guidance for Industry: Questions and Answers Regarding Food Allergen Labeling (Edition 5) and finalized the Guidance for Industry: Questions and Answers Regarding Food Allergen Labeling (Edition 5). These documents were updated to reflect, among other things, the addition of sesame as a major allergen and innovations in food manufacturing (*e.g.*, plant/cell-based production).

The FDA's focus on food safety continued in 2022 with the publication of the following:

- Beverages: Bottled Water final rule (April 2022), which revises the bottled water quality standard for fluoride, not to exceed of 0.7 milligrams per liter
- Action Levels for Lead in Juice draft guidance (April 2022), which is intended to reduce exposure to lead and establishes new action levels for lead of 10 ppb for apple juice on a single-strength (ready-to-drink) basis and an action level for lead of 20 ppb for other single-strength juice types, including juice blends that contain apple juice (the most commonly consumed juice by young children in the United States)
- Reducing Microbial Food Safety Hazards in the Production of Seed for Sprouting guidance (May 2022), which includes recommendations for growing, conditioning, holding and distributing seeds for sprouting considering FDA's concern about the continuing outbreaks of foodborne illness associated with the consumption of sprouts
- Compliance dates for Standards for the Growing, Harvesting, Packing, and Holding of Produce for Human Consumption Relating to Agricultural Water proposed rule, which provides that FDA will exercise enforcement discretion on the compliance dates for the harvest and post-harvest agricultural water requirements for covered produce other than sprouts
- Prevention of Salmonella Enteritidis in Shell Eggs During Production, Storage, and Transportation

(Layers with Access to Areas Outside the Poultry House): Questions and Answers Regarding the Final Rule guidance (August 2022), which identifies, among other things, areas outside of the "poultry house," as that term is defined in 21 C.F.R. § 118.3, and considerations for managing and monitoring the area to prevent *salmonella enteritidis* from contaminating eggs

- Current Good Manufacturing Practice and Preventive Controls, Foreign Supplier Verification Programs, Intentional Adulteration, and Produce Safety Regulations: Enforcement Policy Regarding Certain Provisions (March 2022), which explains specific regulatory requirements that FDA does not intend to enforce based on its current understanding of risks, including certain cGMPs for animal and human food provisions (21 C.F.R. Parts 507 and 117) and other provisions under FSMA
- Requirements for Additional Traceability Records for Certain Foods final rule (November 2022), which establishes additional recordkeeping requirements for persons who manufacture, process, pack or hold foods the agency has designated for inclusion on the Food Traceability List
- Best Practices for Convening a GRAS Panel (December 2022), which provides best practices for convening a Generally Recognized As Safe (GRAS) panel to ensure that it remains unbiased, retains credibility by eliminating the appearance of conflict of interest, and considers data and information that is publicly available.

In Dr. Califf's statements throughout 2022, including his testimony before Congress, Dr. Califf indicated that although the US food supply is safe, the agency requires more resources to protect the public health. In his testimony before Congress, Dr. Califf requested budget increases to support programs such as New Era of Smarter Food Safety initiatives and programs under FSMA.

Looking Ahead to 2023

The food industry continues to evolve with new innovations, manufacturing technologies, expanding palates and diverse consumer expectations. In 2023 we will continue to see new products developed with new plant-based ingredients, further advances in cell-based meats and seafood, and more technologies to meet consumers' expectations for products that are environmentally sustainable. As a result, it will be necessary for FDA to respond to this evolution.

Food labeling, ingredient review and food standards will require the agency's attention and resources. The publication of the "healthy" implied nutrient content claim along with the identification of an additional allergen in 2022 demonstrates FDA's focus on food labeling and safety, which will likely continue in 2023.

If uninterrupted in its efforts, FDA will continue to finalize regulations and implement programs under FSMA and provide continued guidance to food producers on minimizing potential contamination by pathogens. As the impact of the global pandemic begins to normalize, international inspections will likely steadily increase, assuming security and local conditions continue to improve. This will allow FDA inspectors to review foreign food establishments, which will hopefully alleviate current supply chain pressures and increase access to raw materials for food products.

COSMETICS

An important and notable achievement in 2022 was the enactment of the Modernization of Cosmetics Regulation Act of 2022 (MOCRA). This legislation fundamentally changes the regulation of cosmetic products. FDA will promulgate regulations concerning MOCRA and other requirements, such as

testing standards, in the coming years, with active participation by the cosmetic industry.

In particular, MOCRA:

- Requires cosmetic manufacturers to submit adverse event reports to FDA within 15 business days of receipt of such report
- Permits FDA to request lists of ingredients or categories of ingredients in a fragrance or flavor if FDA "has reasonable grounds to believe that an ingredient or combination of ingredients in a fragrance or flavor has caused or contributed to a serious adverse event required to be reported"
- Requires FDA to promulgate regulations on cosmetic cGMP
- Requires cosmetic manufacturers and distributors to register and list products
- Requires manufacturers to ensure there is adequate substantiation regarding cosmetic product safety using "tests or studies, research, analyses, or other evidence or information . . . sufficient to support a reasonable certainty that a cosmetic product is safe"
- Requires that cosmetic products be labeled with contact information to facilitate adverse event reporting, as well as fragrance allergen information
- Requires cosmetic products intended to be used only by a professional to be labeled accordingly
- Provides FDA with mandatory recall authority over cosmetic products if FDA "determines that there is a reasonable probability" a product is adulterated or misbranded and "the use or exposure to such cosmetic will cause serious adverse health consequences or death."

MOCRA expressly preempts local and state laws that are different from its requirements. However, states may continue to prohibit or limit the use of the amount of specific ingredients, and they also may continue to require the reporting of ingredients.

MOCRA also indicates that "[i]t is the sense of the Congress that animal testing should not be used for the purposes of safety testing on cosmetic products and should be phased out with the exception of appropriate allowances."

TOBACCO

In May 2022, FDA issued a pair of proposed rules related to tobacco product standards for cigars and cigarettes to reduce youth and young adult appeal:

- Tobacco Product Standard for Menthol in Cigarettes, to prohibit menthol as a characterizing flavor in cigarettes
- Tobacco Product Standard for Characterizing Flavors in Cigars, to prohibit characterizing flavors (*e.g.*, fruit, candy, chocolate) in cigars and their components and parts.

In August 2022, FDA issued its Tobacco Products: Principles for Designing and Conducting Tobacco Product Perception and Intention Studies, which is intended to assist applicants in designing tobacco product perception and intention (TPPI) studies used to assess individuals' perceptions of tobacco products, consumer understanding of tobacco product information (*e.g.*, labeling, modified risk information) and behavioral intentions to use tobacco products. These TPPI studies may be submitted as part of premarket tobacco product applications (PMTAs), modified risk tobacco product applications(MRTPAs) or substantial equivalence reports. FDA provides guidance on developing TPPI study aims and hypotheses, determining study outcomes, selecting and adapting measures of study constructs, selecting and justifying study samples, and conducting

quantitative and qualitative study analyses and analysis of results.

In its September 2022 Meetings with Industry and Investigators on the Research and Development of Tobacco Products (Revised) guidance, FDA provides updated information about what to include in meeting requests, how and when to submit a request, and what information to submit prior to a meeting for manufacturers, importers, researchers and investigators seeking meetings with the Center for Tobacco Products (CTP) related to research on, and the development and marketing of, tobacco products.

In its September 2022 Tobacco Health Document Submission (Revised) guidance, FDA reiterates that it does not intend to enforce the requirement of immediate and ongoing submissions of *all* health documents (*i.e.*, documents that address the health, toxicological, behavioral or physiological effects of current or future tobacco products, their constituents (including smoke constituents), ingredients, components and additives) on manufacturers and importers of tobacco products, but manufacturers and importers are obligated to preserve such documents for future submissions. FDA's current compliance plan requires manufacturers and importers to submit health documents developed between June 23, 2009, and December 31, 2009, if not previously submitted, at least 90 days prior to a tobacco product's delivery for introduction into interstate commerce.

As required by an order issued by the US District Court for the Eastern District of Texas, in November 2022 FDA issued its Tobacco Products; Required Warnings for Cigarette Packages and Advertisements; Delayed Effective Date final rule, which delayed the effective date for required warnings for cigarette packages and advertisements to November 6, 2023.

CANNABIS

On December 2, 2022, President Joseph Biden signed into law the Medical Marijuana and Cannabidiol Research Expansion Act (Cannabis Research Act), which provides a mechanism for industry and academia to access and research cannabis, including marijuana and other cannabis-derived products, without violating the Controlled Substances Act (CSA). The Cannabis Research Act creates a pathway for researchers to register with the US Department of Justice to legally conduct scientific research on such products subject to certain requirements. The Cannabis Research Act also creates a system to allow drug manufacturers to legally produce FDA-approved products that contain cannabidiol (CBD) or marijuana for commercial sale. Of particular significance for healthcare providers, the Cannabis Research Act includes a doctor-patient relationship provision that permits state-licensed physicians to discuss the "currently known potential harms and benefits of marijuana and its derivatives, including cannabidiol, which may be derived from marijuana or other cannabis products such as hemp, as a treatment."

However, because cannabis, in particular marijuana, has been a Schedule I drug under the CSA for more than 50 years, which means by definition that it has no medical uses and a high risk of abuse, there is little information about potential medical uses of marijuana and its derivatives available for physicians to provide to their patients. Notwithstanding its Schedule I status, marijuana has remained in wide use for recreational and largely self-diagnosed medical purposes, and is now legal in 39 states for one or both purposes. To date, marijuana research has been narrowly limited by the US Drug Enforcement Administration (DEA) and National Institute on Drug Abuse (NIDA). FDA also has failed to issue regulations regarding hemp (*i.e.*, cannabis with less than 0.3% tetrahydrocannabinol, also known as delta-9 tetrahydrocannabinol or THC, which is a principal psychoactive component of non-hemp cannabis/marijuana).

Over the years since marijuana's initial scheduling, many groups have petitioned the DEA to re- or de-schedule it, but the lack of research with respect to marijuana's potential medical benefits has helped to

keep it on Schedule I. A significant reason that marijuana research has been limited in the United States is the requirement that scientific researchers obtain marijuana through NIDA and its single-contracted source, the University of Mississippi. As a result, NIDA not only controls the amount and type of such research, but also the quality of the marijuana tested. FDA and the US Department of Health and Human Services may also make scheduling recommendations but have not done so.

Instead of regulating marijuana or its derivatives more directly, FDA continues to believe that the best way to determine appropriate medical uses for marijuana (including CBD derived from hemp) is clinical research under an IND. However, FDA has only approved three cannabis-related drugs to date: Epidiolex®, which contains a purified form of CBD derived from marijuana to treat certain seizures, and Marinol® and Syndros®, which contain synthetic THC (known as dronabinol) for uses including the treatment of anorexia associated with weight loss in AIDS patients.

FDA also has stated that drugs derived from cannabis, such as CBD and THC, cannot be used in dietary supplements since they are drugs made to be ingested, and has focused its enforcement actions on cannabis products with illegal drug claims. In 2022, FDA also began sending warning letters to companies selling animal drugs containing CBD that are intended for food-producing animals, saying FDA has not approved such drugs and therefore they are illegal to sell. FDA added that the use of CBD drugs on food-producing animals has not been properly studied or approved and could have unintended side effects on both the animals and the people who eat the food they produce. FDA also said that "unproven" claims, including claims about relieving anxiety, may cause animal owners to postpone seeking medical care for animals that require veterinary attention and treatment. FDA also has indicated that information from adverse events regarding cannabis use is "extremely limited" (*i.e.*, primarily from the three drugs mentioned previously), and that "additional information about the safety and effectiveness of cannabis and its constituents is needed." However, for the reasons described above, prior to the enactment of the Cannabis Research Act, the federal government had imposed substantial barriers to conducting such research.

In 2020, FDA added Norman Birenbaum, a senior public health advisor, to CDER to help lead and advise the agency to advance efforts related to research and regulation of cannabis. Birenbaum previously served as the chief cannabis policy advisor to the governors of New York and Rhode Island and led the agencies responsible for cannabis regulation and research in both states. Birenbaum's work in New York helped result in the 2021 passage of the Marijuana Regulation and Taxation Act, which legalized cannabis for adult use in New York and created a consolidated Office of Cannabis Management to oversee all cannabis sectors within the state.

Physicians may continue to face challenges in discussing marijuana as a medical option, since a prescription for a medical use of marijuana is generally considered to be illegal under the CSA. Accordingly, DEA-registered physicians may not prescribe Schedule I drugs such as marijuana because, by definition, there are no medically approved uses of such drugs and therefore issuing such prescriptions could result in significant penalties for the prescribing physician. As a result, physicians in states with medical marijuana programs typically provide their patients with a "recommendation" or "certification," a practice that the courts have generally found not to violate the CSA (*see, e.g.*, *Conant v. Walters*, 309 F.3d 629 (9th Cir 2002), *cert*. denied Oct. 14, 2003; see also *Conant v. McCaffrey*, 172 F.R.D. 681 (N.D. Cal. 1997), and *Conant v. McCaffrey*, 2000 WL 1281174 (N.D. Cal. Sept. 7, 2000)). However, states that require physicians to prescribe forms of marijuana may expose those physicians to loss of their DEA registration and potential criminal liability.

At present, the Cannabis Research Act, only authorizes physicians to provide advice to their

patients about the harms and benefits of marijuana use, even though that information is not generally available to them because of marijuana's long-term Schedule I status.

In November 2022, FDA issued warning letters to five companies for allegedly selling adulterated human or animal food, candy and beverage products containing CBD as a food additive. In these instances, FDA reiterated its prior positions that CBD is a drug and does not meet the GRAS status for use in food (including food additives) or dietary supplements, for humans or animals. In some instances, the products included drug claims for humans or animals, some with CBD and others with delta-8-THC, *e.g.*, treating insomnia (human), stress relief, heartbeat/blood pressure regulation (animal), anxiety (human and animal), arthritis (animal), digestion (animal), cancer (human and animal), seizures (human and animal), sunscreen claims (human), stabilizing bipolar disorder (human), Alzheimer's (human), COVID-19 (human), autism (human), depression (human), diabetes (human), auto-immune disorder (human), fibromyalgia (human), and pain and substance abuse (human).

In four of the five warning letters, FDA found several products to be adulterated because they were in forms that would appeal to children and could be confused with traditional foods, such as cookies and candy, consumed by children. Examples of these products include gummy bears, lollipops and fruit snacks with CBD. Prior to November 2022, FDA warning letters regarding CBD focused on dietary supplements with claims to diagnose, cure, mitigate, treat or prevent various diseases, such as cancer or COVID-19. The most recent warning letters suggest that the agency is pivoting its attention toward food and beverages and, specifically, products that may appeal to children or unsuspecting consumers.

Looking Ahead to 2023

FDA has stated publicly that it plans to either provide proposed regulations or ask for additional statutory authority to regulate CBD, hemp-derived products and other cannabis-derived products. As noted above, FDA has mainly provided guidance via warning letters and statements that CBD and other cannabinoids are "drugs" and cannot be included in food and dietary-supplement-type products. Since cannabinoids are drugs, additional research is required to substantiate the approval of new hemp-derived products that have been de-scheduled, and there are other barriers to researching and filing new drug applications for cannabis products defined as "marijuana," *i.e.*, containing more than 0.3% delta-9-THC. The Cannabis Research Act may provide additional opportunities for new cannabis-derived products to be studied and submitted for market applications, but the process will likely take more time for FDA to develop additional expertise and guidance to support such products.

As of this writing, FDA has concluded that its food and dietary supplement authorities provide limited tools for managing the risks associated with CBD products and that it needs additional authorities from Congress to regulate them. Concurrently, FDA denied three citizen petitions requesting the agency to issue a regulation that would allow CBD products to be marketed as dietary supplements, because the agency does not consider the existing dietary supplement and conventional food pathways to be appropriate for CBD. It remains to be seen whether Congress will respond and establish a separate legal and regulatory framework—and possibly a new FDA center—for CBD, similar to when it passed the 2009 Family Smoking Prevention and Tobacco Control Act, establishing CTP.

CLINICAL INVESTIGATIONS AND DATA

In January 2022, FDA issued its Patient Engagement in the Design and Conduct of Medical Device Clinical Studies guidance, which provides recommendations to sponsors on how they can voluntarily use engagement with patients or patient advisors to incorporate patient

experiences, perspectives and other relevant information in the design and conduct of medical device studies. FDA clarifies that patient engagement activities that engage patient advisors in a consultative or advisory capacity, where the patient advisors are not themselves study participants or engaged as caregivers to study participants, do not constitute research or an activity subject to FDA regulation on their own. Section 3607 of the 2023 Omnibus also requires FDA to issue guidance on "the appropriate use of digital health technologies in clinical trials to help improve recruitment for, retention in, participation in, and data collection during, clinical trials."

In April 2022, FDA issued its draft guidance Diversity Plans to Improve Enrollment of Participants From Underrepresented Racial and Ethnic Populations in Clinical Trials, which provides recommendations to sponsors for developing a race and ethnicity diversity plan to enroll representative numbers of participants from traditionally underrepresented racial and ethnic populations in clinical trials. The race and ethnicity diversity plan should include the sponsor's enrollment goals and plans to leverage other data sources (*e.g.*, published literature and real-world data) to establish enrollment goals, plans to assess race and ethnicity in addition to other covariates with known potential to affect the safety and effectiveness of the product, plans to collect data to evaluate the potential for differences in safety or effectiveness associated with race and ethnicity, and planned clinical pediatric studies. Section 3601 of the 2023 Omnibus codifies this diversity action plan requirement for sponsors of pivotal studies for new drugs or investigational devices.

In September 2022, FDA issued a pair of proposed rules intended to harmonize its requirements, to the extent practicable, with the Federal Policy for the Protection of Human Subjects (Common Rule) in accordance with the Cures Act. In Institutional Review Boards; Cooperative Research, FDA proposes to harmonize its requirements for cooperative research and IRB records with the Common Rule as much as possible. The proposed rule, if finalized, would replace current requirements for FDA-regulated cooperative research with a requirement that any institution in the United States participating in FDA-regulated cooperative research rely on review and approval by a single IRB for that portion of the research conducted in the United States. It would also require documentation of an institution's reliance on an external IRB for research oversight and the responsibilities that each entity will undertake. Protection of Human Subjects and Institutional Review Boards would make a series of changes to 21 C.F.R. Parts 50 (Protection of Human Subjects) and 56 (Institutional Review Boards). The proposed rule also would revise 21 C.F.R. § 812.150 to align with IRB continuing review obligations in 21 C.F.R. Part 56.

In its September 2022 Ethical Considerations for Clinical Investigations of Medical Products Involving Children draft guidance, FDA outlines specific concepts that IRBs should consider when reviewing clinical investigations in children in addition to the requirements in 21 C.F.R. Part 50, Subpart D and Part 56:

- Principle of scientific necessity: Children should not be enrolled in a study unless their participation is necessary to answer an important scientific or public health question directly relevant to their health and welfare (*e.g.*, extrapolation of data in adults is insufficient).
- Without prospect of direct benefit: Interventions or procedures *without* prospect of direct benefits should present no more than minimal risk as defined in 21 C.F.R. § 56.102(i), or no more than a minor increase over minimal risk posing no significant threat to the child's overall health or wellbeing.
- Prospect of direct benefit: The direct benefit should result from the intervention or procedure, not ancillary procedures or interventions (*e.g.*, exams). The prospect of direct benefit may be

derived from animal or relevant device modeling and simulation data or, for conditions that extend into adulthood, the prospect of direct benefit may be demonstrated by a favorable effect on biomarkers or surrogate endpoints linked to the causal pathway (*i.e.*, it may be several years before the direct benefit manifests).

- Component analysis: Where there are multiple research interventions or procedures, the IRB should assess whether the procedure is with or without prospect of direct benefit, further assessed under the preceding two bullet points.
- Assessment of risk: For interventions or procedures with the prospect of direct benefit, the risk still must be justified by the anticipated benefit.

Note that procedures without a prospect of direct benefit and risk that exceeds a minor increase over minimal risk must be reviewed and approved by FDA under 21 C.F.R. § 50.54. The guidance also addresses specific application of 21 C.F.R. Part 50, Subpart D, to pediatric clinical investigations, including data that may support the conduct of such studies, study design considerations and study procedures.

In its October 2022 Multiple Endpoints in Clinical Trials, FDA addresses the challenges of interpreting and analyzing studies involving multiple endpoints. Because many diseases and conditions result in more than one symptom, altered function or clinical event, many studies include endpoints to examine the effect of the drug on more than one aspect of the disease or condition. Failure to account for these multiple endpoints can lead to false conclusions regarding the efficacy of a study drug. The guidance discusses general statistical principles that should be considered when a study has multiple endpoints, such as Type I errors (erroneously concluding that the null hypothesis, *i.e.*, a hypothesis that does not demonstrate any significant difference, is necessarily false) and Type II errors (failing to reject a false null hypothesis, *i.e.*, where the results failed to show the effect of a drug when there actually is one). The guidance also includes methodological considerations and a detailed appendix with specific statistical methods commonly used to address multiplicity problems.

COVID-19

The Centers for Devices and Radiological Health announced its intention to finalize its Transition Plan for Medical Devices That Fall Within Enforcement Policies Issued During the Coronavirus Disease 2019 (COVID-19) Public Health Emergency and Transition Plan for Medical Devices Issued Emergency Use Authorizations (EUAs) During the Coronavirus Disease 2019 (COVID-19) Public Health Emergency draft guidance documents in FY 2023. The draft guidance documents are discussed in detail in our 2021 Year in Review.

The current PHE under § 319 of the Public Health Service Act, renewed on January 11, 2023, is set to expire on April 11, 2023. On January 30, 2023, President Biden told Congress that the administration will briefly extend the PHE to May 11, 2023, before terminating it and the still-in-effect National Emergency Concerning the Coronavirus Disease of 2019 (COVID-19) Pandemic.

ADVERTISING AND PROMOTION

In February 2022, FDA issued the proposed rule Certain Requirements Regarding Prescription Drug Marketing, which proposes to amend certain prescription drug marketing regulations to align with changes to the FDCA resulting from the enactment of the DSCSA. Notably, the definitions of "Authorized distributor of record," "Emergency medical reasons," and "Unauthorized distributor and wholesale distribution" in 21 C.F.R. § 203.3 would be modified or deleted.

Section 3630 of the 2023 Omnibus effectively codifies the key provisions of the June 2018 Drug and Device Manufacturer Communications With Payors, Formulary Committees, and Similar Entities – Questions and Answers guidance (discussed in depth here) by amending § 502 of the FDCA. "[N]o drug or device shall be deemed to be misbranded under such paragraph through the provision of truthful and not misleading product information to a payor, formulary committee, or other similar entity with knowledge and expertise in the area of health care economic analysis carrying out its responsibilities for the selection of drugs or devices for coverage or reimbursement if the product information relates to an investigational drug or device or investigational use of a drug or device that is approved, cleared, granted marketing authorization, or licensed" provided that the product information includes the following:

- A clear statement that the product has not been approved, cleared, granted marketing authorization or licensed
- Information related to the stage of development (*e.g.*, status of studies, how the studies relate to the overall development plan, whether a marketing application has been submitted)
- Material aspects of study design (including limitations related to design, methodology and results), as applicable
- Updated information, as applicable.

Product information may not include information that represents that the product has been approved, cleared, granted marketing authorization or licensed, or otherwise been determined to be safe or effective for the purposes for which it is under investigation.

On November 10, 2022, the Federal Trade Commission (FTC) announced a new policy statement relating to § 5 of the FTC Act (which prohibits "unfair methods of competition in or affecting commerce"). This newly adopted policy provides for a significantly more expansive view of the FTC's authority under § 5 and indicates that the FTC intends to investigate conduct it believes to be coercive, exploitative or abusive. Among other "unfair methods of competition," the FTC highlighted "false or deceptive advertising or marketing which tends to create or maintain market power" as an area on which it intends to focus. The FTC has been aggressively enforcing consumer protection standards, and this policy suggests that aggressive posture is likely to continue.

In December 2022, FTC announced requests for public comment on its Guides for the Use of Environmental Marketing Claims (Green Guides). With increased attention to environmentally friendly or sustainable claims, the FTC is seeking to update the Green Guides to reflect current technologies, innovations and consumer perception of these claims.

FTC also issued Health Products Compliance Guidance, discussed in detail here. The guidance supersedes its 1998 Dietary Supplements: An Advertising Guide for Industry. This new guidance addresses advertising statements and substantiation for a wider category of health products, such as food, dietary supplements, devices and smartphone apps, and the use of third-party literature. It also appears to memorialize *POM Wonderful, LLC v. FTC*, in that it limits FTC's historical position for two randomized placebo controlled clinical trials. *See POM Wonderful, LLC v. F.T.C.*, 777 F.3d 478 (D.C. Cir. 2015), cert. denied, 136 S. Ct. 1839 (2016)). The new guidance specifically states that there is no requirement for a specific number of randomized controlled trials, and that the totality of evidence should be considered.

Enforcement

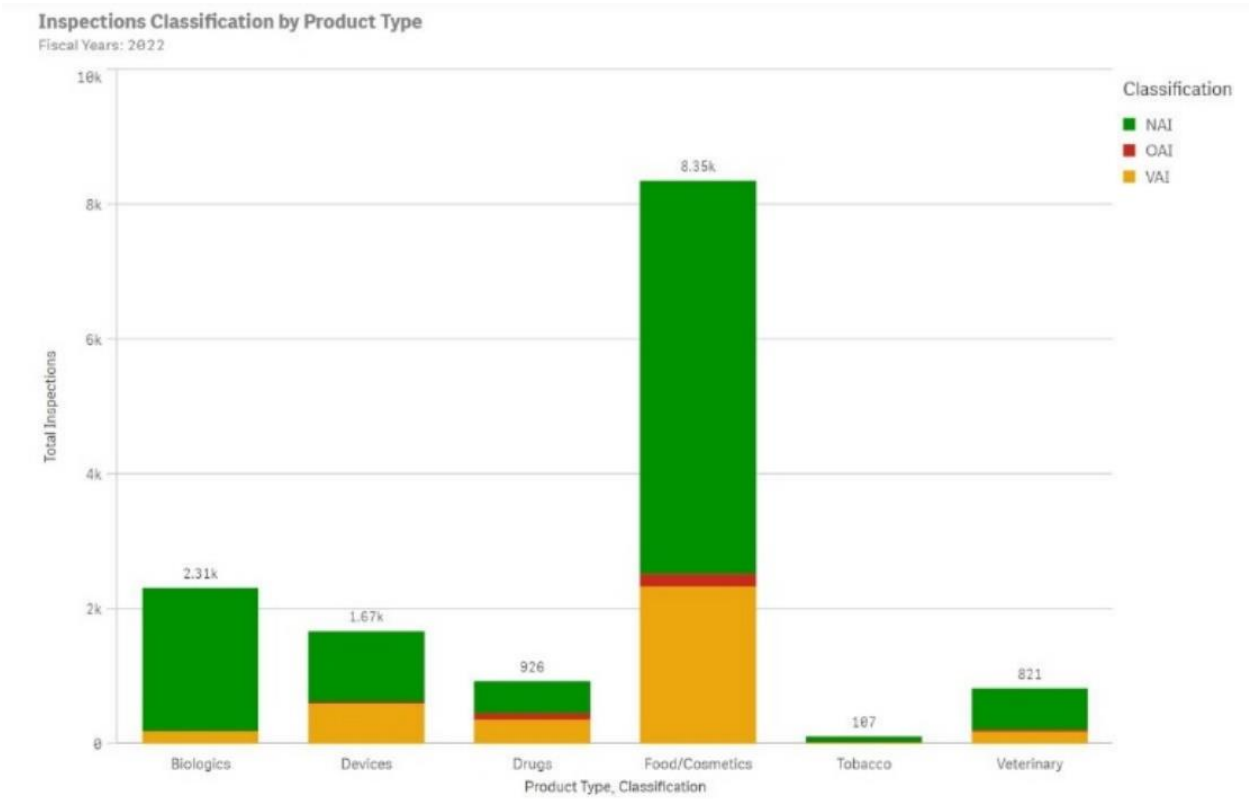
The past year saw very little Office of Prescription Drug (OPDP) enforcement. OPDP issued a single warning letter related to misbranding of an investigational drug. It also issued three untitled letters relating to false or misleading risk presentation, benefit information and claims about efficacy.

ENFORCEMENT

Inspections

Section 707(b) of the 2012 Food and Drug Administration Safety and Innovation Act required FDA to issue guidance defining circumstances that would constitute delaying, denying or limiting inspection or refusing to permit entry or inspection for purposes of § 501(j) of the FDCA, which deems adulterated a drug that is manufactured, processed, packed or held in a factory, warehouse or establishment for which the owner, operator or agent delays, denies or limits an inspection or refuses to permit entry or inspection. In December 2022, FDA issued a revised Circumstances that Constitute Delaying, Denying, Limiting, or Refusing a Drug or Device Inspection: Draft Guidance for Industry, which when finalized will replace the October 2014 Circumstances that Constitute Delaying, Denying, Limiting, or Refusing a Drug Inspection. Critically, the new guidance would extend to device facilities, as the FDA Reauthorization Act of 2017 amended § 501(j) of the FDCA to include devices.

Over the course of 2022, there was a noticeable increase in FDA inspections following a long period of slowed activity due to the COVID-19 pandemic. FDA resumed routine surveillance inspections, which marked a significant shift away from its policy of conducting limited inspections for mission-critical issues (*e.g.*, for illnesses resulting from food contamination). According to FDA's Compliance Dashboard, most FY 2022 inspections occurred within the "Food/Cosmetics" product category:



**This graph is from FDA's Compliance Dashboard, filtered for FY 2022. Classifications are defined as No Action Indicated (NAI), Voluntary Action Indicated (VAI) and Official Action Indicated (OAI).*

Following the release the Data Modernization Action Plan, the Office of Data Analytics Research launched dashboards to support strategies to carry out surveillance inspections according to FDA's Modernization in Action 2022 plan.

To mitigate issues stemming from delayed inspections, such as instances in which foreign surveillance inspections have been postponed, FDA has employed creative approaches and alternative tools. For example, FDA adjusted screening tools, such as the algorithm in its Predictive Risk-Based Evaluation for Dynamic Import Compliance Targeting (PREDICT), to increase oversight of shipments arriving from locations where surveillance inspections have been paused. *See* January 11, 2022, Testimony of Janet Woodcock to the Senate Committee on Health, Education, Labor, and Pensions. The recent uptick in inspections has prompted the agency to update procedures to account for lessons learned during the pandemic. According to the FY 2022 Justification of Estimates for the Appropriations Committees, FDA will continue to implement technological resources to improve oversight across consumer product categories. FDA has worked to modernize infrastructure to allow for the analysis and management of data in recent years, and this trend will likely continue for the foreseeable future. FDA also updated compliance program guides, such as those relating to pre-approval inspections, to formally include inspection tools. The compliance program guide on pre-approval inspections under 7346.832 was updated on October 17, 2022, and it includes reference to alternative tools, such as remote regulatory assessments and remote interactive evaluations.

In 2022, FDA continued to use its significant authority at ports of entry to detain products that "appear" to be violative. Import alerts and detentions provide a means for FDA to enforce against a product or company using minimal resources and placing the burden to demonstrate compliance on the importer of record. Foreign food facilities that refused inspection or could not be inspected due to security or other local conditions were subject to detention without examination (including being identified on the red list). *See* Import Alert 99-32 Detention Without Examination of Products From Firms Refusing FDA Foreign Establishment Inspection. These detentions as well as significant delays at the ports contributed to supply chain and other challenges for companies in 2022.

The 2023 Omnibus also expanded FDA's inspection authorities. Notably, §§ 3611 and 3612 authorize FDA to request "other information" in addition to records prior to (or in lieu of) device and bioresearch monitoring inspections.

FDA's Office of Digital Transformation's Strategic Plan for 2023 to 2025 suggests that FDA plans to use data to support inspection activities through available resources by implementing modernized tools, such as master data management. The agency plans to integrate such tools into its inspection process to more efficiently and effectively use data across multiple systems by the end of FY 2023.

Warning Letters

Despite a slight decline in overall warning letter numbers in 2022 compared to 2021, FDA continues its enforcement efforts to ensure that adulterated, unapproved or misbranded COVID-19-related products are kept off the market. FDA and FTC jointly issued five warning letters to companies allegedly selling unapproved products that make deceptive or false or misleading claims about their ability to treat COVID-19. Outside of the COVID-19-related warning letters, FDA's CTP issued the most warning letters in 2022. The vast majority of the CTP-issued warning letters were related to products manufactured and sold without the required PMTAs.

For food, FDA issued a substantial number of warning letters from import offices under the FSVP. FDA's Center for Food Safety and Applied Nutrition (CFSAN) issued more than a dozen warning letters for adulterated dietary supplements and CBD products containing unsafe food additives or new dietary ingredients.

For drugs, FDA's CDER issued more warning letters than the previous year. Many warning letters issued by CDER or other offices and divisions cited cGMP violations, suggesting a continued focus in this area. As discussed in the Cannabis section of this article, for the first time FDA issued warning letters for products containing delta-8 THC. Several of these warning letters also included violations related to CBD products. CDER also issued warning letters to big box retailers and e-commerce platforms for distributing products containing undeclared drug ingredients to consumers on behalf of third parties through the companies' fulfillment services. These warning letters are noteworthy because FDA has not historically taken action against retailers. FDA's actions in this respect may signal increased agency scrutiny of online retailers selling or enabling the sale of unlawful products.

Notably, 2022 marked a significant downturn compared to 2021 for warning letters issued by FDA's CDRH and other offices related to medical devices. However, almost all the warning letters that did issue cited QSR/cGMP violations, suggesting that this remains an important issue.

Recalls

In March 2022, FDA published its Initiation of Voluntary Recalls Under 21 CFR Part 7, Subpart C: Guidance for Industry and FDA Staff final guidance on March 4, 2022. The guidance describes how firms should develop and implement necessary recall plans and procedures, including training and recordkeeping, to effectively plan, prepare and initiate a voluntary recall to adequately protect the public from a product potentially violative of the FDCA. The final guidance makes minor changes to an April 2019 draft version with the same name, and it reflects the agency's ongoing commitment to work closely with regulated firms to ensure that products in violation of the FDCA or other laws enforced by FDA are quickly taken off the market to protect public health.

The final guidance clarifies the agency's recommendations regarding how regulated firms in a product distribution chain should prepare to facilitate timely initiation of a voluntary recall, respond to an indication that there may be a problem with a distributed product, and initiate a voluntary recall. The guidance applies to voluntary recalls of products subject to FDA's jurisdiction, including food, drugs and devices intended for human or animal use; cosmetics and biological products intended for human use; tobacco products intended for human use; and items subject to a quarantine regulation under 21 C.F.R. Part 1240. The guidance can also inform actions by manufacturers and distributors to remove or correct a product under circumstances that would not meet the definition of a recall (*e.g.*, market withdrawal). The final guidance includes editorial changes to improve clarity, the addition of the terms "correction" and "market withdrawal," and the addition of language encouraging the use of electronic communications for transmitting voluntary recall communications about FDA-regulated products.

Recall Readiness

In the final guidance, FDA emphasizes that regulated firms must be "recall ready." This not only means that firms should make recall plans and initiation procedures that are specific to the firm or facility in advance of when a recall may be needed, but also that firms should consider writing additional plans or procedures as appropriate to suit their business. FDA recommends that firms make the following preparations in advance of when a recall may be needed:

- Identify and assign recall-related responsibilities to personnel. Firms should, and sometimes must, task recall-related responsibilities to specific personnel who possess the authority to take the required steps to implement a product recall. The establishment of a "recall team" composed of a defined group of employees may be appropriate in certain situations, such as where recall efforts are

particularly complex or involve other complicating factors.

- Train personnel. Personnel identified to perform recall activities should be regularly educated on recall procedures. Firms should consider additional preparatory steps, such as conducting mock recalls and establishing specific metrics appropriate to a recall plan. Modifications to procedures should be made as necessary.
- Establish a recall communications plan. This plan should contain draft templates (*e.g.*, notification letters) and identify points of contact to help promptly issue recall communications. In the final guidance, FDA encourages the use of electronic communications, such as email, for transmitting voluntary recall communications.
- Identify potential reporting requirements. Firms should know whether there are requirements associated with their products that trigger an obligation to report to FDA.
- Use appropriate product coding. Firms should use coding that allows for identification of the production and control data for each lot, batch or unit, and positive lot identification to facilitate the effective recall of all violative lots. For products that have mandatory identifiers, such as blood product container label codes or medical device unique device identifiers (UDIs), these coding systems may be sufficient. For products that do not have mandatory coding or identification requirements, the agency recommends that firms develop alternate coding and identifications systems based on lot, batch or other manufacturing data.
- Maintain distribution records. Recalling firms should keep distribution records beyond the product's shelf life and expected use in order to facilitate the location of recalled products. The maintenance period should be, at a minimum, the length of time specified in applicable records retention regulations. The records should identify the name, address and telephone number of the direct accounts that received the recalled product, and records must conform to all applicable requirements. Direct accounts that distribute the product should maintain records of their own direct accounts in turn, to ensure that the recalling firm's instructions extend to all consignees in the chain of distribution.

Firms also should prepare, maintain and document written recall initiation procedures that assign responsibility and describe the steps necessary for initiating a recall, as appropriate to the firm or facility. The recall initiation procedures should include the following:

- Ceasing distribution, shipment or sales of affected product
- Developing a recall strategy
- Promptly and timely notifying direct accounts
- Notifying the public of a recalled product that presents a health hazard.

The final guidance builds on the draft guidance by advising firms that their recall strategy should take into account the possibility that a recall's scope may expand if additional lots or products are affected, and by suggesting that personnel be trained on the recall initiation procedures. FDA recommends that firms with recall communications plans that allow for communications with direct accounts by telephone also require that these telephone communications be subsequently confirmed in writing.

Responding to an Indication of a Problem with a Distributed Product

FDA recommends that firms implement the following steps in their procedures if there is an indication of a problem with a distributed product:

- Identify the problem. Firms should implement procedures to identify indicators that there may be a problem with a distributed product. Indicators include internal reports of product specification deviations, inspectional observations and laboratory analytical results.
- Investigate the problem. The procedures should describe the steps to investigate a problem with a distributed product, including timely investigation and prompt evaluation by a qualified person following established criteria. The final guidance states that a recalling firm is not required to wait to initiate a voluntary recall until the investigation or evaluation is complete.
- Make decisions. The procedures should describe the steps necessary to control defective and potentially harmful products in a timely manner. The procedures should address the decision whether to initiate a voluntary recall and, if initiated, the appropriate scope and depth of the recall.
- Consult with FDA. Firms should engage with FDA while the investigation is ongoing. FDA recall coordinators are the agency points-of-contact for recalling firms. FDA recall coordinators can also assist by referring recalling firms to other government agencies that are primarily responsible for monitoring the product recall. Firms can visit FDA's website for FDA recall coordinators' contact information.
- Initiate a voluntary recall. Firms can initiate a voluntary recall by promptly notifying the affected direct accounts and by issuing a press release or other public notice, if appropriate. The final guidance recommends that a recalling firm conduct follow-up communications with direct accounts that fail to respond to a recall communication. FDA considers the date of a firm's first communication about a recall, either to its direct accounts or to the public, to constitute the date of initiation. FDA recommends that a recalling firm follow the initiation procedures in its recall plan to implement the recall in accordance with 21 CFR § 7.46 (firm-initiated recall). A recalling firm is not required to delay initiation of a voluntary recall pending FDA's review of its recall strategy or communications.

The final guidance presents a helpful framework for firms to prepare to quickly and effectively implement recall procedures. Stakeholders should consider reviewing their current recall plans and procedures in light of the final guidance.

Looking Ahead to 2023

In 2023, we expect FDA to continue to ramp up inspection efforts and implement new methodologies to leverage data to support inspections. FDA's FY 2023 budget dedicates $33.8 million to the agency's inspection efforts. According to the FY 2023 Justification of Estimates for Appropriations Committees, FDA plans to use this funding to build out its operations and workforce to enhance the agency's ability to harness data to "increase the efficiency and productivity" of operations. This allocation will also be used to streamline inspection efforts by improving cross-agency inspection analysis to "optimize end-to-end inspection processes and improve overall inspection operations."

2023 OUTLOOK

Despite forecasts and concerns that 2023 may bring economic challenges across multiple sectors, innovation and strategic investment in long-term growth areas remain a priority for FDA and the industries it regulates. The agency will continue to focus on realigning program areas and processes to encourage greater innovation in areas such as gene therapy, platform technologies for drugs and biologics, food safety and digital health. Issues such as cybersecurity and global harmonization of quality and manufacturing standards remain a focus for FDA as supply chains become more global, decentralized, automated and complex. These regulatory priorities may drive strategic investment by manufacturers in outsourced services that optimize existing procedures for cybersecurity, manufacturing, quality, and research and development.

FDA's continued focus on patient-centered product development may drive continued investment from industry in data analytic tools and solutions that optimize their understanding of patient experiences with products. IVDs, LDTs, at-home testing and other solutions that leverage technology to put diagnostic tools in the hands of patients will continue to be a focus in the wake of the COVID-19 pandemic. Greater certainty regarding the regulatory regime for digital health may drive both drug and device manufacturers with cash reserves to evaluate targeted investments in technologies and early-state therapies that enhance their current product portfolios, expand the patent life of existing drug products, or optimize patient access or adherence. FDA will continue to focus its enforcement efforts and resources in strategic areas such as manufacturing and quality, but overall enforcement may remain static, as the number of warning letters and enforcement actions arising from advertising and promotional activities has declined in past years.

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