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The US Food and Drug Administration’s (FDA’s) 2017 regulatory agenda was marked by inactivity in the months following the presidential inauguration. Since FDA Commissioner Scott Gottlieb’s Senate confirmation in May 2017, the agency has implemented a number of initiatives that were in the pipeline from the prior administration as well as several new legislative and regulatory mandates. FDA has taken steps to reduce regulatory barriers to market entry for innovative products, identified outdated guidance and regulations that will be eliminated or modified, implemented key provisions of the 21st Century Cures Act and emphasized global harmonization. FDA issued important rulemakings and guidance documents throughout 2017, especially in the latter half of the year.

In this article we review notable legislation, regulations, guidance and enforcement actions that shaped FDA-regulated industries and products in 2017 and offer insight into the agency’s 2018 priorities and expected actions.

**FDA Reauthorization Act of 2017**

On August 18, 2017, President Trump signed the [FDA Reauthorization Act of 2017](https://www.fda.gov/ AboutFDA/ Congressional/ReauthorizationAct) (FDARA) into law. The legislation contained substantive provisions on drugs, devices and pediatric studies in addition to the typical user fee program
Reauthorizations viewed as “must-pass” legislation every five years.

Reauthorization of User Fee Programs

FDARA reauthorized four user fee programs for an additional five fiscal years: Prescription Drug User Fee Act, Medical Device User Fee Amendments, Generic Drug User Fee Amendments and Biosimilar User Fee Act. In FDARA, Congress also modified existing user fee programs and created additional performance and other data reporting requirements. For example, in the title reauthorizing medical device user fees, Congress added a new fee to handle the increasing number of *de novo* device classification requests, which apply to novel devices for which there is no currently marketed “predicate.” That user fee provision does not apply where a device’s proposed conditions of use are solely for a pediatric population. As another example, the title reauthorizing biosimilar biological product user fees eliminated the requirement that an independent accounting or consulting firm study FDA’s workload volume and costs associated with the process for the review of biosimilar biological product applications.

Key Drug Provisions

Title VIII of FDARA contained provisions on improving generic drug access, which followed FDA’s June 2017 efforts to encourage the submission of abbreviated new drug applications (ANDAs) for off-patent, off-exclusivity drugs with no approved ANDA by publishing a list of such drugs. FDARA mandates updates to the list every six months. FDARA also requires priority review and action on ANDAs submitted for drugs with not more than three approved drug products that are off-patent and off-exclusivity, effectively codifying FDA’s June 2017 policy announcement that the agency would prioritize review of ANDAs until there were three approved generics. The agency must prioritize ANDAs for drugs on the drug shortage list and may expedite review of ANDAs for “competitive generic therapies” if there is “inadequate generic competition”—not more than one approved drug that is the reference listed drug (RLD) or a generic drug with the same RLD as the drug for which designation as a competitive generic therapy is sought. FDARA created a new 180-day exclusivity period for first approved applicants of competitive generic therapies, provided the applicant markets the competitive generic therapy within 75 days of the application’s approval.

FDARA created new marketing status reporting requirements for holders of new drug applications (NDAs) and ANDAs. By February 14, 2018, NDA and ANDA holders must review the Orange Book (i.e., FDA’s *Approved Drug Products with Therapeutic Equivalence Evaluations*) and submit a one-time report to FDA that states whether the drugs listed in the active section of the Orange Book are available for sale, were never available for sale or have been withdrawn from sale. Holders of approved applications under Federal Food, Drug, and Cosmetic Act (FDCA) sections 505(c) or (j) must now notify FDA 180 days prior to withdrawing the approved drug from sale or as soon as practicable, and must notify FDA if the approved drug will not be available for sale within 180 days of the approval date.

The law also amended the definition of “patient experience data” submitted as part of an NDA or Biologics License Application to include physical and psychosocial impacts of a disease or condition or related therapy or clinical investigation. FDARA
permits FDA to require responsible persons to include, as part of a Risk Evaluation and Mitigation Strategies plan, information about limitations or patient care implications of drug formulations or properties, and how such formulations or properties may be related to serious adverse events. FDARA increased penalties for knowingly making, selling, dispensing, or holding for sale or dispensing counterfeit drugs.

**Key Device Provisions**

FDARA changed FDA’s inspection schedule of device establishments from every two years to a risk-based schedule to be created by the agency, which may take into consideration a device establishment’s participation in international device audit programs in which the United States participates or that it recognizes. The law requires FDA to issue draft and final guidance regarding amendments to the inspection process for foreign and domestic device establishments, that include a requirement for FDA to provide nonbinding feedback within 45 days of a request by an owner, operator or agent in charge related to proposed actions that involve a public health priority, implicate major or systemic actions, or relate to emerging safety issues. FDARA also reauthorized the third-party inspection program for five more years and, regardless of other statutory provisions regarding inspections by accredited persons, permits the FDA to recognize auditing organizations that are recognized by organizations established by governments to facilitate international harmonization for conducting inspections of device establishments.

FDARA amended provisions regarding the process for initial classification and reclassification of an accessory by which FDA may classify an accessory based on the risk of the accessory when used as intended and the level of regulatory controls necessary to provide a reasonable assurance of the accessory’s safety and effectiveness, regardless of the classification of a device with which the accessory is intended to be used. FDARA also amended the approval, clearance or classification of diagnostic imaging devices (applicable medical imaging devices) that use approved contrast agents in different concentrations, rates of administration or routes of administration; different regions, organs or systems of the body; different patient populations; or different imaging modalities than in the contrast agent’s approved labeling. The legislation also added new types of devices to the list of devices that are not appropriate for the third-party accredited persons review program, including devices intended to be permanently implanted, life-supporting devices and life-sustaining devices.

FDARA included several provisions regarding medical device pilot programs. For example, the law required FDA to establish a new conformity assessment pilot program under which testing laboratories may become accredited to assess the conformance of a device with performance standards necessary to provide reasonable assurance of safety and effectiveness. FDARA also permits voluntary post-market pilot programs that use electronic health data to provide information on the safety and effectiveness of approved medical devices. The law also contained provisions regarding specific devices, such as over-the-counter hearing aids, on which FDA must issue regulations. FDARA preempts state and local laws that would restrict or interfere with the servicing, marketing, sale, dispensing, use, customer support or distribution of such hearing aids.
Provisions Regarding Pediatric Drugs and Devices

Title V of FDARA included changes to existing laws and reporting requirements related to pediatric studies, pediatric cancer, pediatric drug labeling and pediatric devices. FDARA also required FDA to hold public meetings on pediatric medical devices and molecularly targeted cancer drugs. The agency must issue final guidance on molecularly targeted cancer drugs and draft guidance on clinical pharmacology considerations for neonatal studies of drugs and biologics within two years of FDARA’s enactment.

Generic Drugs

Developments in 2017

As noted, since Commissioner Gottlieb’s confirmation, FDA has taken several actions to increase generic competition, and Congress also mandated efforts aimed at enhancing generic competition in FDARA. In June 2017, FDA released two lists of off-patent pharmaceuticals with limited or no competition. The first includes drugs “for which FDA could immediately accept an ANDA without prior discussion,” and the second is for drugs “involving potential legal, regulatory, or scientific issues which should be addressed with the agency prior to submission of an ANDA.” FDA intends to develop a similar list for individual NDA drug products that lack competition. FDA also updated its Manual of Policies and Procedures (MAPP) 5240.3 Rev. 3, Review Order of Original ANDAs, Amendments, and Supplements, to prioritize the review of ANDAs for which there are fewer than three ANDAs approved for the RLD.

The lists and changes to the MAPP are part of FDA’s implementation of FDARA and the agency’s Drug Competition Action Plan, an overall initiative to balance innovation with access and price-reducing measures for drugs. The agency also held a public meeting in July 2017 to receive input on these issues.

Looking Ahead to 2018

We anticipate that the next list of off-patent pharmaceuticals—perhaps including NDAs—will be released soon. On January 3, 2018, FDA released two draft guidance documents: Good ANDA Assessment MAPP to streamline the Center for Drug Evaluation and Research’s (CDER’s) ANDA review process, and a Good ANDA Submission Practices guidance document to assist industry by identifying common recurring deficiencies in ANDAs and provide advice on how to avoid them.

Digital Health

Developments in 2017

As discussed here, the 21st Century Cures Act, signed into law in December 2016, set a tone of innovation and increased access to digital health products in 2017. FDA maintained its commitment to innovation through digital health by continuing to address areas of stakeholder uncertainty and perceived barriers to timely market authorization. For example, FDA approved the first digitally enabled prescription pill for the treatment of adult schizophrenia and other specified conditions; the first
mobile application to treat substance abuse disorders; and several other novel
products that incorporate artificial intelligence (AI), clinical decision support (CDS)
tools and virtual reality technology.

In July 2017, FDA published its Digital Health Innovation Action Plan. As described
here, the agency acknowledged that the traditional regulatory approach toward
moderate and higher risk medical devices is not well suited for the fast-paced,
iterative design, development and type of validation used for digital health software
products today. The agency therefore announced its intent to explore an innovative
approach to the regulation of digital health products that consists of three prongs:
the implementation of the Digital Health Software Precertification (PreCert)
Program, the issuance of new guidance, and an internal expansion of FDA’s digital
health capabilities.

A pilot of the PreCert Program began in September 2017 with nine software
developers as participants. The pilot’s purpose is to develop a new firm-based
approach toward regulating digital technology under which FDA’s Center for Devices
and Radiological Health (CDRH) could “pre-certify” eligible digital health
developers that demonstrate “a culture of quality and organizational excellence”
based on the objective criteria identified in the PreCert pilot. Pre-certified
developers could, in theory, qualify to market their lower-risk devices without
additional FDA review or with a streamlined premarket review. FDA indicated that it
intends to leverage participant input to create this new and potentially faster
regulatory pathway.

FDA also issued a number of guidance documents—some of which were promised in
the Digital Health Innovation Action Plan—that affect digital health product
development and compliance activities, analyses regarding the regulatory status of
products in the United States, and the overall regulatory strategy for those products:

- Pursuant to authority granted to FDA in the 21st Century Cures Act, FDA issued
  the IRB Waiver or Alteration of Informed Consent for Clinical Investigations
  Involving No More Than Minimal Risk to Human Subjects guidance, indicating
  that it intends to revise its regulations to allow Institutional Review Board
  (IRB) waiver or alteration of informed consent when an IRB finds that (1) the
  clinical investigation presents no more than minimal risk to subjects, (2) the
  waiver or alteration will not adversely affect the rights and welfare of subjects,
  (3) the clinical investigation could not practicably be carried out without the
  waiver or alteration, and (4) whenever appropriate, subjects will be given
  additional pertinent information after participation. In the meantime, FDA has
  indicated that it does not intend to object to the conduct of a minimal risk
  investigation for which an IRB waives or alters informed consent according to
  the above criteria.

- In August 2017, FDA issued the Use of Real-World Evidence to Support
  Regulatory Decision-Making for Medical Devices final guidance (RWE
  Guidance). The RWE Guidance describes FDA’s position that data derived from
  real-world sources may be used to support FDA regulatory decisions and
  clarifies the criteria by which FDA evaluates real-world data to determine
  whether the data is sufficient for generating the types of real-world evidence
  that can be used in regulatory decision-making. Notably, the RWE Guidance
expressly maintains the “reasonable assurance of safety and effectiveness”
evidentiary threshold that FDA-regulated devices must meet, but confirms that
it is possible for real-world evidence to satisfy this standard if the underlying
data were generated at clinically relevant intervals throughout the device
lifecycle and are otherwise reliable and appropriately validated.

- In September 2017, in light of the rapid development of innovative digital
technologies that connect medical devices to each other and to other
technologies such as smartphones, FDA issued a final guidance
document, Design Considerations and Pre-Market Submission Recommendations
for Interoperable Medical Devices, which outlines the agency’s
recommendations for safely and effectively connecting these systems through
appropriate functional, performance and interface requirements (i.e.,
standardized architecture and communication protocols) to ensure these
systems can properly “speak” to each other. In a blog post that accompanied
the release of the guidance, FDA’s associate director for digital health in
CDRH, Bakul Patel, reiterated that FDA’s key priorities are safety and
transparency.

- In October 2017, FDA issued the Deciding When to Submit a 510(k) for a
Software Change to an Existing Device final guidance (the 510(k) Guidance)
and Deciding When to Submit a 510(k) for a Change to an Existing Device. The
510(k) Guidance assists in determining when a software, including firmware,
change to a device may require a manufacturer to submit a new 510(k)
premarket notification. The purpose of the 510(k) Guidance is to increase the
predictability, consistency and transparency of the “when to submit” decision-
making process by outlining the applicable regulatory framework and guiding
principles.

- On December 5, 2017, FDA issued the Technical Considerations for Additive
Manufactured Medical Devices final “leapfrog” guidance on 3D printing. 3D
printing facilitates the manufacture of medical devices and other personalized
or “patient-matched” technology and enables the creation of models (e.g.,
patient-specific organs) used to educate, inform or enhance clinical procedures,
such as surgery. The guidance followed an August 2017 Joint Meeting on 3D
Printed Patient-specific Anatomic Models between CDRH and the Radiological
Society of North America 3D Printing Special Interest Group. Because the field
of 3D printing continues to rapidly change, FDA sought to share “initial
thoughts” to guide manufacturers through technical considerations associated
with additive manufacturing processes. The guidance includes
recommendations for the testing and characterization of devices that include at
least one additively manufactured component or additively fabricated step.

- On December 7, 2017, FDA published its highly anticipated Clinical and Patient
Decision Support Software draft guidance (CDS Draft Guidance). As
discussed here, the CDS Draft Guidance describes how the agency intends to
exercise oversight over CDS and patient decision support software.
Simultaneously, FDA issued a draft guidance document that states how the
agency intends to revise four previously issued digital health final guidance
documents for consistency with the 21st Century Cures Act, which amended the
FDCA definition of “device” to exclude software with several types of functions
(including certain CDS functionalities). The software excluded in the amended
definition of “device” could include AI and machine learning (ML)
functionalities. Advances in AI or ML applications have also generated
compliance uncertainty across a variety of industry and settings, including about which legal and regulatory frameworks should apply to current and future iterations (discussed further here). To meet the device definition’s exemption, the software product must not be intended to serve as the sole basis for a diagnostic or treatment decision. While some media and trade reports suggest that uncertainty remains if and how FDA will and should regulate AI and ML products, the CDS Draft Guidance, existing regulatory framework and recent device clearances make clear that FDA intends to regulate AI and ML tools that provide diagnostic, clinical and medical device functions that fall within FDA’s jurisdiction.

- Also on December 7, 2017, FDA released the International Medical Device Regulators Forum (IMDRF)-supported Software as a Medical Device (SAMD): Clinical Evaluation guidance document (SAMD Guidance). As discussed here, the purpose of the SAMD Guidance is to establish a common understanding of clinical evaluation and principles for demonstrating the safety, effectiveness and performance of SAMD. As with previously issued IMDRF guidance documents, the SAMD Guidance provides an evidentiary and technical framework that FDA intends to consider in the development of its regulatory approaches for digital health technologies.

FDA also plans to hire new staff for its Digital Health Program, including Entrepreneur-in-Residence (EIR) Fellows. New staff will work with “reviewers, compliance officers, and others within FDA to improve the quality, predictability, consistency, timeliness, and efficiency of decision making on individual products and firms,” while EIR fellows will support various aspects of the development of the PreCert Program.

For an in-depth review of these and other 2017 digital health developments, click here.

Looking Ahead to 2018

Taken together, the Digital Health Innovation Action Plan and guidance documents clarify how developers should approach certain development, classification, post-market product decisions and surveillance for software-based devices in 2018. As FDA clears and approves innovative products, stakeholders may identify trends that indicate the perceived risk profile and regulatory pathway of functionalities and types of digital health products. However, certain important questions remain unanswered, most notably the following:

- If FDA chooses to further pursue a precertification regulatory pathway for digital health software products, what might the pathway require of both developers and products
- How will FDA regulate CDS software that relies on complex ML functionality?
- Will FDA issue specific guidance on the implementation of its Medical Device Quality System Regulation (QSR) for digital health products and software-based medical devices?

CDRH issued and prioritized the guidance documents that it intends to publish in FY 2018, which includes the draft guidance Multifunctional Device Products: Policy and Considerations. The guidance will hopefully clarify how FDA plans to regulate
multifunction software products that provide multiple intended uses and both regulated and potentially unregulated functions.

**Additional 21st Century Cures Act Implementation Updates**

*Developments in 2017*

In 2017, FDA created the Regenerative Medicine Advanced Therapy (RMAT) designation program, under which products granted designation may engage in additional and earlier interactions with FDA to facilitate an efficient development program. Products eligible for RMAT designation must be regenerative medicine therapies (e.g., cell therapies, human cell and tissue products); drugs intended to treat, modify, reverse or cure a serious or life-threatening disease or condition; and drugs that preliminary clinical evidence indicates have the potential to address unmet medical needs for such disease or condition. Interactions with FDA may include discussions of appropriate approval pathways and clinical trial sizes.

In November 2017, the agency issued two draft RMAT guidance documents on devices used in recovery, isolation or delivery of RMAT products and on the expedited pathway for eligible products: Evaluation of Devices Used with Regenerative Medicine Advanced Therapies and Expedited Programs for Regenerative Medicine Therapies for Serious Conditions. FDA also issued two final RMAT guidance documents in November 2017 regarding the scope of the same surgical procedure exception for products removed from and implanted into the same person in the same surgical procedure, and regarding agency interpretations of the terms “minimal manipulation” and “homologous use” with respect to regulatory considerations for human cells, tissues, and cellular and tissue-based products.

FDA issued draft guidance on the new Breakthrough Devices Program in October 2017, describing policies the agency intends to use to implement the 21st Century Cures Act. The Breakthrough Devices Program is aimed at helping patients with life-threatening or irreversibly debilitating diseases or conditions receive timely access to devices through expedited development, assessment and review. Separately, FDA took action pursuant to section 3054 of the 21st Century Cures Act, which provided that FDA may determine whether certain types of Class I and Class II devices require a report to provide reasonable assurance of safety and effectiveness. FDA exempted more than 70 Class I device types and more than 1,000 Class II device types from the 510(k) submission requirement.

With respect to drugs, FDA published a five-year plan for issuing guidance documents on the collection and review of patient-focused data for drug development; included a new subsection on drug and biological product review documents on patient experience data; and held a public workshop on collecting comprehensive and representative patient input. The agency also created an Oncology Center of Excellence to fulfill congressional mandates to establish inter-center—e.g., CDER, CDRH and Center for Biologics Evaluation and Research (CBER)—institutes to coordinate activities in major disease areas. According to Commissioner Gottlieb, other areas under consideration for disease-specific offices are immunology and neuroscience. Along these lines, FDA piloted an inter-center consult process to improve the efficiency of combination product consultations and
trained more than 1,000 review staff in CDER, CDRH and CBER.

Looking Ahead to 2018

FDA has several 2018 statutory deadlines under the 21st Century Cures Act, which involve the issuance of guidance documents, reports and plans, as well as the hosting of public meetings. The topics of draft guidance due to be published by mid-June 2018 include patient-focused drug development, limited population pathways and the humanitarian device exemption. The agency is also required to produce several reports in 2018, including reports to Congress on regenerative advanced therapies (February); limited population pathways (June); hiring authority for scientific, technical and professional personnel (June); susceptibility test interpretive criteria for microorganisms and antimicrobial susceptibility testing devices (December); and progress made on harmonizing FDA and US Department of Health and Human Services regulations on protection of human research subjects (December). Expected public meetings include one on the qualification of drug development tools and another on novel clinical trial designs.

Drug Quality Security Act Implementation

Compounding

In January 2017, FDA published the Human Drug Compounding Progress Report, which summarized implementation of the Drug Quality Security Act since its enactment in November 2013. In this Report, FDA indicated that it planned to continue regulation, active oversight and “robust enforcement” of the compounding industry by finalizing draft guidance, proposing rulemaking, convening Pharmacy Compounding Advisory Committee meetings and collaborating with stakeholders. Also in January 2017, under the Obama Administration, FDA issued two final guidance documents on the agency’s interim policy on compounding using bulk drug substances under sections 503A and 503B.

Commissioner Gottlieb reaffirmed the agency’s focus on providing “robust oversight over human drug compounding.” FDA took a number of regulatory enforcement actions in 2017 against compounding pharmacies and physicians, including issuing Warning Letters, Untitled Letters and Form FDA 483s.

The Drug Supply Chain Security Act

FDA took significant steps to further implement and clarify certain aspects of Title II of the Drug Quality Security Act—the Drug Supply Chain Security Act (DSCSA). DSCSA’s goal is to create “an electronic, interoperable system to identify and trace drugs.” FDA’s actions in 2017 represent progress toward meeting the law’s deliverables and the agency’s Implementation Plan. FDA conducted two public meetings; provided notice that the agency intends to establish a DSCSA pilot program to develop the electronic, interoperable system; and published multiple guidance documents (some of which are described below). The next public meeting on February 28, 2018, will focus on further refinement of enhanced drug distribution security needs and on building capacity for a unit-level system.
• In June 2017, the agency released the Product Identifier Requirements Under the Drug Supply Chain Security Act draft guidance, which explains that FDA does not intend to take action against manufacturers that do not add a product identifier to each package and homogenous case of product intended to be introduced in a transaction into commerce before November 27, 2018. This represents a one-year delay in enforcement of . The guidance also states that FDA does not intend to take action against manufacturers and other trading partners that transact such product or verify it for investigatory purposes or saleable returns without using the product identifier.

• In August 2017, FDA issued the Identifying Trading Partners Under the Drug Supply Chain Security Act draft guidance. The purpose of the guidance is to (1) assist industry and state and local governments in understanding the applicability of DSCSA requirements to various entities in the supply chain that participate in the distribution of drugs, and (2) help clarify whether certain entities are engaged in activities that require licensure and annual reporting, as well as compliance with other authorized trading partner requirements.

• In November 2017, FDA published the Grandfathering Policy for Packages and Homogenous Cases of Product Without a Product Identifier draft guidance. Issuance of the guidance is mandated by the text of DSCSA. The guidance specifies whether and under what circumstances packages and homogenous cases of product that are not labeled with a product identifier and are in the pharmaceutical distribution supply chain are exempted as “grandfathered” from certain DSCSA requirements.

Medical Device Developments in the United States and Europe

Developments in 2017

In 2017, FDA’s approach to the regulation of devices emphasized efficiency, flexibility and global harmonization. The agency was especially active rolling out new guidance and pilots, finalizing prior guidance and holding numerous public meetings, some of which were discussed previously in this report.

On December 15, 2017, FDA issued draft guidance entitled The Least Burdensome Provisions: Concept and Principles. Under the FDA Modernization Act of 1997, Congress directed FDA to take a least burdensome approach to medical device premarket evaluation to eliminate unnecessary burdens that may delay the marketing of new products. The guidance defines “least burdensome” as “the minimum amount of information necessary to adequately address a regulatory question or issue through the most efficient manner at the right time,” and describes the guiding principles and recommended approach for FDA staff and industry to facilitate consistent application of the principles. Notably, the guidance states that the concept applies to all products that meet the statutory definition of a device and applies throughout the total product lifecycle—including both pre- and post-market regulatory activities.

In addition to medical device developments in the United States, 2017 heralded significant regulatory change in Europe. In May 2017, the new Regulation on Medical Devices (MDR) and the new Regulation on In Vitro Diagnostics (IVDR) were published in the European Official Journal. The Regulations became effective on May
26, 2017, and will be fully applicable after a transition period of three years for the MDR and five years for the IVDR, respectively. During the transition periods, manufacturers may choose whether they want a medical device to be certified under the old or the new regime. However, four years after the MDR effective date, i.e., in 2024, all European Conformity certificates issued under the old rules of the MDR will expire. By then—at the latest—all medical devices marketed in the European Union will have to comply with the new regime. For more information, find our summary here.

Looking Ahead to 2018

In mid-December 2017, FDA proposed to modernize the 510(k) premarket notification framework and support innovation under an “alternate [regulatory] approach.” This approach will rely on “modern, science-based, consensus standards and FDA-developed performance criteria as the comparator for device review for certain well-understood technologies.” The draft guidance will be published as the Expansion of the Abbreviated 510(k) Program: Demonstrating Substantial Equivalence through Performance Criteria, and publication is expected in 2018.

The regulatory guidance and changes noted above require medical device manufacturers to review and evaluate current operations and quality systems to ensure compliance with new and enhanced requirements. While the new European regulations reflect a trend toward greater harmonization of EU and US requirements, companies with global operations, distribution and products should take a holistic approach toward compliance and implement regulatory and compliance processes that are appropriate, adaptable and scalable across the enterprise for the ever-growing global marketplace.

Laboratory-Developed Tests and Precision Medicine

Developments in 2017

In January 2017, FDA posted a discussion paper outlining a substantially revised “possible approach” to the oversight of laboratory-developed tests (LDTs), which have historically been subject to FDA enforcement discretion. The discussion paper explicitly states that it is not a final version of the July 2014 draft guidance on LDTs, in which the agency outlined its intent to end enforcement discretion for many types of LDTs, and that it does not represent the agency’s “formal position.” Rather, the document represents the latest iteration of FDA’s thinking on LDTs, which the agency posted to “spur further dialogue.”

In the discussion paper, which we analyzed here, FDA indicates its willingness to consider grandfathering LDTs currently on the market (except where necessary to protect the public health), exempting several categories of new and significantly modified LDTs from premarket review and QSR requirements, and taking enforcement action against LDT developers in four cases:

- If an LDT is not analytically or clinically valid
- If there is an absence of data to support the LDT’s analytical or clinical validity
- If the LDT developer is engaged in deceptive promotion
If there is a reasonable probability that the LDT will cause death or serious adverse health consequences

In November 2017, FDA announced the clearance of a tumor profiling test under a novel, streamlined FDA premarket review pathway for certain next generation sequencing (NGS)-based tumor profiling tests. Key elements of the streamlined pathway include regulation of NGS-based tumor profiling tests as Class II medical devices subject to the 510(k) requirement; exclusion of companion diagnostic claims from the scope of labeling; the ability to make certain modifications to the tests without a new 510(k); and third-party review by the New York State Department of Health (Wadsworth Center), to which FDA granted accreditation as a third-party reviewer. The creation of this pathway represents a significant pro-industry shift with respect to the FDA regulatory requirements that might apply to tumor profiling tests. See our examination of this pathway here.

Looking Ahead to 2018

Congressional staff are expected to continue drafting legislation—e.g., the Diagnostic Accuracy and Innovation Act—that, if enacted, would substantially overhaul FDA’s authority to regulate all diagnostic tests, including LDTs. To date, however, no legislation has been officially introduced in either chamber. Additionally, we anticipate that FDA will continue to encourage clinical laboratories that have traditionally performed their tests as LDTs to voluntarily come under FDA’s jurisdiction by establishing streamlined pathway(s) to meet premarket requirements.

Tobacco

Developments in 2017

FDA issued two key final guidance documents and one major draft guidance in 2017. In October 2017, FDA released the final guidance The Prohibition of Distributing Free Samples of Tobacco Products to clarify that the ban on distributing free samples of tobacco products applies to all products under its tobacco product authority, including those covered under the 2016 deeming rule. In its September 2017 Compliance Policy for Required Warning Statements on Small-Packaged Cigars final guidance, FDA stated that it would exercise enforcement discretion for the size and placement requirements for warning statements under 21 CFR § 1143.5(a)(2) for cigars in packaging that is too small or otherwise unable to accommodate a label with sufficient space to bear the required warning statements, provided that the information and specifications required under 21 CFR §§ 1143.5(a) (1) and (2) appear on the carton or other outer container or wrapper.

FDA issued a January 2017 draft guidance titled Interpretation of and Compliance Policy for Certain Label Requirement; Applicability of Certain Federal Food, Drug, and Cosmetic Act Requirements to Vape Shops. The draft guidance’s key provisions follow below:

- Under FDCA § 903(a)(2)(C), a tobacco product in package form is misbranded if its label does not include an accurate statement of the percentage of the
tobacco used in the product that is domestically grown tobacco and the percentage that is foreign grown tobacco. FDA clarified (1) that it interprets this provision as applying only to tobacco products that are made or derived from tobacco (i.e., the requirement does not apply to tobacco products not made or derived from tobacco, such as certain components, parts or accessories), and (2) that it does not intend to enforce the provision for tobacco products made or derived from tobacco (e.g., cigarettes, smokeless tobacco, smokeless tobacco or other tobacco-derived products such as liquid nicotine) because of the difficulty of quantifying the percentage of foreign and domestic tobacco use.

- Vape shops that are tobacco product manufacturers are subject to the requirements in FDCA §§ 904(a) and (c), including the requirements to provide ingredient listings, report harmful and potentially harmful constituents, and submit health documents. Vape shops that modify a product so that it is a new tobacco product as defined in FDCA § 910 are required to comply with the premarket authorization requirements. Finally, vape shops that are engaged in the manufacture, preparation, compounding or processing of tobacco products are required to comply with establishment registration and product listing in accordance with FDCA § 905. The guidance document also discusses whether particular activities would subject vape shops to these requirements, and the activities for which FDA does not intend to enforce compliance. For example, refilling a closed system electronic nicotine delivery systems (ENDS) would result in a new tobacco product, but FDA does not intend to enforce the requirements if a vape shop refills an open system ENDS, assuming that the vape shop does not make any further modifications to the device or e-liquid before, during or after the refill that are outside the existing marketing authorization for that product and/or are not inconsistent with the original manufacturer’s specifications, if applicable.

Most significantly, in July 2017, Commissioner Gottlieb announced a Comprehensive Approach to Nicotine and Tobacco. Central to the announcement was a charge to take a fresh approach to nicotine regulation and the potential impact of the delivery mechanism on addiction. In September 2017, FDA formed a Nicotine Steering Committee to focus on the use of therapeutic nicotine for combustible tobacco product cessation.

Looking Ahead to 2018

FDA is currently evaluating modified risk tobacco product applications, but as of the date of this publication, FDA’s Center for Tobacco Products (CTP) has yet to approve a modified risk order. Given the agency’s shift in its approach to nicotine, with Commissioner Gottlieb acknowledging the continuum of risk and potential for innovation to lead to less harmful products, 2018 may bring FDA’s first modified risk orders.

Executive Orders 13771 and 13777

President Trump’s Executive Order (EO) 13771 on agency rulemaking, Reducing Regulation and Controlling Regulatory Costs, requires a minimum of two existing regulations to be “identified for elimination” for every new rule “issued.” The order does not actually require agencies to repeal two rules for every rule issued. FDA and
other agencies must simply identify regulatory actions for repeal to offset the cost of a new rule. EO 13777, *Enforcing the Regulatory Reform Agenda*, required the designation of Regulatory Reform Officers and the establishment of Regulatory Reform Task Forces to evaluate existing regulations and make recommendations regarding their repeal, replacement or modification. In particular, such task forces are tasked with identifying rules that eliminate jobs or inhibit job creation; are outdated, unnecessary or ineffective; impose costs that exceed benefits; create a serious inconsistency with regulatory reform initiatives; implement now-rescinded EOs or other presidential directives; or are inconsistent with the requirements of the Information Quality Act and related guidelines on objectivity, quality, utility and integrity of information disseminated by federal agencies.

The Office of Management and Budget (OMB) issued several memoranda to Regulatory Policy and Regulatory Reform Officers that provided guidance regarding particular provisions of the two EOs. For example, OMB guidance issued in February 2017 addressed whether EO 13771 covered regulatory actions likely to result in a rule that may have an annual effect on the economy of less than $100 million, whether that EO applied to guidance documents, and the types of significant regulatory actions that would qualify for waivers under the EO (e.g., emergencies addressing critical health or safety matters).

In September 2017, FDA published seven requests for comments as part of the agency’s implementation of the EOs to help FDA identify existing rules and paperwork requirements that could be repealed, replaced or modified. The requests for comment were published by CDER, CDRH, CTP, CBER, the Center for Veterinary Medicine, and the Center for Food Safety and Applied Nutrition. FDA published a general regulatory and information collection request for comment as well. As comments were due December 7, 2017, we anticipate several proposed rules in 2018 related to the modification or elimination of existing regulations, and *Federal Register* announcements on outmoded or other information collection requirements that fit the parameters of EO 13771 and 13777.

**Advertising and Promotion**

In the waning days of the Obama Administration, FDA issued a number of documents regarding unapproved uses of approved or cleared medical products, or off-label communications. These included a final rule, *Clarification of When Products Made or Derived From Tobacco Are Regulated as Drugs, Devices, or Combination Products: Amendments to Regulations Regarding “Intended Uses,”* discussed in depth [here](#), which was delayed by the Trump Administration until March 2018. FDA also issued two draft guidance documents: *Medical Product Communications that are Consistent with the FDA-Required Labeling – Questions and Answers*, and *Drug and Device Manufacturer Communications with Payors, Formulary Committees, and Similar Entities – Questions and Answers*. In-depth discussions of the draft guidance documents can be found [here](#) and [here](#). Finally, FDA issued a memorandum, Public Health Interest and First Amendment Considerations Related to Manufacturer Communications Regarding Unapproved Uses of Approved or Cleared Medical Products.

These documents, highly anticipated following the 2016 *public meeting* regarding
off-label communications and a flurry of First Amendment litigation in recent years, reinforced FDA’s authority to regulate such communications while narrowing the scope of audiences and types of communications to which it will extend its regulatory authority. In the memorandum, a considerable portion of FDA’s discussion focused on the substantial government interests related to health and safety in regulating off-label communications. These documents do not necessarily represent the current administration’s approach to communications regarding unapproved uses or off-label communications.

Despite the Obama Administration regulations, guidance and policy statements, FDA’s Office of Prescription Drug Promotion issued a historically low number of Warning Letters for false or misleading advertisements. In 2017, FDA issued only three Warning Letters and one Untitled Letter to pharmaceutical companies for false or misleading advertising. FDA issued 11 in 2016, nine in 2015, nine in 2014 and 24 in 2013. This shift may signal the new leadership’s approach to off-label communications, or indicate that FDA is continuing to take a cautious approach to enforcement in this area following First Amendment litigation that reaffirmed the limits of FDA’s authority to regulate truthful and non-misleading speech. Given recent litigation and ongoing efforts by industry groups to loosen restrictions on truthful and non-misleading off-label communications, the agency may further narrow its scope of enforcement through guidance or in practice.

**Part 11 Guidance**

In the first significant update on the agency’s thinking on electronic records and electronic signatures in almost 14 years, FDA issued its draft guidance *Use of Electronic Signatures in Clinical Investigations Under 21 CFR Part 11 – Questions and Answers*. This Part 11 draft guidance outlines FDA’s expectations with respect to the use of cloud computing, electronic health records, mobile applications and telecommunications systems in activities subject to 21 CFR Part 11. Consistent with previous guidance, FDA indicated in the draft guidance that it intends to take a risk-based approach for electronic systems validation, electronic records audit trails and archived records under 21 CFR Parts 312 and 812 (FDA’s record-keeping requirements for clinical investigations of drugs and medical devices, respectively). The draft guidance also outlines how to structure security, audit and other systems based on the risks and underlying regulatory requirements associated with certain types of electronic data or systems, and provides additional information to assist sponsors and regulated entities (e.g., contract research organizations and IRBs) in making decisions on implementing controls and otherwise complying with Part 11.

The draft guidance addresses the applicability of Part 11 requirements in various electronic systems used in clinical investigations: mobile technology, telecommunication systems (telephones, email, live chat, and telemedicine or video conferencing), systems owned or managed by sponsors or other regulated entities, outsourced electronic services (e.g., cloud computing services) and systems primarily used in the provision of medical care. FDA does not intend to assess compliance of systems designed for medical care of patients not enrolled in a clinical investigation and owned and managed by the institutions providing medical care, such as electronic health records, with Part 11.
In the draft guidance, FDA reiterated its position that it will exercise enforcement discretion with respect to the validation, audit trail, record retention and record copying requirements under Part 11—in other words, failure to implement these requirements would not constitute a violation of Part 11. However, failure to implement these requirements may still be a violation under a predicate rule. For example, FDA’s current Good Manufacturing Practice (cGMP) and Good Clinical Practice regulations impose various record-keeping, record-retention and validation requirements on manufacturers and sponsors of clinical research, and failure to comply with these requirements may result in FDA enforcement action.

The Part 11 draft guidance confirms that “new” technology, including certain ubiquitous mobile apps, must maintain compliance with Part 11 insofar as it is being used for a regulated purpose. The draft guidance is another example of FDA’s efforts to encourage practical and risk-based approaches to regulatory compliance that also take into account rapid advancements in technology. Still, industry and regulated entities must interpret the provisions and ensure that they are making thoughtful and well-reasoned choices, characterizing risks, ensuring the criticality and integrity of data, and implementing controls and validation methods that are rational, defensible and compliant. The draft guidance presents and refines the scope of Part 11 to assist companies in making these decisions.

**Manufacturing and Good Manufacturing Practice**

In June 2017, CDER and the FDA Office of Regulatory Affairs (ORA) entered into a **Concept of Operations** agreement to integrate facility evaluations and inspections for human drugs. The objectives of this agreement are to ensure alignment between FDA’s field professionals and the agency’s review staff by:

- Ensuring consistency, efficiency and transparency in facility evaluations, inspections and regulatory decision-making for marketing applications across FDA
- Advancing strategic alignment across CDER and ORA functional units by creating clear roles and responsibilities
- Improving FDA’s operational capacity by enhancing collaboration between various CDER and ORA offices
- Enhancing the quality of and increasing access to facility and regulatory decisional information across FDA
- Meeting user fee commitments and improving the timelines for regulatory, advisory and enforcement actions to protect public health and promote drug quality, safety and effectiveness

In 2017 FDA and the European Union entered into a Mutual Reliance Initiative to use each other’s good manufacturing practice inspection results for pharmaceutical manufacturing facilities. The Initiative became effective November 2, 2017. FDA is currently in the process of evaluating each of the 28 EU countries’ drug inspectorates to determine whether they are capable of meeting FDA’s requirements. As of the date of publication, the following countries’ regulatory authorities have been deemed capable: Austria, Croatia, France, Italy, Malta, Spain, Sweden and the United Kingdom. The Mutual Reliance Initiative will enable FDA to avoid duplication, reduce costs and focus its resources in other parts of the world.
where there is greater public health and safety risk.

In January 2017, FDA issued a Current Good Manufacturing Practice Requirements for Combination Products final guidance. The guidance document clarifies how cGMP requirements apply to certain products such as prefilled syringes, drug-coated mesh and drug-eluting stents. It also noted that while combination product manufacturers must demonstrate compliance with all of the cGMP regulations applicable to their combination product under 21 CFR § 4.3, they may alternatively demonstrate compliance with the drug cGMPs and medical device QSR requirements through one of the streamlined approaches outlined in 21 CFR § 4.4(b).

In 2017, the most common violations cited in CDER’s Office of Manufacturing Quality’s Warning Letters were data integrity deviations and issues surrounding the relationship between sponsors and contract manufacturing organizations. Yet with its December 2017 Drug Products Labeled as Homeopathic draft guidance, FDA signaled that it may be willing to pursue enforcement action where it did not previously, including when there are significant violations of cGMP in the manufacture of homeopathic drug products. The draft guidance lists categories of homeopathic drugs for which FDA intends to take a stricter enforcement approach. These include products with reported safety concerns, products with routes of administration other than oral and topical, and products with unproven or unsafe ingredients. This guidance updates FDA’s previous Compliance Policy Guide on Homeopathic Drugs and reflects the agency’s renewed focus on the category.

**Enforcement**

FDA’s enforcement actions—including Warning Letters, Civil Monetary Penalties, No-Tobacco-Sale Orders, Import Alerts, Seizures, Injunctions and Criminal Prosecutions—tapered in 2017, perhaps in an indication of the agency’s current focus on deregulation or its continuing focus on risk-based decision-making. Overall Warning Letter numbers decreased, including in key areas of historical focus, such as medical device quality and labeling and prescription drug marketing and promotion.

FDA focused enforcement in historically overlooked areas, such as homeopathic drugs and drug claims made for products marketed as cosmetics. While FDA’s enforcement action against cosmetics marketing claims peaked in 2016, FDA continued to issue Warning Letters to manufacturers and retailers for drug claims for products marketed as cosmetics at higher numbers than in prior years.

FDA also increased its focus on foreign entities that manufacture or distribute products for the US market. In 2012, the Food and Drug Administration Safety and Innovation Act, which amended FDCA § 510(h), eliminated the distinction between domestic and foreign inspections and directed FDA to take a risk-based approach to inspecting both domestic and foreign drug manufacturing establishments. FDA formalized its process for selecting establishments for inspection based on risk factors specified by FDCA § 510(h) in 2015. Thus, 2016 and 2017 reflected this increased focus on foreign-regulated entities.

**The Year Ahead**
FDA’s activities and initiatives in 2017 suggest that 2018 will bring continued focus on innovation, in terms of both innovative and breakthrough products and innovative approaches to regulating them. Recent efforts to restructure FDA’s drug review and inspection programs may require drug manufacturers to take a fresh look at existing inspection protocols and manufacturing practices and contracts. The continuing focus on novel products and new expedited review processes for digital health, regenerative therapies and novel devices may mean fewer barriers to market entry for novel products, but more significant and ongoing post-market data collection, research and reporting obligations. While there was a marked decrease in Warning Letters and enforcement in areas of historical focus such as prescription drug advertising in 2017, the industry may see an uptick in Warning Letters as FDA clears its backlog of pending actions or prioritizes its enforcement focus in specific program areas or product categories that have not been a focus in prior years. Companies seeking to enter the US market may benefit from FDA’s ongoing efforts to harmonize product approval, manufacturing, quality and clinical data requirements with global standards and to increase transparency and communication with significant regulators outside the United States.

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