Private Equity Guide to Life Sciences Investing Under the Trump Administration: Food and Drug Administration (FDA) Developments

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Overview

As the Trump administration enters its second year, it is an ideal time for private equity funds and investors active in the life sciences arena to reflect on the impact of the new administration—and a new commissioner—on the Food and Drug Administration ("FDA"). Of all the potential Trump nominees to head the agency, Dr. Scott Gottlieb, a physician, was clearly the most mainstream choice. Commissioner Gottlieb previously served as FDA's Deputy Commissioner for Medical and Scientific Affairs and, before that, as a senior advisor to the FDA Commissioner. As a cancer survivor, he also had first-hand experience as a patient—perhaps informing some of the regulatory strategies he has pursued.

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Those strategies have been significant. While many other federal regulatory agencies have been marginalized or victims of regulatory paralysis, FDA, under Scott Gottlieb's leadership, has forged ahead with sweeping initiatives intended to accelerate drug and device approvals and clearances, embrace innovation and new technologies, lower regulatory burdens, and enhance therapeutic opportunities.[1]

This fast-moving regulatory landscape, combined with robust innovation in the life sciences sector, creates both opportunities and challenges for private equity sponsors. In recent years, private equity sponsors have continued to prioritize investments in both the healthcare and life sciences industries and

[1] When Gottlieb took the reins at FDA, the agency was already focused on a number of ongoing initiatives such as the implementation of the 21st Century Cures Act, enacted at the end of 2016, and the passage of the FDA Reauthorization Act of 2017 ("FDARA"). Commissioner Gottlieb also confronted a challenging political environment, as opioid addiction and drug pricing were prominent issues during the Presidential campaign. FDA under Gottlieb's leadership has implemented a number of policies intended to address these important societal and political issues.

there are no signs that this sector focus will abate in the near future. While private equity investing continues to be strongest in the healthcare services sector (including hospitals, ambulatory care clinics, computer systems, home and hospice care, and pharmacy benefit managers ("PBMs"), among others), there is also strong interest in pure life sciences businesses, including pharma (particularly on the generics side), biotech, and medical devices companies (including mobile and digital health businesses targeting consumer health).

The comprehensive regulatory diligence typically conducted on a potential target needs to be accompanied by a basic understanding of the larger complex and multifaceted regulatory developments in the industry. This insight will help sponsors identify promising new areas for investment and to structure transactions in non-traditional ways to take advantage of, or reduce exposure to, regulatory changes by using put/call technology, option structures, or collaboration and licensing approaches (particularly given the growing convergence of licensing and M&A). Regulatory developments can also be important considerations in managing exit timing and structure. Moreover, the healthcare system in the United States is closely integrated, and regulatory changes that could affect reimbursement or drug prices, for instance, are likely to have secondary effects on many subsectors, including hospitals, supply line management businesses, PBMs, and physician practices, among many others.

By taking a thoughtful and creative approach to regulation, FDA under the Gottlieb regime has safeguarded public health while promoting innovation and investment. In this quickly changing environment, with new FDA policies and guidance documents issued in rapid succession, the likely winners will be companies that are nimble, capable of maneuvering within a new regulatory framework, and willing to compete in a more dynamic market. To give one example of the complexity being instilled in the market: FDA is pursuing a number of initiatives intended to accelerate innovator drug approvals while at the same time accelerating generic drug approvals when innovator drugs lose patent protection and marketing exclusivity. The moving terrain provides a challenging but potentially rewarding landscape for opportunistic investing.

In fact, this may be the ideal time to invest in life sciences as FDA's focus on reducing obstacles to innovation will likely continue over at least the next few years. Many of FDA's initiatives may be accomplished in the absence of notice-and-comment rulemaking, thereby staying clear of the Trump Administration's requirement that regulatory agencies withdraw two

regulations for every one they enact.[2] It is important to note, however, that policies enunciated through guidance documents or agency enforcement decisions may be easily reversed in the next administration—or even during this one—unless supported by statutory or regulatory changes.

This article provides an overview of FDA developments affecting life sciences investing during the first year of the Gottlieb regime and how private equity funds may capitalize on these changes. The article is divided into two sections. The first addresses innovative FDA regulatory developments that provide an overall constructive environment for life sciences investing; this section is divided into subsections addressing drugs and biologics, and medical devices, diagnostics and digital health. The article's second section addresses FDA regulatory developments where the implications are more nuanced, involving opioids, drug compounding, and generic drug approvals. Although not addressed in this article, FDA has also pursued innovative reforms impacting other regulatory areas subject to its jurisdiction, such as food and tobacco.

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[2] FDA has taken the position that new regulations that arguably "deregulate" are not subject to the two-for-one requirement. Published reports suggest that the Office of Management and Budget adheres to FDA's interpretation.

Table of Contents

FDA Regulatory Initiatives Favorably Impacting Life Sciences Investing

Drug and Biologic Investment

Many of FDA's new policies and initiatives help foster innovation and create an overall favorable environment for life sciences investing, both for companies working on innovative therapies and those producing generics and biosimilars.

Accelerated Innovator Drug Approvals

In his confirmation hearings, Gottlieb discussed the importance of accelerating the drug approval process, and the use of innovative science to inform new policies and speed

approvals is a key pillar in FDA's 2018 Strategic Policy Roadmap.[3] The agency's goal is to "minimize the likelihood that its requirements become an obstacle to the translation of beneficial scientific discoveries into practical solutions for patients, while continuing to strengthen its gold standard of regulatory oversight."[4] In the roadmap, FDA cited its intent to embrace technologies such as predictive toxicology methods and computational modeling and make new investments in high-performance, scientific computing.[5]

FDA has taken several concrete steps to fulfill this goal. One such initiative is the establishment of policies that support adaptive clinical trials. Adaptive trials, unlike traditional clinical trials, can be altered (in accordance with a pre-existing protocol) in response to early results, allowing researchers to shift the study population or objectives, for example. A single adaptive trial could replace multiple lengthy and expensive trials, and could lead to a shorter, less expensive approval process. In addition to adaptive trials, Gottlieb has also emphasized the use of computation modeling in a potential effort to abandon, or at least modify, the typical three stages of clinical trials. This new approach would not be limited to drug development—FDA's Center for Biologics Evaluation and Research ("CBER") has also indicated that it will encourage flexible trial designs, including adaptive trials, for regenerative medicine therapies. FDA will be releasing guidance on the use of complex adaptive and other novel trial designs by the end of 2018.

FDA is also working to develop policies to streamline cancer drug approvals. This may include approvals based on intermediate clinical endpoints, which could result in shorter trials. It could also include the addition of new indications for approved cancer drugs with less rigorous requirements for phase IV trials (*i.e.*, post-marketing, confirmatory trials).

Takeaway: Life sciences companies focusing on novel trial design, including clinical trial simulations and predictive toxicology, may represent a good opportunity for private equity investment in what could quickly become a fast-growing industry.

Use of Real-World Evidence

FDA has placed a priority on using real-world data and real-world evidence to support its decision making. *Real-world data* is data on patient health status or healthcare delivery

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[3] FDA, *Healthy Innovation, Safer Families: FDA's 2018 Strategic Policy Roadmap* (Jan. 2018), https://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/UCM592001.pdf.

[4] *Id.* at 9.

[5] *Id.* FDA also mentioned the implementation of a streamlined facility inspection process. *Id.* at 17. FDA's Office of Regulatory Affairs, responsible in part for conducting inspections of FDA-regulated manufacturing facilities, was reorganized shortly after Gottlieb was sworn in. Inspectors are now organized by product category rather than by region, aligning them with the review staff members who evaluate the products being manufactured in the facilities. FDA believes that this will, among other things, increase the efficiency of the review and approval process.

collected outside of clinical trials (*e.g.*, through electronic health records or billing activities). *Real-world evidence* uses real-world data to provide information on the risks or benefits of a particular product.

Real-world data is already being used in a variety of ways. The healthcare community, for example, is using real-world data to support coverage decisions and to develop treatment guidelines. Drug companies are using real-world data to design smarter clinical trials and to develop innovative treatment approaches. And in the future, more data may come directly from patients with advances in digital health products such as wearables and mobile apps.

FDA for its part, uses real-world data to monitor post-market safety and adverse events and to make regulatory decisions. The 21st Century Cures Act requires FDA to go beyond these efforts and to develop a regulatory framework and guidance to determine how real-world evidence can be used to support approval of new indications for approved drugs or to support or satisfy post-approval study requirements. The agency is also now examining how real-world evidence can be incorporated into drug development programs, and hosted a public workshop on the topic in September 2017. In addition, Gottlieb recently suggested that FDA may begin to accept real-world evidence to support updates to drug labeling to ensure that labels reflect the current state of the science. If FDA continues to expand the uses for real-world evidence, data capabilities may prove incredibly valuable for both pre- and post-approval programs.

Takeaway: Companies focused on collecting data and extracting clinical insights may provide sponsors with good investing opportunities, particularly with FDA's burgeoning acceptance of the many ways real-world evidence can support drug and device development.

Gene Therapy and Regenerative Medicine

Last year, FDA issued its first three approvals for gene therapy drugs. The first two approvals were for therapies known as Car-T treatments, which use genetically engineered T-cells to attack cancer. Novartis' Kymriah, approved in August 2017, treats a form of leukemia in children and young adults. Gilead's Yescarta, approved in October 2017, treats adults with advanced lymphoma. Both therapies reportedly command a hefty price tag—$475,000 for Kymriah and $373,000 for Yescarta. In December 2017, Spark Therapeutics received approval for Luxturna, the first therapy designed to replace a single faulty gene with a functional gene, treating patients with a rare form of vision loss caused by genetic mutation. The cost of the therapy will be $850,000.

These therapies are part of a larger wave of immunotherapies—an active area of research that could one day lead to products such as cancer vaccines. There are currently hundreds of gene- and cell-based treatments in clinical trials.

FDA clearly recognizes the promise of these new therapies. In November 2017, the agency announced a comprehensive policy framework (including multiple guidance documents) to support the development and oversight of gene therapy and regenerative medicine products. A draft guidance document issued the same month describes expedited programs that may be available for regenerative medicine therapies, including the new Regenerative Medicine Advanced Therapy ("RMAT") designation. RMAT designation would provide qualifying investigational therapies with the benefits of FDA's fast track and breakthrough designations, including the opportunity to hold early discussions with FDA that could lead to accelerated approval.[6] FDA has already designated a number of products as RMAT therapies. Other guidance documents will be released for specific high-priority diseases, with the first guidance document expected to focus on hemophilia.

While optimistic about the promise of regenerative medicine, Gottlieb also stressed that FDA intends to protect patients from therapies that pose potential significant risk. In the 2018 Strategic Policy Roadmap, FDA stated that while it will advance frameworks to facilitate the efficient development of regenerative medicine, the agency also plans to take new steps to address products that are putting patients at risk and making deceptive health claims.[7] For example, in 2017 FDA took action against several clinics selling unapproved and potentially dangerous stem cell therapies.

Takeaway: The promise of gene therapy and regenerative medicine is finally beginning to come to fruition and FDA is actively taking steps to bring additional therapies to market. But FDA has no tolerance for entities or products that exploit the excitement surrounding regenerative medicine by putting patients at risk or making deceptive health claims.

Orphan Drugs and Targeted Therapies

FDA announced its "Orphan Drug Modernization Plan" in June 2017 and by the end of year had eliminated the entire backlog of pending orphan drug designation requests and approved a record number of drugs with orphan indications.[8] In addition, Gottlieb has expressed his intention to issue guidance closing a loophole in the orphan drug program that allows sponsors to avoid an obligation to study drugs in pediatric indications and to more generally review the program to ensure that sponsors cannot use orphan designations to sidestep regulatory obligations.

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6 FDA, *Draft Guidance for Industry: Expedited Programs for Regenerative Medicine Therapies for Serious Conditions* (Nov. 2017), https://www.fda.gov/downloads/biologicsbloodvaccines/guidancecomplianceregulatoryinformation/guidances/cellularandgenetherapy/ucm585414.pdf.

7 FDA, *Healthy Innovation, Safer Families: FDA's 2018 Strategic Policy Roadmap* 14 (Jan. 2018), https://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/UCM592001.pdf.

8 Orphan drugs are those that treat rare diseases or conditions.

FDA has acknowledged both the challenges and promise of developing targeted therapies for small subpopulations, which may require a different development framework than therapies that target all patients with a particular disease. The promise of these targeted therapies, which may be extremely effective for certain subpopulations but not for others, has prompted FDA to issue guidance on developing clinical trials for targeted therapies for small numbers of patients[9] and on the diagnostic devices used alongside these therapies to identify patients eligible for treatment.[10] Gottlieb issued a statement in conjunction with these guidance documents stating that FDA "hopes to enable more efficient access to safe and effective, novel targeted therapies for the patients who need them" and "remain[s] committed to assisting the medical community as it further modernizes and individualizes approaches to care, to increase the public health benefit offered by new medical technologies."[11]

Takeaway: FDA is very supportive of novel development approaches for orphan therapies and is committed to getting these drugs to market as soon as possible.

Rare Pediatric Diseases

FDA aims to encourage the development of drugs targeting rare pediatric diseases. From FDA's recent guidance document, it is clear that the agency is considering creative approaches to encourage development of these drugs.[12] For example, the guidance addresses the possibility of large, multi-company clinical trials to enhance the efficiency of drug development by testing multiple promising investigational drugs at once, and the extrapolation of data from adult studies to demonstrate efficacy in children.

Takeaway: FDA is very supportive of companies developing drugs targeting rare pediatric diseases and of novel development approaches.

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9 FDA, *Draft Guidance for Industry: Developing Targeted Therapies in Low-Frequency Molecular Subsets of a Disease* (Dec. 2017), https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM588884.pdf.

10 FDA, *Draft Guidance for Industry, Food and Drug Administration Staff, Sponsors, and Institutional Review Boards: Investigational IVDs Used in Clinical Investigations of Therapeutic Products* (Dec. 18, 2017), https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM589083.pdf.

11 Statement from FDA Commissioner Scott Gottlieb, M.D. on New FDA Efforts to Support More Efficient Development of Targeted Therapies (Dec. 15, 2017), https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm589248.htm.

12 FDA, *Draft Guidance for Industry: Pediatric Rare Diseases—A Collaborative Approach for Drug Development Using Gaucher Disease as a Model* (Dec. 2017), https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM587660.pdf.

Material Threat Medical Countermeasures

Medical countermeasures are defined as medical products intended to diagnose, prevent, or treat diseases or conditions associated with chemical, biological, radiological, and nuclear threats and emerging infectious diseases. The 21st Century Cures Act seeks to promote the development of certain medical countermeasures by allowing companies that develop such countermeasures to receive vouchers from FDA that will allow the company to obtain a priority review for a subsequent drug application. FDA recently issued guidance on various aspects of the program, including how to determine whether a product will qualify for a voucher.[13] These priority review vouchers, like those received through other programs, can be sold to third parties and thus could be valuable assets in their own right.

Takeaway: Priority review vouchers can be obtained through the new medical countermeasures program and these vouchers, which may be sold to third parties, are valuable assets.

Expanding Over-the-Counter Access to Former Prescription Drugs

In what would be a significant deregulatory move, FDA is planning to propose regulations this year that will increase access to prescription drugs by allowing them to be sold over-the-counter with added safeguards. FDA intends to promote innovative approaches to ensure that customers can self-select appropriate drugs on their own. Gottlieb stated that the new rule could include the "use of self-selection questions on a mobile medical app prior to permitting access to the drug, or other innovative technologies to improve safety."[14]

Takeaway: Allowing additional prescription drugs to be sold over-the-counter could provide unique opportunities for sponsors who follow the development of these regulations.

Over-the-Counter Monograph Reform

Over-the-counter monographs provide "recipes" for therapeutic categories (*e.g.*, sunscreens or acne drugs) covering acceptable ingredients, indications, and labeling. A drug marketed consistent with these conditions may be sold without pre-approval by FDA. Unfortunately, the monograph process has been moving at a glacial pace and many monographs have yet to be finalized since the process started in 1972. In addition, updating monographs based upon evolving scientific developments requires a lengthy process involving notice-and-comment rulemaking.

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[13] FDA, *Guidance for Industry: Material Threat Medical Countermeasure Priority Review Vouchers* (Jan. 2018), https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-afda-gen/documents/document/ucm592548.pdf.

[14] Scott Gottlieb, M.D., "Looking Ahead: Some of FDA's Major Policy Goals for 2018," *FDA Voice* (Dec. 14, 2017), https://blogs.fda.gov/fdavoice/index.php/2017/12/looking-ahead-some-of-fdas-major-policy-goals-for-2018/.

Gottlieb has acknowledged that the current over-the-counter monograph procedure is out of date. Congress has been contemplating Over-the-Counter Drug Review legislative reform for a number of years, and now appears poised to act. In September 2017, the House of Representatives released a draft of a monograph reform bill that would create an over-the-counter monograph user fee program, allow for more efficient reviews, and create an exclusivity period for new products to encourage innovation in this space. A similar bill was introduced in the Senate in January. If Congress and/or FDA acts to accelerate monograph review, there could be implications for over-the-counter drugs currently on the market that are not subject to final monographs. For example, if a product does not conform to requirements in a finalized monograph, the product would have to be adjusted to conform or be removed from the market.

Takeaway: In conducting diligence, sponsors looking to acquire over-the-counter companies or products should be aware of the status of the monograph for the particular product and carefully evaluate the potential for future change that could affect the product's marketing status. Potential exclusivity periods for new over-the-counter products, as proposed in draft legislation, may provide sponsors with good investing opportunities in innovative over-the-counter drug companies.

Medical Device, Digital Health, and Diagnostics Investment

Gottlieb has repeatedly expressed his desire for the agency to embrace modern technology and encourage innovation in the medical device space. In its 2018-2020 Strategic Priorities, FDA's Center for Devices and Radiological Health ("CDRH") established a goal of increasing the number of novel technologies needed in the U.S. market that are first introduced in the United States, in order to meet its commitment to provide Americans with first access to high-quality medical devices.[15] FDA acknowledged that to meet this goal, it must provide incentives for manufacturers to bring their products to the U.S. marketplace despite rigorous regulatory standards. We are beginning to see signs of this effort in a number of policy announcements and guidance documents aimed at modernizing processes and lowering regulatory hurdles for bringing devices to market. In the rapidly evolving medical device market, sponsors will need to be nimble in an effort to take advantage of these deregulatory moves.

Increased Transparency and Lowered Regulatory Burdens in the Medical Device Review Process and 510(k) Modifications

In an effort to ease regulatory burdens and uncertainty in the device approval and clearance processes, FDA has issued a series of guidance documents aimed at increasing

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[15] "Our Measure of Success: By December 31, 2020, more than 50 percent of manufacturers of novel technologies for the U.S. market intend to bring their devices to the U.S. first or in parallel with other major markets." FDA Center for Devices and Radiological Health, *2018-2012 Strategic Priorities* at 8 (Jan. 2018), https://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHVisionandMission/UCM592693.pdf.

transparency and lowering regulatory burdens associated with the medical device review process.

First, FDA issued final guidance in October 2017, updating policy guidelines on the types of device modifications that require a new 510(k) instead of mere documentation by the manufacturer.[16] In the guidance, FDA attempts to provide greater clarity for industry and lessen the uncertainty surrounding 510(k) applications, so manufacturers could more accurately predict whether a device could be updated or changed without a new clearance. Industry groups have been generally supportive of the guidance.

Second, FDA updated two "least burdensome" guidance documents at the end of 2017—the first time these documents had been updated in well over a decade.[17] These documents apply Congress's directive to FDA to take a "least burdensome" approach to medical device regulation by eliminating unnecessary burdens that may delay the marketing of beneficial new products. For example, when seeking to resolve a regulatory question or issue, FDA must request the minimum information necessary from manufacturers to do so. In its 2018-2020 Strategic Priorities, FDA reaffirmed its commitment to avoiding unnecessary burdens in the regulatory process.[18]

Takeaway: FDA is focusing on ways to encourage industry innovation. Less burdensome review processes may result in the ability to get devices to market on a shorter timeline and transparency initiatives may allow sponsors to more easily evaluate options by providing insight into how FDA evaluates applications.

Modernization and Increased Efficiency of Medical Device Review Process

Gottlieb has announced a number of initiatives to modernize the device review process and speed products' entry to market. By choosing to focus on a "benefit-risk based" review process, it is clear that Gottlieb believes that the reduction of regulatory burdens will allow for innovative devices to reach patients more quickly. The modernization of FDA's policy framework in this area has the potential to be extremely beneficial to device companies.

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16 FDA, *Guidance for Industry and Food and Drug Administration Staff: Deciding When to Submit a 510(k) for a Change to an Existing Device* (Oct. 25, 2017), https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm514771.pdf.

17 FDA, *Guidance for Industry and Food and Drug Administration Staff: Developing and Responding to Deficiencies in Accordance with the Least Burdensome Provisions* (Sept. 29, 2017), https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm073680.pdf; FDA, *Draft Guidance for Industry and Food and Drug Administration Staff: The Least Burdensome Provisions: Concepts and Principles* (Dec. 15, 2017), https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM588914.pdf.

18 FDA Center for Devices and Radiological Health, *2018-2012 Strategic Priorities* (Jan. 2018).

First, FDA announced plans to issue draft guidance in early 2018 "expanding" the 510(k) program by allowing manufacturers to demonstrate substantial equivalence, and obtain device clearance, using objective safety and performance criteria. This is in contrast to the current program, which focuses on comparisons between a new device and specific predicate devices. Under the proposed plan, for devices in certain prespecified categories, a company would simply need to identify a lawfully marketed predicate device with the same intended use but would not need to compare technological aspects of the current device to the predicate. FDA plans to identify categories of devices for which this voluntary, alternative pathway will be available, focusing on devices for which safety and performance criteria that meet or exceed the performance of existing, legally-marketed devices can be identified. In his announcement, Gottlieb suggested that these categories may include ultrasound imaging machines, common in vitro diagnostic devices, and blood pressure monitors.[19] Gottlieb believes that the new program would reduce unnecessary obstacles for device manufacturers and increase the speed of review, because predicate devices may be decades old and difficult to obtain for comparative purposes.

Second, FDA plans to issue draft guidance in early 2018 that will place increased focus on post-market follow-up studies in order to accelerate medical device market entry and facilitate patient access to innovative products. This may include reliance on post-market real world data collected from patients using a device. The guidance will outline acceptable levels of uncertainty for FDA to approve a device, relying on post-market data to provide a more complete efficacy and safety profile after approval. FDA intends to consider several factors when considering a new device: the extent of public health need, the seriousness of the disease the device will treat or diagnose, the size of the population that could benefit, and the risk-benefit profile of alternative devices. While critics are concerned that this may result in unsafe products getting to market, this approach has the potential to be extremely beneficial to the medical device industry depending on how widely it is applied. If applied in a risk-based manner as expected, manufacturers of low-risk products could see the biggest benefits in terms of shortened review times.

Third, FDA is reorganizing the Center for Devices and Radiological Health by combining a number of its review, compliance, and surveillance functions into one large office, the Office of Product Evaluation and Quality. FDA expects this reorganization to increase the efficiency of the Center's activities, including application review.

Takeaway: FDA is actively embracing modern processes and technology. The agency's new regulatory approaches provide an ideal environment to bring innovative, first-in-class devices to market, particularly if the product is low risk, high reward.

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[19] Scott Gottlieb, M.D., "Advancing Policies to Promote Safe, Effective MedTech Innovation", *FDA Voice* (Dec. 11, 2017), https://blogs.fda.gov/fdavoice/index.php/2017/12/advancing-policies-to-promote-safe-effective-medtech-innovation/.

Digital Health Initiatives

In June 2017, Gottlieb introduced the "Digital Health Innovation Action Plan," outlining FDA's efforts to foster digital health innovation. In his announcement, Gottlieb stated that FDA can "help reduce the development costs for [digital health] innovations by making sure that [FDA's] own policies and tools are modern and efficient, giving entrepreneurs more opportunities to develop products that can benefit people's lives."[20] As part of the plan, which implements Congress's goals in the 21st Century Cures Act, FDA is in the process of issuing new draft and final guidance documents related to medical software, including guidance clarifying which categories of medical software functions and digital health technologies are subject to FDA's jurisdiction.

In October 2017, FDA released a final guidance addressing when to submit a 510(k) for a software change to an existing device. Like the more general 510(k) guidance addressed above, this provided industry with greater predictability.[21] FDA also recently issued draft guidance documents addressing whether a software program or mobile medical app will fall under FDA's jurisdiction as a medical device. One such guidance document explains how FDA will implement a section of the 21st Century Cures Act that places certain software functions outside of the medical device definition and thus significantly lowers the regulatory burden for the creation of these software products.[22] For example, software meant for administrative support, electronic patient records, and to help maintain or encourage a healthy lifestyle will not be regulated as medical devices.[23] These areas may be particularly attractive for new development.

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[20] Scott Gottlieb, M.D., "Fostering Medical Innovation: A Plan for Digital Health Devices," *FDA Voice* (June 15, 2017), https://blogs.fda.gov/fdavoice/index.php/2017/06/fostering-medical-innovation-a-plan-for-digital-health-devices/.

[21] FDA, *Guidance for Industry and Food and Drug Administration Staff: Deciding When to Submit a 510(k) for a Change to an Existing Device* (Oct. 25, 2017).

[22] FDA, *Draft Guidance for Industry and Food and Drug Administration Staff: Changes to Existing Medical Software Policies Resulting from Section 3060 of the 21st Century Cures Act* (Dec. 8, 2017), https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM587820.pdf.

[23] According to the guidance document, "software with healthy lifestyle claims, such as weight management, physical fitness, relaxation or stress management, mental acuity, self-esteem, sleep management, or sexual function, are not devices when not related to the diagnosis, cure, mitigation, prevention, or treatment of a disease or condition." *Id*. at 8. FDA provides the following examples of products that would not be devices: (1) "A mobile application that plays music to soothe and relax an individual and to manage stress;" (2) "A mobile application that solely monitors and records daily energy expenditure and cardiovascular workout activities to allow awareness of one's exercise activities to improve or maintain good cardiovascular health;" and (3) "A mobile application that monitors and records food consumption to manage dietary activity for weight management and alert the user, healthcare provider, or family member of unhealthy dietary activity." *Id*. at 9.

FDA has also attempted to clarify the type of clinical decision support ("CDS") software that will be subject to oversight and/or enforcement. In draft guidance, FDA stated that patient decision support software, such as programs designed to remind patients to take medication on time, will not be subject to FDA regulation.[24] In addition, software that allows physicians to independently review the program's clinical recommendations may also not be regulated as a device, but FDA will continue to enforce oversight of software programs that are intended to process or analyze medical information. Critics claim that the guidance is overly ambiguous and does not recognize that physicians may not be able to review recommendations in some instances—such as when a program uses a complicated algorithm—but that these programs may nonetheless be sufficiently low risk to make FDA oversight unnecessary.

We expect FDA to continue to focus its regulatory efforts on high-risk products, while loosening the regulatory burdens on lower-risk digital health products, consistent with the mandates of the 21st Century Cures Act. For example, FDA has recently introduced the Software Precertification (Pre-Cert) Pilot Program, where FDA focuses on the developer of the technology rather than the product itself. In the pilot program, FDA is reviewing a number of companies' quality systems for software design, validation, and maintenance, to potentially precertify the companies and allow for a lower bar for any new digital health products distributed by those companies—perhaps by allowing them to submit less information or even forgo premarket review altogether. Participants in the pilot program include Apple, Fitbit, Johnson & Johnson, and Roche, among others. If the program is successful, FDA may expand it to other product categories in the future.

In addition, FDA announced in October 2017 that the first qualification of a medical device development tool ("MDDT") was awarded to a product designed to provide engineers developing heart failure devices with tools to measure the benefits of the device. FDA expects to qualify additional MDDTs for different purposes in the coming months, and has stated that these tools have the potential to "minimize the use of animal studies, reduce the duration of testing, or require fewer patients in a study by optimizing patient selection or improving on the ability to measure benefit and risk through the availability of measurements that are more sensitive for assessing these outcomes."[25]

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[24] FDA, *Draft Guidance for Industry and Food and Drug Administration Staff: Clinical and Patient Decision Support Software* (Dec. 8, 2017), https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm587819.pdf.

[25] Statement from FDA Commissioner Scott Gottlieb, M.D., on New Steps to Advance Medical Device Innovation and Help Patients Gain Faster Access to Beneficial Technologies (Oct. 24, 2017), https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm581861.htm.

Takeaway: FDA recognizes its role in shepherding digital health products to market and aims to reduce hurdles to product approval. The agency is working to foster innovation, particularly in areas with frequent iteration and product updates. Traditional regulatory frameworks must be adjusted, however, and sponsors should be aware that it may take creativity and persistence to work through the regulatory requirements.

3D Printing

FDA has embraced what it calls a "new era of 3D printing of medical products" by issuing guidance addressing technical considerations for manufacturers.[26] In the statement announcing the guidance, FDA acknowledged that it has reviewed "more than 200 devices currently on the market that were manufactured on 3D printers," including patient-matched anatomical devices such as knee replacements and facial reconstruction implants, and that "there is the potential for this same technology to eventually be used to develop replacement organs."[27]

FDA is in the process of developing a regulatory framework for manufacturers of 3D-printed personalized devices, but the guidance could result in higher regulatory burdens—including decreased flexibility and higher costs—for nontraditional manufacturers such as university hospitals that are already manufacturing 3D-printed devices for individual patients. For example, if FDA chooses to apply its stringent quality requirements and standards to any entity that owns a 3D printer used to produce medical devices, it may prohibit healthcare providers from being able to print devices cost effectively and may make the technology less attractive if they can no longer create devices in-house.

Takeaway: There is considerable potential for 3D printing to transform the medical device market, but interested sponsors should pay close attention as FDA develops the regulatory framework in order to take advantage of opportunities and avoid regulatory pitfalls.

Breakthrough Devices

In October 2017, FDA issued a new draft guidance document addressing priority review and other incentives authorized for breakthrough devices, as mandated by the 21st Century Cures Act.[28] To accelerate the review process, FDA may allow flexible clinical

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[26] FDA, *Guidance for Industry and Food and Drug Administration Staff: Technical Considerations for Additive Manufactured Medical Devices* (Dec. 5, 2017), https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM499809.pdf.

[27] Statement by FDA Commissioner Scott Gottlieb, M.D., on FDA Ushering in New Era of 3D Printing of Medical Products; Provides Guidance to Manufacturers of Medical Devices (Dec. 4, 2017), https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm587547.htm.

[28] FDA, *Draft Guidance for Industry and Food and Drug Administration Staff: Breakthrough Devices Program* (Oct. 25, 2017),

trial designs and shift certain data collection requirements to post-approval. In order to qualify as a breakthrough device, the device must provide for more effective treatment or diagnosis of life-threatening or irreversibly debilitating diseases.

Takeaway: FDA is very supportive of companies developing breakthrough devices and the approval process may be faster than ever for this category.

Direct-to-Consumer Genetic Tests

Companies offering certain types of direct-to-consumer genetic tests had several regulatory burdens reduced in November 2017.[29] First, FDA issued an order exempting genetic carrier screening tests from premarket review. This was followed by notice of the agency's intent to allow "genetic health risk assessment" (*i.e.*, predictive) tests to be exempted from premarket review under certain conditions. If finalized, manufacturers would only need a one-time review to ensure that they meet FDA's requirements, after which they may market new tests without further review. (This approach is similar to the precertification program proposed for digital health technologies.) In its 2018-2020 Strategic Priorities, CDRH highlighted this new initiative as an example of how the agency plans to adopt flexible regulatory paradigms to expand access to certain products while still ensuring that they are safe and effective.[30]

Finally, in March 2018, FDA approved for the first time a direct-to-consumer genetic test (using saliva) to test for three genetic mutations associated with breast cancer in people of Ashkenazi (Eastern European) Jewish descent.

Takeaway: Companies offering direct-to-consumer genetic tests may present private equity sponsors with intriguing investing opportunities due to lowered regulatory burdens.

Laboratory-Developed Tests

The debate surrounding the regulation of laboratory-developed tests ("LDTs") continues, with the device industry pitted against clinical labs that develop and market diagnostics in the absence of FDA oversight (but subject to other Federal and state regulatory requirements). LDTs are in vitro diagnostic tests that are designed, manufactured and used within a single laboratory (*e.g.*, a hospital's in-house laboratory). FDA has traditionally exercised enforcement discretion for these tests and has not enforced premarket review or other applicable requirements. Because LDTs are ubiquitous, FDA

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https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM581664.pdf.

[29] Statement from FDA Commissioner Scott Gottlieb, M.D., on Implementation of Agency's Streamlined Development and Review Pathway for Consumer Tests that Evaluate Genetic Health Risks (Nov. 6, 2017), https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm583885.htm.

[30] FDA Center for Devices and Radiological Health, *2018-2012 Strategic Priorities* (Jan. 2018).

has been hesitant to alter the status quo, much to the frustration of companies marketing equivalent FDA-cleared tests.

Based upon statements made prior to becoming Commissioner, Gottlieb is generally in favor of FDA regulating LDTs due to safety and efficacy concerns but believes that it should be Congress that establishes the framework for doing so. To that end, FDA has been offering technical assistance to refine the "Diagnostics Accuracy and Innovation Act," which would cover LDT regulation. The bill would combine in vitro diagnostics and LDTs in a new category distinct from medical devices, and the members of Congress developing the bill have expressed a desire to move quickly.

In the meantime, FDA is generally allowing traditional LDTs to remain on the market but will enforce as necessary if an LDT presents a safety risk (*e.g.*, by requiring premarket review). FDA encourages LDTs to seek voluntary approval and is pursuing ways to make the approval or 510(k) clearance process less burdensome. As one example, FDA accredited the New York State Department of Health as an FDA third-party reviewer of in vitro diagnostics. This means that going forward, certain laboratories with specific tests approved by that agency will not need to submit a separate application to FDA for clearance—instead, the New York application can simply be forwarded to FDA for review. Accreditation of additional third-party reviewers is expected to reduce regulatory burdens for entities desiring FDA clearance of their in vitro diagnostics.

Takeaway: Sponsors should pay attention to developments in Congress, as new legislation could provide intriguing investing opportunities in the in vitro diagnostic market.

FDA Regulatory Initiatives with More Nuanced Implications for Life Sciences Investing

The implications of a number of FDA initiatives will depend on where the company sits in the market. For example, the current public focus on drug pricing may have negative effects for innovator companies that are able to command high prices, but it will undoubtedly benefit generic and biosimilar companies that may be able to enter the market more quickly as a result of FDA policy initiatives. For companies that sell traditional opioids, increased scrutiny and enforcement will result in an uncertain environment, but companies developing novel approaches to address the opioid crisis may benefit from FDA developments. Finally, increased enforcement related to pharmacy compounding and outsourcing facilities may be detrimental to many of those entities but advantageous to those remaining pharmacies that have deployed the necessary resources to navigate the complex FDA regulatory requirements.

Generic Drugs

President Trump has threatened on many occasions to take action to address what he sees as unreasonably high drug prices.[31] Although he has not yet implemented a concrete plan for addressing this issue—there have been rumors about an executive order that has not yet materialized—Gottlieb has certainly taken note of this concern.[32] Although FDA does not have the legal authority to investigate or control drug pricing, it can effect pricing indirectly by encouraging competition through new policies and programs.[33] Although these efforts may threaten innovator companies that rely on high drug prices, there are new opportunities for generic manufacturers. In fact, in 2017, FDA recorded the highest annual total of generic drug approvals (1,027) in the agency's history.[34]

Crackdown on Alleged Innovator Delay Tactics

Gottlieb has repeatedly expressed frustration with innovator companies that allegedly attempt to delay the entry of generic drugs into the market. He has cautioned those companies to "end the shenanigans" and in particular criticized two such tactics that innovator companies are suspected of using: refusing to negotiate with generic companies regarding a single, shared Risk Evaluation and Mitigation Strategies ("REMS") plans, and limiting generic company access to innovator drugs in order to

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[31] As one potential solution to decrease drug prices, President Trump has suggested allowing importation of prescription drugs from other countries. Gottlieb, however, has generally been critical of this proposal for a variety of reasons, including potential safety concerns arising from shipment outside of the "closed distribution system" established in the United States. In addition, pharmaceutical companies may be reluctant to increase output abroad and undermine their own interests in the United States, and second, other countries would likely be opposed to a policy that may create local shortages by funneling drugs to the United States. The ultimate policy outcome is, as of this writing, unclear.

[32] Congress is also actively considering actions to address drug pricing. On December 12, 2017, the Senate Committee on Health, Education, Labor and Pensions convened a full committee hearing regarding a report by The National Academies of Sciences, Engineering, and Medicine titled "Making Medicines Affordable: A National Imperative." The report made a number of FDA-related recommendations, such as to "[a]ccelerate the market entry and use of safe and effective generics as well as biosimilars, and foster competition to ensure the continued affordability and availability of these products" and "[e]nsure that financial incentives for the prevention and treatment of rare diseases are not extended to widely sold drugs." The National Academies of Science, Engineering & Medicine, "Making Medicines Affordable: A National Imperative" (Nov. 2017).

[33] There are currently a number of drug pricing initiatives under consideration in Congress—including some that would involve FDA—such as the Creating and Restoring Equal Access to Equivalent Samples Act of 2017 (the "CREATES Act"), which targets innovator companies' alleged attempts to slow generic approvals.

[34] Scott Gottlieb, M.D., "Reflections on a Landmark Year for Medical Product Innovation and Public Health Advances and Looking Ahead to Policy in 2018", *FDA Voice* (Jan. 9, 2018), https://blogs.fda.gov/fdavoice/index.php/2018/01/reflections-on-a-landmark-year-for-medical-product-innovation-and-public-health-advances-and-looking-ahead-to-policy-in-2018/.

perform the bioequivalence studies necessary for generic approval. (Innovator and generic companies are, in certain situations, expected to share a single system.)[35]

REMS are post-market risk management plans required by FDA for certain high-risk products. The plans may include items such as patient or provider education, healthcare professional certification, patient monitoring, patient testing (*e.g.*, pregnancy testing), etc. Because innovator and generic companies are, in certain situations, expected to share a single REMS system and generics cannot be sold until the system is in place, innovator companies could use negotiations over this system to slow down generic entry to market—indeed, Gottlieb has alleged that certain innovator companies are doing so.[36] In response, FDA recently issued a guidance document reducing the paperwork necessary for a shared REMS system.[37]

While the recently issued guidance only addresses technical details of REMS negotiations and therefore may not actually result in generics getting to market faster, FDA action has brought further attention to the REMS system as a key issue and the agency has promised additional guidance on the subject. In addition, Gottlieb has indicated that FDA will more frequently waive the single-shared REMS requirement and has promised guidance on this issue in the first quarter of 2018. FDA is also expected to release guidance addressing other alleged innovator delay tactics, such as restricting generic company access to innovator drugs to perform the bioequivalence studies necessary for generic approval.[38]

Priority ANDA Review

FDA updated its policy and procedures related to the prioritization of ANDA review by expanding the number of ways applicants can qualify for priority review. ANDAs may be eligible for "priority review" if, for example, there are three or fewer other generics approved for the particular innovator drug. Priority review may take as little as eight months.

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35 Scott Gottlieb, M.D., Remarks by Dr. Gottlieb at the FTC (Nov. 8, 2017), https://www.fda.gov/NewsEvents/Speeches/ucm584195.htm.

36 Statement from FDA Commissioner Scott Gottlieb, M.D., on New Steps to Improve FDA Review of Shared Risk Evaluation and Mitigation Strategies to Improve Generic Drug Access (Nov. 8, 2017), https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm584259.htm.

37 FDA, *Guidance for Industry: Format and Content of a REMS Document* (Oct. 2017), https://www.fda.gov/downloads/Drugs/.../Guidances/UCM184128.pdf.

38 Statement from FDA Commissioner Scott Gottlieb, M.D. on New Steps to Facilitate Efficient Generic Drug Review to Enhance Competition, Promote Access and Lower Drug Prices (Jan. 3, 2018), https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm591184.htm.

Other Efforts to Encourage Competition

Other efforts by FDA to encourage competition and streamline approval and post-approval processes for generic drugs include:

- Issuing multiple guidance documents intended to increase the efficiency of generic application review. In "Determining Whether to Submit an ANDA or 505(b)(2) Application," FDA aimed to clarify regulatory expectations for abbreviated approval pathways.[39] In a separate guidance document, the agency addressed common deficiencies in applications in an effort to advise generic companies on ways to avoid unnecessary delays in processing applications.[40]

- Facilitating approval of generic versions of "complex drugs." Complex drugs include drugs that act locally (*e.g.*, an eye drop that acts on the eye's surface) or drugs that require administration through a device such as a metered dose inhaler or auto-injector. These drugs possess features that may make it difficult for an ANDA sponsor to satisfy the requirement of establishing equivalence to the branded drug. FDA is developing guidance documents to facilitate development of such complex generic drugs—for example, FDA has indicated that it will distribute guidance allowing label differences between complex generics and innovator drugs as long as they only reflect design differences. FDA has also developed channels for increased communication between FDA and the sponsors of complex generics to allow for more efficient development and regulatory review of such drugs.

- Including patent submission dates in Orange Book listings and issuing a list, updated every six months, of approved innovator drugs that are off-patent and off-exclusivity.[41] While this information has long been publicly available, these actions by FDA make it more accessible, encouraging generic drug makers to identify and prioritize opportunities for drug development where there is little or no competition.[42]

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[39] FDA, *Draft Guidance for Industry: Determining Whether to Submit an ANDA or a 505(b)(2) Application* (Oct. 2017), https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM579751.pdf.

[40] FDA, *Draft Guidance for Industry: Good ANDA Submission Practices* (Jan. 2018), https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM591134.pdf.

[41] FDA, *List of Off-Patent, Off-Exclusivity Drugs Without an Approved Generic*, https://www.fda.gov/downloads/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/UnderstandingGenericDrugs/UCM564441.pdf.

[42] It appears that industry is already taking note. Four major U.S. hospital systems—Intermountain Healthcare, Ascension, SSM Health, and Trinity Health—have announced plans to jointly launch a nonprofit generic drug company that will prioritize production of generics for drugs that lack competition.

- Working with the U.S. Pharmacopeial Convention ("USP") to develop standards for drugs that FDA has highlighted as off-patent, off-exclusivity, and without generic competition, to encourage competition for these drugs.

Takeaway: The continuing focus on drug prices may have negative effects for certain innovator companies charging high prices, but sponsors may find generic and biosimilar companies to be intriguing investing opportunities in this climate. There is considerable support at FDA and in Congress for increasing competitive pressure on innovator companies by getting generic and biosimilar products to market as quickly as possible.

Biosimilars

Gottlieb believes that biosimilar development, and resulting FDA approvals, is poised to significantly increase in the near future. Speaking at *The Washington Post's* "Chasing Cancer" summit on September 18, 2017, Gottlieb said that FDA was in the midst of reviewing 10 biosimilar applications and that 27 sponsors had asked for guidance on applications. He believes FDA will see "a real pickup in the rate of biosimilar development" and that "we're at the early stages of biosimilar [development], similar to where we were 30 years ago with generic drugs."[43] In 2017, FDA approved five biosimilars and we expect to see additional approvals over the next few months.

Gottlieb indicated that the agency will be releasing a Biosimilar Innovation Plan during 2018, intended to encourage biologics competition. FDA sees this initiative as another way to address the drug pricing issue in addition to its policies encouraging generic competition.

Takeaway: As is the case for generic drugs, FDA's focus on drug pricing creates opportunity for sponsors to invest in biosimilar manufacturers but may hurt innovator biologics companies.

Opioids

On October 26, 2017, President Trump declared the national opioid crisis a public health emergency, outlining a series of steps to combat the epidemic. Even before that announcement, FDA had been taking steps to address the crisis. While opioid products and their manufacturers continue to face heightened regulatory scrutiny, Gottlieb has endorsed policies that encourage innovations to treat opioid addiction and the development of abuse-deterrent generic formulations of opioid products already on the market. The agency's response to the epidemic is quickly evolving: the agency's Opioid

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[43] Washington Post Live, Transcript: Chasing Cancer Summit, *The Washington Post* (Sept. 19, 2017), https://www.washingtonpost.com/blogs/post-live/wp/2017/09/19/transcript-chasing-cancer-summit/?utm_term=.52ab423f6018.

Policy Steering Committee convened on January 30, 2018 in a step toward eventual recommendations for new policy approaches.

Areas for Caution

The following developments could negatively affect investments in the opioid industry:

- **Removal of products from the market**. In June 2017, FDA took the unprecedented step of requesting that Endo Pharmaceuticals remove its opioid pain medication, Opana ER, from the market, due to "concerns that the benefits of the drug may no longer outweigh its risks."[44] FDA based its decision on a review of postmarket data, which showed a shift in the route of abuse from nasal to injection, and injection abuse of Opana ER had been associated with an outbreak of HIV and hepatitis C. Similar action may be taken against other opioid products deemed to have a high risk for abuse or that pose other safety concerns; clearly FDA is primed to take a more active role in regulating individual opioid products. In addition, FDA is considering whether certain OTC products that have been abused should be made prescription-only.

- **Label changes to control prescribing patterns and provide additional warnings**. Gottlieb has expressed a desire to draft guidelines that can be incorporated into drug labeling—for example, by limiting the duration of treatment for immediate release opioids. FDA is also developing changes to immediate release opioid labeling, including additional warnings and safety information that incorporate elements similar to those already required on extended release or long-acting opioids.

- **Packaging changes to limit abuse**. FDA recently asked that manufacturers of Loperamide (Imodium) voluntarily change the packaging to contain a limited amount of the drug appropriate for short-term use (*e.g.*, by using blister packs or other single dose packaging and by limiting the number of doses in a package) after reports of serious heart problems and deaths due to abuse. FDA has also asked Congress to grant it the authority to require packaging changes.

- **Potential litigation**. Litigation accusing opioid manufacturers and distributors/wholesalers of deceptively marketing the safety of their painkillers—or distributing more opioids to certain geographic areas than projected need suggests—has continued to increase. President Trump has instructed the Department of Justice to pursue lawsuits against opioid manufacturers, wholesalers, and individuals who illegally prescribe and traffic opioids, and the Department of Justice recently launched a task force for this purpose. On January 11, 2018, the U.S. Attorney's Office for the Southern District of Florida issued a grand jury subpoena to Endo Pharmaceuticals (the manufacturer of Opana ER, discussed above) asking for

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[44] FDA Requests Removal of Opana ER for Risks Related to Abuse (June 8, 2017), https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm562401.htm.

information about its opioid products. A coalition of 41 state attorneys general are also working together to investigate opioid manufacturers.

- **Drug Enforcement Administration action to reduce opioid distribution**. The Drug Enforcement Administration has announced that it intends to decrease the number of opioids produced in 2018 by 20 percent by using its authority to establish quotas for the number of opioids that can be distributed by wholesalers.

- **More burdensome review processes**. FDA has announced its intention to consider the risk of illicit use or potential for abuse when deciding whether to approve new opioid products.

- **More stringent post-approval obligations**. FDA has informed many immediate-release opioid manufacturers that their drugs will be subject to a more stringent set of post-approval requirements, including training for health care providers that addresses safe prescribing practices and consideration of non-opioid alternatives. FDA is also closely scrutinizing opioid promotion. In February 2018, FDA issued a Warning Letter to a manufacturer of an abuse-deterrent opioid for allegedly understating the risks of the product by deemphasizing the limits of the abuse-deterrent technology, which makes abuse more difficult but not impossible.

- **Other policy changes being considered by FDA**. FDA is currently considering requiring sponsors to create nationwide Prescription Drug Monitoring Programs (PDMPs), mandating additional prescriber documentation when prescribing opioids above a certain threshold, imposing additional measures to improve patient storage and handling of opioids, and requiring sponsors create mandatory opioid take-back programs.

Areas of Investment Opportunity

Despite setbacks for manufacturers of certain opioid products, there exists considerable opportunity for creative companies to address the epidemic. For example, Gottlieb has indicated that FDA is developing policies that will help developers create more innovative and varied treatments for opioid addiction. In addition, in the 2018 Strategic Policy Roadmap, FDA announced its intention to support the development of abuse-deterrent formulations for opioids, including generic versions, and alternative, non-addictive pain remedies. Just in the past few months, FDA has approved multiple therapies to treat opioid addiction, including a drug-device combination product (monthly buprenorphine injections) and a neurostimulator device developed by Innovative Health Solutions, Inc.

Takeaway: Opioid products and their manufacturers continue to face heightened regulatory scrutiny, but sponsors may find opportunities to invest in companies pursuing innovative treatments to address the epidemic.

Drug Compounding

FDA has indicated that it aims to strengthen its oversight over compounding pharmacies and outsourcing facilities and intends to enforce higher quality standards. In a recent article, FDA officials noted that since the 2012 meningitis outbreak that focused attention on the issue,[45] the agency has conducted more than 425 inspections of compounding pharmacies and outsourcing facilities and observed "problematic conditions during the vast majority of these inspections" and has overseen more than 140 recalls of compounded drugs.[46]

FDA is particularly focused on large outsourcing facilities that compound drugs for many hospitals and clinics. In addition, FDA is working with the Department of Justice to pursue compounding facilities operating under substandard conditions. For example, on March 1, 2018, the Department of Justice and FDA filed a preliminary injunction against a compounding center in an attempt to stop the company from manufacturing and to require it to conduct a recall of all of its products currently on the market. Gottlieb said that despite FDA's concerns about safety at the compounding facility (including many inspection citations and a Warning Letter over the past few years), the company continued to compound and distribute drugs without addressing the issues.

Notably, a private equity fund was recently named in a Department of Justice lawsuit targeting a compounding pharmacy for violations of the False Claims Act. The Justice Department alleged that the pharmacy paid illegal kickbacks to induce prescriptions for compounded drugs reimbursed by the Federal government, and named a private equity firm based in Los Angeles for its involvement in the alleged kickback scheme. Although there are unique facts associated with this case, it serves as a reminder of potential legal exposure for PE funds and investors.

Takeaway: The increased regulatory and enforcement focus on compounding pharmacies and outsourcing facilities has resulted in increased barriers to entry.[47] Accordingly, companies that can successfully navigate the changing—and more onerous—landscape may reap the rewards.

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[45] In late 2012, a meningitis outbreak originating from the New England Compounding Center caused approximately 800 people to fall ill and resulted in the 64 deaths. Many blamed the lack of regulatory oversight of compounding facilities as contributing to the tragic outcome.

[46] Janet Woodcock & Julie Dohm, "Toward Better-Quality Compounded Drugs—An Update from the FDA," *New Eng. J. Med.* (2017) 377:2509-2512.

[47] This includes state-level scrutiny and regulatory requirements. The Pew Charitable Trusts and the National Association of Boards of Pharmacy recently released a report praising states for adopting and implementing new regulatory requirements and increasing state oversight of the industry.

Conclusion

Private equity sponsors investing in the life sciences sector should be encouraged by the direction FDA is currently taking. Many of FDA's new policies and initiatives create exciting opportunities for investment in drugs, biologics, and devices by encouraging innovation and reducing regulatory burdens. In many areas, FDA has moved toward a risk-benefit approach: low-risk products or products for which there is extreme need may see the greatest rewards.

At the same time, there are some areas of caution. FDA and Congress have focused on certain areas resulting in an increased level of scrutiny and enforcement, such as opioids, compounding, and high-priced drugs. In addition, it is important to remember that even where FDA reduces regulatory burdens, states or private parties may step in to fill any regulatory void, and even FDA policy is not set in stone. Guidance documents, for example, may be easily reversed in the next administration unless supported by statutory or regulatory changes.

Successful sponsors will be those who keep abreast of the changes and who can be nimble and creative as policies evolve. In emerging areas such as regenerative medicine, gene therapy, 3D printing, and digital health, FDA is in the process of establishing modern regulatory approaches that may be in place for years to come. Understanding the nuanced ramifications of the many new FDA initiatives is critical to making thoughtful and forward-looking investments in this industry. It is equally important that private equity sponsors ensure that any FDA-regulatory company has a sophisticated regulatory infrastructure in place to address compliance on an ongoing basis.

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Please do not hesitate to contact us with any questions.

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