MERRIMACK PHARMACEUTICALS INC
Form 10-K
March 06, 2019

UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

WASHINGTON, D.C. 20549

FORM 10-K

(Mark One)

ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934
For the fiscal year ended December 31, 2018

or

TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934
For the transition period from to

Commission file number 001-35409

Merrimack Pharmaceuticals, Inc.

(Exact name of registrant as specified in its charter)

Delaware	04-3210530
(State or other jurisdiction of incorporation or organization)	(I.R.S. Employer Identification No.)
One Kendall Square, Suite B7201	
Cambridge, MA	02139
(Address of principal executive offices)	(Zip Code)

Registrant’s telephone number, including area code: (617) 441-1000

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	Name of each exchange on which registered
Common Stock, $0.01 par value	Nasdaq Global Market

Securities registered pursuant to Section 12(g) of the Act: None

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes No

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Act. Yes No

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes No

Indicate by check mark whether the registrant has submitted electronically every Interactive Data File required to be submitted pursuant to Rule 405 of Regulation S-T (§232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit such files). Yes No

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K is not contained herein, and will not be contained, to the best of registrant’s knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K.

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, a smaller reporting company, or an emerging growth company. See the definitions of “large accelerated filer,” “accelerated filer,” “smaller reporting company,” and “emerging growth company” in Rule 12b-2 of the Exchange Act.

Large accelerated filer	Accelerated filer
Non-accelerated filer	Smaller reporting company
	Emerging growth company

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act.

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Exchange Act). Yes No

The aggregate market value of the voting and non-voting common equity held by non-affiliates of the registrant, based on the last sale price for such stock on June 29, 2018, was $62,302,160.

As of February 27, 2019, there were 13,342,784 shares of Common Stock, $0.01 par value per share, outstanding.

DOCUMENTS INCORPORATED BY REFERENCE

The registrant intends to file a definitive proxy statement pursuant to Regulation 14A in connection with its 2019 Annual Meeting of Stockholders. Portions of such proxy statement are incorporated by reference into Part III of this Annual Report on Form 10-K.

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FORWARD-LOOKING STATEMENTS

This Annual Report on Form 10-K contains forward looking statements that involve substantial risks and uncertainties. All statements, other than statements of historical facts, contained in this Annual Report on Form 10-K, including statements regarding our strategy, future operations, future financial position, future revenues, projected costs, prospects, plans and objectives of management, are forward looking statements. The words "anticipate," "believe," "estimate," "expect," "intend," "may," "plan," "predict," "project," "target," "potential," "will," "would," "could," "should," "c expressions are intended to identify forward looking statements, although not all forward looking statements contain these identifying words.

The forward looking statements in this Annual Report on Form 10-K include, among other things, statements about:

- our plans to develop and commercialize our product candidates and diagnostics;
- our ongoing and planned discovery programs, preclinical studies and clinical trials;
- the timing of the completion of our clinical trials and the availability of results from such trials;
- the anticipated cost savings in connection with our restructuring efforts;
- our plans to explore strategic alternatives;
- our ability to establish and maintain collaborations for our product candidates;
- our receipt of payments related to the milestone events under the asset purchase and sale agreement with Ipsen S.A. or under the license and collaboration agreement between Ipsen S.A. and Les Laboratoires Servier SAS (as assignee from Shire plc), when expected or at all;
- the timing of and our ability to obtain and maintain regulatory approvals for our product candidates;
- the rate and degree of market acceptance and clinical utility of our product candidates;
- our intellectual property position;
- our commercialization, marketing and manufacturing capabilities and strategy;
- the potential advantages of our approach to drug research and development; and
- our estimates regarding expenses, future revenues, capital requirements and needs for additional financing.

We may not actually achieve the plans, intentions or expectations disclosed in our forward-looking statements, and you should not place undue reliance on our forward-looking statements. Actual results or events could differ materially from the plans, intentions and expectations disclosed in the forward-looking statements we make. We have included important factors in the cautionary statements included in this Annual Report on Form 10-K, particularly in Part I, Item 1A. Risk Factors, that could cause actual results or events to differ materially from the forward-looking statements that we make. Our forward-looking statements do not reflect the potential impact of any future acquisitions, mergers, dispositions, joint ventures, collaborations or investments that we may make.

You should read this Annual Report on Form 10-K and the documents that we have filed as exhibits to this Annual Report on Form 10-K completely and with the understanding that our actual future results may be materially different from what we expect. We do not assume any obligation to update any forward-looking statements, whether as a result of new information, future events or otherwise, except as required by law.

NOTE REGARDING TRADEMARKS

ONIVYDE® is a registered trademark of Ipsen S.A. Any other trademarks, trade names and service marks referred to in this Annual Report on Form 10-K are the property of their respective owners.

PART I

Item 1. Business

Overview

We are a clinical stage biopharmaceutical company based in Cambridge, Massachusetts that is outthinking cancer by targeting biomarker-defined cancers. Our vision is to ensure that cancer patients and their families live fulfilling lives. Our mission is to transform cancer care through the smart design and development of targeted solutions based on a deep understanding of cancer pathways and biological markers. Our strategy is to (1) understand the biological problems we are trying to solve, (2) design specific solutions against the problems we are trying to solve and (3) develop those solutions for biomarker-selected patients. This three-pronged strategy seeks to ensure optimal patient outcomes. We own worldwide development and commercial rights to all of our clinical and preclinical programs.

Our only clinical stage asset in active development is MM-310. MM-310 is an antibody-directed nanotherapeutic that targets the ephrin receptor A2, or EphA2, receptor and contains a novel cytotoxic taxane. The EphA2 receptor is highly expressed in most solid tumor types, such as prostate, ovarian, bladder, gastric, pancreatic and lung cancers. We are conducting a Phase 1 clinical trial to evaluate safety and preliminary activity of MM-310 in patients with solid tumors and to identify the maximum tolerated dose.

Our two most promising preclinical programs are MM-401, an agonistic antibody targeting a novel immuno-oncology target, TNFR2, and MM-201, a highly stabilized agonist-Fc fusion protein targeting death receptors 4 and 5.

On June 25, 2018, we announced top-line results from our global, double-blinded, placebo-controlled, Phase 2 randomized CARRIE clinical trial evaluating the addition of MM-141 (istiratumab) to standard-of-care treatment in patients with previously untreated metastatic pancreatic cancer and high serum levels of the insulin-like growth factor 1, or IGF-1. The CARRIE clinical trial did not meet its primary or secondary efficacy endpoints in patients who received MM-141 in combination with nab-paclitaxel and gemcitabine, compared to nab-paclitaxel and gemcitabine alone. These results were consistent in all subgroups analyzed. Based on these results, we are not devoting additional resources to and have ceased all of our development activities for MM-141.

On October 19, 2018, we announced the termination of our global, open-label, biomarker-selected, Phase 2 randomized SHERLOC clinical trial evaluating MM-121 (seribantumab) in combination with docetaxel in patients with heregulin positive non-small cell lung cancer, or NSCLC. The decision to terminate the SHERLOC clinical trial was made based on an interim analysis triggered by the occurrence of 75% of events required for trial completion, which demonstrated that the addition of MM-121 to docetaxel did not improve progression free survival over docetaxel alone in this patient population.

On November 7, 2018, based on the results of the interim analysis of the randomized Phase 2 SHERLOC clinical trial that were announced on October 19, 2018, we announced that we are discontinuing development of all ongoing MM-121 programs, including terminating the global, double-blinded, placebo-controlled, biomarker-selected, Phase 2 randomized SHERBOC clinical trial evaluating MM-121 in combination with fulvestrant in patients with heregulin positive, hormone receptor positive, ErbB2 (HER2) negative, metastatic breast cancer.

On November 7, 2018, we also announced that we were implementing a reduction in headcount as part of a corporate restructuring, after which we expected to have approximately 27 employees. The corporate restructuring followed a comprehensive review of our drug candidate pipeline. The reduction in headcount was completed in February 2019.

In connection with the corporate restructuring, we also announced on November 7, 2018 that we have retained external advisors to explore strategic alternatives.

On April 3, 2017, we completed the sale, or the asset sale, to Ipsen S.A., or Ipsen, of our right, title and interest in the non-cash assets, equipment, inventory, contracts and intellectual property primarily related to or used in our business operations and activities involving or relating to developing, manufacturing and commercializing ONIVYDE, our first commercial product, and MM-436, or the commercial business. Our non-commercial assets, including our clinical and preclinical development programs described above, or the pipeline business, were not included in the asset sale and remain assets of ours.

Our Approach to Cancer Research

We are executing a three-pronged strategy as the basis for our approach to drug development. Our process begins with identifying the problems we are trying to solve and developing a fundamental understanding of how cancer cell signaling pathways and drug metabolism affect those problems. We then engineer product candidates, which include both antibodies and antibody-directed nanotherapeutics, which are designed to match the problem and fit our understanding of the target. Finally, we test our product candidates in biomarker-defined populations that are more homogenous than the general unselected disease population. This strategy improves our ability to detect a clear signal early in clinical development and enables us to pursue smaller, shorter, more personalized studies with lower development costs and a potentially accelerated timeframe to clinically meaningful data.

Step 1: Understand the problem

To understand the problems we are trying to solve, we begin by developing a deep understanding of how cancer pathways and drug metabolism affect those problems. Using systems biology and systems pharmacology, our goal is to understand how the complex molecular interactions that occur within cell signaling pathways, or networks, lead to cancer. Our approach utilizes proprietary, dynamic biological data generated in a high-throughput method in which we test multiple biological or chemical parameters using engineering, analytical and modeling expertise, and from which we build computational models of cell biology to further our drug discovery, design and predictive development. We have developed an expertise in generating kinetic data, describing molecular changes or interactions over time, to illuminate the dynamic interactions that occur within biological systems. We apply those insights throughout the research and development process, including for target identification, lead compound design and optimization, diagnostic discovery and the design of clinical trial protocols.

Our models are constructed and validated using internally generated and proprietary data sets. Following the validation of a comprehensive model of a cell signaling network, we are able to use the model for drug discovery. A significant portion of our discovery work takes place in silico, or using the model for computer simulation, which we believe is a more efficient and productive approach for drug discovery and development than traditional approaches.

Step 2: Design a specific solution

Once we understand the problem that we are trying to solve and have developed a clear target, we design a very specific solution to fit our deep understanding of the target, using two internal platforms: our engineered antibody platform and our antibody-directed nanotherapeutics platform.

Human monoclonal antibodies

Human antibodies are a key component of many of our targeted therapies based on a range of favorable attributes, including significant target specificity and avidity relative to small molecules and well-understood pharmacokinetic properties. Our human monoclonal antibody engineering platform provides us with the ability to create antibodies that are designed to inhibit specific nodes responsible for tumor growth and survival, or to address inherent drug resistance by simultaneously targeting redundant signaling pathways. We have designed antibodies both for use as stand-alone therapeutics and as targeting or docking agents for our antibody-directed nanotherapeutics. We have worked with several antibody formats, including:

- fully human recombinant monoclonal antibodies and fragments of fully human recombinant monoclonal antibodies that include the antibody binding domain. Monoclonal antibodies and antibody fragments are proteins that bind specifically to one defined site on a cell surface protein or receptor;
- stabilized ligand-fusions, either alone or in a bispecific targeted format with an antibody domain;
- multi-specific antibody formats, which are comprised of two or more antibodies or antibody fragments linked to a common scaffold molecule to produce a single molecule that binds to distinct epitopes on two or more target cell surface proteins or receptors; and
- oligoclonal antibody mixtures, which are comprised of defined ratios of two or more recombinant human monoclonal antibodies that target two or more distinct epitopes on a single cell surface protein or receptor.

Antibody-directed nanotherapeutics

Our antibody-directed nanotherapeutics platform is a next-generation antibody drug conjugate, or ADC, that enables us to create actively targeted liposomes that can contain different chemotherapeutic agents. Our targeted nanotherapeutics are lipidic particles constructed to stably encapsulate active drug payloads. Nanoscale objects typically, though not exclusively, have dimensions on the order of 100 nanometers or smaller. We believe that our

nanotherapeutics offer the following potentially favorable attributes:

- a multi-layered targeting strategy that includes an antibody targeting ligand against a preferentially expressed cell-surface receptor on tumor cells, size-controlled accessibility to the tumor microenvironment but not to most normal tissues, and a selective active payload for delivery;
- a uniform nanoscale size, which is intended to enable targeting and preferential deposition within tumors by taking advantage of the enhanced permeability and retention effect to selectively enter, and subsequently accumulate in, tumors with leaky vasculature;
- a formulation designed to minimize the leakage of active drug payload out of the particle before the nanotherapeutic has reached the tumor, with the goal of limiting systemic exposure and the associated occurrence of adverse events, while maximizing the amount of active drug that reaches the target;

- encapsulation of small molecules or nucleic acids in lipidic nanoparticles, designed to protect the active drug payload as it passes through the circulation and organs of the body, such as the liver, and to prevent premature clearance or metabolism of the active drug, and thereby extend the pharmacokinetic profile and enable more convenient dosing regimens; and
- a customizable payload by which our nanotherapeutics can contain a variety of drug payloads, including chemotherapies, cytotoxics, molecularly targeted small molecule drugs, and nucleic acids, such as siRNA and genes. Unlike conventional ADCs, our antibody-directed nanotherapeutics do not require the use of ultra-high potency drugs or direct conjugation to the antibody, both of which can constitute considerable limitations to the conventional ADC platform.

Step 3: Test the solution in a homogenous patient population

With a clear understanding of the problem and a custom-designed solution, we target our product candidates to biomarker-defined populations. Every program must utilize a biomarker signature, and accordingly our companion diagnostics are being designed to test for such biomarkers and thereby provide prognostic and predictive value for enrichment of the patient populations. Utilizing companion diagnostics to identify the biomarker-defined population, our clinical trials are designed to test our product candidates in more homogenous patient populations.

Ultimately, we believe that our approach will result in better treatments for complex diseases by incorporating the identification of biomarkers and the development of associated companion diagnostics into the drug development process. We believe this may enable physicians to better deliver the right drug to the right set of patients at the right time, which may in turn improve patient outcomes, reduce the overall costs of treating and caring for cancer patients, and ultimately may provide a basis for seeking favorable reimbursement of approved drugs from payors.

Our Product Candidates

MM-310

MM-310 overview

MM-310 is an antibody-directed nanotherapeutic that encapsulates a newly engineered form of the highly potent chemotherapy docetaxel as a prodrug in an EphA2 targeted liposome. In preclinical studies, MM-310 demonstrated increased antitumor activity in multiple models compared to free docetaxel. In the preclinical studies, EphA2-targeted liposomes delivered the cytotoxic to the tumor while minimizing exposure to healthy tissues. MM-310 is designed to result in prolonged exposure of the active drug at the tumor site and in preclinical studies had a significantly longer half-life than free docetaxel. In a sampling of approximately 200 tumors, EphA2 was found to be expressed in tumor cells, myofibroblasts and/or tumor-associated blood vessels. EphA2 overall prevalence was found to range from 50% to 100% across multiple indications. In cell models, a high level of specificity was observed in the MM-310 EphA2 targeted liposome, with a more than 100-fold increase in liposome cell association when compared to non-targeted liposomes. MM-310 is not approved for any indication by the U.S. Food and Drug Administration, or FDA, or any other regulatory agency.

Our three-pronged drug development strategy informs our approach to our MM-310 program:

Understand the problem. Conventional ADCs, which typically incorporate an ultra-high potency drug conjugated to a targeting antibody and which do not utilize liposomes to encapsulate the payload, can be highly effective therapies but are often accompanied by significant toxicities that limit tolerable dosage levels and duration of use. Other potential limitations of conventional ADCs include the need for direct conjugation of the drug to the antibody, which requires subsequent cleavage of the bond to release the drug, and the uptake of the conventional ADC into normal tissue due to both the small size of the ADC and the presence of the accessible target receptor on normal tissue. Docetaxel, the

payload for MM-310, is a highly effective and well validated cancer chemotherapy with a conventional potency range, but it is often accompanied by significant toxicity that limits its dosage levels and duration of use. Our hypothesis is that a more sustained release of the drug should result in lower plasma levels and extended exposure at the tumor, and thus less toxicity and improved efficacy. We also believe that EphA2 is an attractive target due to the fact that it is expressed at a very high level on and internalized by cancer cells.

Design a specific solution. MM-310 is an antibody-directed nanotherapeutic that is designed to improve the therapeutic window of the active drug by incorporating it in the form of a drug precursor encapsulated in a nanoliposome to ensure a slower and more sustained release of the drug. The small size of the nanotherapeutic may allow it to take advantage of the leaky vasculature of the tumor through the permeability and retention effect and potentially deliver docetaxel more preferentially, while restricting distribution in normal tissues. The nanoliposome utilizes antibodies to the EphA2 receptor, a receptor often over-expressed in solid tumors, to help target more of the chemotherapy payload to the tumor site.

Test the solution in a homogenous patient population. After identifying the maximum tolerated dose and the drug's safety profile in humans, future clinical trials will test the drug in tumor types that over-express the EphA2 receptors.

MM-310 Phase 1 clinical trial

In March 2017, we initiated a Phase 1 clinical trial of MM-310 to evaluate its safety and preliminary activity in patients with solid tumors and to identify the maximum tolerated dose. Although early data from the clinical trial from the every three week dosing schedule regimen showed signs of encouraging antitumor activity in four patients, emerging cumulative grade 3 peripheral neuropathy following multiple cycles of treatment was observed in three patients. Pharmacokinetic and preclinical data indicate that lengthening the time between dosing may improve the tolerability of MM-310. As a result, on November 7, 2018, we announced an amendment to the clinical trial to extend the dosing interval of MM-310 from every three weeks to every four weeks.

On March 6, 2019, we provided an update regarding the patients dosed on the amended protocol, noting that three patients have been enrolled in the 360 mg every four weeks dose cohort under the amended protocol, which matches the highest dose level reached during the prior version of the protocol at every three weeks. As of March 4, 2019, all three patients in the 360 mg every four weeks dose cohort continued to be treated in the study: one patient had completed 98 days of treatment and received four cycles of MM-310, reaching stable disease as a best response to date; the second patient had completed 56 days of treatment and received two cycles of MM-310; and the third patient received the first dose 21 days prior. Importantly, no instances of grade 3 peripheral neuropathy were reported in this cohort. If all three patients in the 360 mg every four weeks dose cohort successfully complete the observation period for dose-limiting toxicities, which is expected to occur in mid-March, we would plan to begin enrolling the next dose-escalation cohort at 420 mg of MM-310 every four weeks.

MM-310 diagnostic development

We utilize a validated test to retrospectively evaluate patients for EphA2 receptor expression in our ongoing Phase 1 clinical trial of MM-310.

Preclinical Product Candidates

We are developing preclinical product candidates for a range of solid tumor indications. Our two most promising preclinical programs are MM-401, an agonistic antibody targeting a novel immuno-oncology target, TNFR2, and MM-201, a highly stabilized agonist-Fc fusion protein targeting death receptors 4 and 5.

CARRIE, SHERLOC and SHERBOC Clinical Trials

We have discontinued development of our MM-121 and MM-141 product candidates based on results from our CARRIE, SHERLOC and SHERBOC clinical trials of such candidates.

MM-121 (seribantumab)

MM-121 is a fully human monoclonal antibody that targets ErbB3 (HER3), a cell surface receptor that is activated by its ligand heregulin. Heregulin-driven ErbB3 (HER3) signaling has been implicated as a mechanism of tumor growth and broad resistance to cytotoxic, anti-endocrine, targeted and immuno-oncology therapies. When used in combination with anti-cancer drugs, MM-121 is designed to block heregulin-driven ErbB3 (HER3) signaling and enhance the anti-tumor effect of combination therapy partners.

In February 2015, we initiated the global, open-label, biomarker-selected, Phase 2 randomized SHERLOC clinical trial evaluating MM-121 in combination with docetaxel, versus docetaxel alone, in patients with heregulin positive NSCLC. On October 19, 2018, we announced the termination of the SHERLOC clinical trial based on an interim analysis triggered by the occurrence of 75% of events required for trial completion, which demonstrated that the

addition of MM-121 to docetaxel did not improve progression free survival over docetaxel alone in this patient population.

In February 2018, we dosed the first patient in our global, double-blinded, placebo-controlled, biomarker-selected Phase 2 randomized SHERBOC clinical trial evaluating MM-121 in combination with fulvestrant, versus fulvestrant alone, in patients with heregulin positive, hormone receptor positive, ErbB2 (HER2) negative, metastatic breast cancer. On November 7, 2018, we announced that we are discontinuing development of all ongoing MM-121 programs, including terminating the SHERBOC clinical trial based on the results of the interim analysis of the SHERLOC clinical trial.

We previously evaluated MM-121 in multiple Phase 1 and Phase 2 clinical trials in combination with both chemotherapies and other targeted agents across a wide spectrum of solid tumor patient populations, including patients with ovarian, breast and lung cancers. Over 700 patients were treated with MM-121 in those previous clinical trials. The goal of these clinical trials was to explore the efficacy and safety of MM-121 in combination with other agents and to establish and validate clinically meaningful biomarkers to identify patients most likely to benefit from MM-121.

MM-141

MM-141 is a fully human tetravalent bispecific antibody designed to block tumor survival signals by targeting receptor complexes containing the insulin-like growth factor 1 receptor, or IGF-1R, and ErbB3 (HER3) cell surface receptors. A tetravalent bispecific antibody is a single molecule that has four binding sites, two for each of two different target cell surface receptors. IGF-1R and ErbB3 (HER3) both activate a major signaling pathway, PI3K/AKT/mTOR, that allows tumor cells to grow and develop resistance to chemotherapy. We designed MM-141 to suppress the PI3K/AKT/mTOR signaling pathway by reducing the levels of IGF-1R and ErbB3 (HER3) that trigger the pathway.

In May 2015, we initiated the global, double-blinded, placebo-controlled, Phase 2 randomized CARRIE clinical trial evaluating MM-141 in combination with nab-paclitaxel and gemcitabine, versus nab-paclitaxel and gemcitabine alone, in patients with previously untreated metastatic pancreatic cancer with high serum levels of free insulin-like growth factor 1, or IGF-1. In June 2018, we announced top-line results from the CARRIE clinical trial, showing that the trial did not meet its primary or secondary efficacy endpoints in patients who received MM-141 in combination with nab-paclitaxel and gemcitabine, compared to nab-paclitaxel and gemcitabine alone. These results were consistent in all subgroups analyzed. Based on these results, we are not devoting additional resources to and have ceased all of our development activities for MM-141.

Manufacturing

We do not have any manufacturing facilities or personnel. We have relied on contract manufacturing organizations to manufacture our product candidates in order to meet our operational objectives for clinical testing, as well as for commercial manufacture if our product candidates receive marketing approval. We have also outsourced all fill finish, packaging, labeling and distribution activities. We are not currently planning to manufacture bulk product for any of our product candidates in 2019.

We do not currently have manufacturing arrangements in place for our active product candidates. To the extent we advance any product candidates, we expect that we would identify and qualify manufacturers to provide the active pharmaceutical ingredient and fill finish services as a part of such development.

We are identifying, developing and testing diagnostic assays for predictive biomarkers in an internal laboratory and through collaborations with third-parties. Upon completion of the development of the diagnostic tests, we plan to evaluate external as well as internal options for manufacturing and commercialization of the tests.

Sources and Availability of Raw Materials

We currently rely on single source suppliers for certain raw materials that we use for our antibody and nanoliposome manufacturing processes. We purchase these materials from our suppliers on a purchase order basis and do not have long-term supply agreements in place.

Competition

The biotechnology and pharmaceutical industries are characterized by rapidly advancing technologies, intense competition and a strong emphasis on proprietary products. While we believe that our integrated research, development experience and scientific knowledge provide us with competitive advantages, we face potential competition from many different sources, including major pharmaceutical, specialty pharmaceutical and biotechnology companies, academic institutions and governmental agencies and public and private research institutions. Any product candidates that we successfully develop and commercialize will compete with existing

therapies and new therapies that may become available in the future.

Many of our competitors have significantly greater financial resources and expertise in research and development, manufacturing, preclinical testing, conducting clinical trials, obtaining regulatory approvals and marketing approved products than we do. Mergers and acquisitions in the pharmaceutical, biotechnology and diagnostic industries may result in even more resources being concentrated among a smaller number of our competitors. These competitors also compete with us in recruiting and retaining qualified scientific and management personnel and establishing clinical trial sites and patient registration for clinical trials, as well as in acquiring technologies complementary to, or necessary for, our programs. Smaller or early stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies.

The key competitive factors affecting the success of all of our product candidates, if approved, are likely to be their efficacy, safety, convenience, price, the effectiveness of diagnostics in guiding the use of related therapeutics, the level of generic competition and the availability of reimbursement from government and other third-party payors.

Our commercial opportunity could be reduced or eliminated if our competitors develop and commercialize products that are safer, more effective, have fewer or less severe side effects, are more convenient or are less expensive than any products that we may develop. Our competitors also may obtain FDA or other regulatory approval for their products more rapidly than we may obtain approval for ours. In addition, our ability to compete may be affected because in many cases insurers or other third-party payors seek to encourage the use of generic products. There are many generic products currently on the market for the indications that we are pursuing, and additional products are expected to become available on a generic basis over the coming years. If our product candidates are approved, we expect that they will be priced at a significant premium over competitive generic products.

The initial focus of our business is to develop therapeutics and diagnostics for the treatment of solid tumor cancers. Cancer is the second most common cause of death in the United States, exceeded only by heart disease. There are a variety of available drug therapies marketed for solid tumors. Although there has been considerable progress over the past few decades in the treatment of solid tumors and the currently marketed therapies provide benefits to many patients, generally these therapies all are limited to some extent in their efficacy and frequency of adverse events, and none of them are successful in treating all patients. As a result, the level of morbidity and mortality from solid tumor cancers remains high. In many cases, these drugs are administered in combination to enhance efficacy. Some of these drugs are branded and subject to patent protection, and others are available on a generic basis. Many of these approved drugs are well established therapies and are widely accepted by physicians, patients and third-party payors.

In addition to any marketed therapies for solid tumors, there are a number of products in late stage clinical development to treat solid tumors. These products in development may provide efficacy, safety, convenience and other benefits that are not provided by currently marketed therapies. As a result, they may provide significant competition for any of our product candidates for which we obtain marketing approval.

The following table sets forth information about certain solid tumor cancer indications that are eligible for inclusion in our Phase 1 clinical trial of MM-310. The U.S. estimated annual incidence is based on information from the American Cancer Society, Cancer Fact & Figures 2019.

Tumor Type	U.S. Annual Incidence
Lung and bronchus	228,150
Bladder	80,470
Endometrial	61,880
Pancreatic	56,770
Gastric	55,750
Ovarian	22,530
Sarcomas (soft tissue)	12,750

Collaboration and License Agreements

We are party to certain collaboration and license agreements. We consider the following agreements to be material to our business.

Ipsen

On April 3, 2017, we completed the asset sale with Ipsen. Pursuant to the Asset Purchase and Sale Agreement, dated as of January 7, 2017, or the asset sale agreement, between us and Ipsen, Ipsen acquired our right, title and interest in the commercial business. Pursuant to the asset sale agreement, we received $575.0 million in cash, plus a working capital adjustment of $5.7 million, and are eligible to receive up to $450.0 million in additional regulatory approval-based milestone payments. Ipsen has agreed pursuant to the asset sale agreement to use commercially reasonable efforts to develop ONIVYDE in connection with obtaining the regulatory approval by the FDA of ONIVYDE for certain indications. We also retained the right to receive net milestone payments that may become payable for the ex-U.S. development and commercialization of ONIVYDE for up to $33.0 million pursuant to a license and collaboration agreement between Ipsen and Les Laboratoires Servier SAS, or Servier (as assignee from Shire plc), which we refer to as the Servier agreement. To date, we have received $28.0 million of the potential $33.0 million in milestone payments under the Servier agreement. We entered into the Servier agreement in 2014, and on April 3, 2017, the Servier agreement was assigned to Ipsen in connection with the completion of the sale of the commercial business.

In connection with the asset sale, we entered into a sublease agreement with Ipsen under which Ipsen is subleasing approximately 64,550 square feet of our leased space in Cambridge, Massachusetts through the end of our lease term on June 30, 2019.

Intellectual Property

Our success will significantly depend on our ability to obtain and maintain patent and other proprietary protection for our commercially important technology, inventions and know-how, defend and enforce our patents, preserve the confidentiality of our trade secrets, establish and protect our commercial brands and operate without infringing the valid and enforceable patents and proprietary rights of third parties. To accomplish this, we rely on a combination of intellectual property rights, including patents, trade secrets, copyrights and trademarks, as well as regulatory exclusivity and contractual protections. We aggressively strive to protect the proprietary technology that we believe is important to our business, including seeking and maintaining patents intended to cover our products and compositions, their methods of use and processes for their manufacture, as well as our diagnostic and drug discovery technologies and any other inventions that are commercially important to the development of our business. In some circumstances, we also rely on trade secrets to protect aspects of our business that are not amenable to, or that we do not consider appropriate for, patent protection, such as our proprietary network modeling programs and large scale protein and liposome production methods.

We seek to protect our proprietary technology and processes, in part, by confidentiality agreements with our employees, consultants, scientific advisors and contractors. We require each of our employees, consultants and advisors to execute a confidentiality and inventions assignment agreement before beginning their employment, consulting or advisory relationship with us. These agreements generally provide that the individual must keep confidential and not disclose to other parties any confidential information developed or learned by the individual during the course of their relationship with us except in limited circumstances. These agreements also generally provide that we will own all inventions conceived by the individual in the course of rendering services to us. We also seek to preserve the integrity and confidentiality of our data and trade secrets by maintaining physical security of our premises and physical and electronic security of our information technology systems. While we have confidence in these individuals, organizations and systems, agreements or security measures may be breached, and we may not have adequate remedies for any breach. In addition, our trade secrets may otherwise become known or be independently discovered by competitors. To the extent that our consultants, contractors or collaborators use intellectual property owned by others in their work for us, disputes may arise as to the rights in related or resulting know-how and inventions.

Our commercial success will depend in part on obtaining and maintaining patent protection and trade secret protection of the use, formulation, manufacture and composition of our products and product candidates, as well as successfully asserting and/or defending these patents against third-party challenges. Our ability to protect our products and product candidates from unauthorized making, using, selling, offering to sell or importing by third parties is dependent on the extent to which we have rights under valid and enforceable patents that cover these activities.

As of January 31, 2019, we owned or controlled a total of 15 issued U.S. patents and 121 corresponding issued foreign patents, in addition to 25 pending U.S. patent applications and 113 pending patent applications in the rest of the world. We intend to continue to protect our proprietary technology with additional filings as appropriate. We do not have patents or patent applications in every jurisdiction where there is a potential commercial market for our product candidates. We continually evaluate our patent portfolio and patent strategy and believe our owned and licensed patents and patent applications, as well as applicable periods of regulatory exclusivity available after new product approval, provide us with a competitive advantage; however, if markets where we do not have patents or patent applications become commercially important, our business may be adversely affected.

The term of individual patents depends upon the legal term for patents in the countries in which they are obtained. In most countries, including the United States, the patent term is 20 years from the earliest filing date of a non-provisional patent application.

In the United States, a patent's term may be lengthened by patent term adjustment, which compensates a patentee for administrative delays by the U.S. Patent and Trademark Office in examining and granting a patent, or may be shortened if a patent is terminally disclaimed over an earlier filed patent. In the future, if and when our product candidates receive approval by the FDA or foreign regulatory authorities, we expect to apply for patent term extensions on issued patents covering those products, depending upon the length of the clinical trials for each drug and other factors, including those involved in the filing of a new drug application, or NDA, or a biologics license application, or BLA. The Drug Price Competition and Patent Term Restoration Act of 1984, or the Hatch-Waxman Act, permits a patent restoration term of up to five years as compensation for patent term lost during product development and the FDA regulatory review process, provided the total patent term restoration cannot extend the remaining term of a patent beyond a total of 14 years from the product's approval date. The patent term restoration period is generally calculated as one-half the time between the effective date of an investigational new drug application, or IND, and the submission date of an NDA, plus the time between the submission date of an NDA and the FDA's approval of that application. Only one patent applicable to each approved drug is eligible for the extension and the application for extension must be made prior to expiration of the patent. The U.S. Patent and Trademark Office, in consultation with the FDA, reviews and approves the application for any patent term extension or restoration.

Similar provisions are available in Europe and other foreign jurisdictions to extend the term of a patent that covers an approved drug. The stated patent exclusivity dates for patent exclusivity outside of the United States may also be eligible for further extension, and/or regulatory market and/or data exclusivity in certain countries, upon product approval in individual countries for various reasons, including supplemental protection certificate(s) after product approval in eligible countries outside the United States, and/or conducting certain investigations of pediatric exclusivity or use of products covered by the applicable patent.

MM-310

We have an exclusive license to pending patent applications covering the MM-310 composition through at least 2037 (if issued) from the University of California. In addition, we own multiple pending patent applications covering the MM-310 liposome composition, companion diagnostic technology for MM-310 and therapeutic uses of MM-310 through at least 2037 (if issued). Our latest-expiring granted patent covering the composition or use of MM-310 in the United States will expire in 2031, and the latest-expiring granted patent covering MM-310 in one or more countries outside the United States will expire in 2031. The expiration dates above do not include any additional exclusivity available after product approval from patent term extension, supplemental protection certificates and/or pediatric exclusivity.

Government Regulation

Government authorities in the United States, at the federal, state and local level, and in other countries extensively regulate, among other things, the research, development, testing, manufacture, including any manufacturing changes, packaging, storage, recordkeeping, labeling, advertising, promotion, distribution, marketing, post-approval monitoring and reporting, import and export of pharmaceutical products, biological products and medical devices, such as those we are developing.

United States drug and biological product approval process

In the United States, the FDA approves new drug products under the Federal Food, Drug, and Cosmetic Act, or FDCA, while new biologic products are licensed for marketing under the Public Health Service Act, or PHSA. Both drugs and biologics are regulated under the FDCA and implementing regulations. The process of obtaining regulatory approvals and the subsequent compliance with appropriate federal, state, local and foreign statutes and regulations requires the expenditure of substantial time and financial resources. Failure to comply with the applicable United States requirements at any time during the product development process, approval process or after approval may subject an applicant to a variety of administrative or judicial actions, including, among other things, the FDA's refusal to approve pending applications, withdrawal of an approval, imposition of a clinical hold, issuance of untitled or warning letters, product recalls, product seizures, total or partial suspension of production or distribution injunctions, fines, refusals of government contracts, restitution, disgorgement of profits, civil penalties and criminal prosecution.

Generally, the process required by the FDA before a drug or biological product may be marketed in the United States involves the following:

- completion of preclinical laboratory tests and animal studies in compliance with the FDA's good laboratory practice, or GLP, regulations;
- completion of process development and manufacturing studies in compliance with current good manufacturing practices, or cGMP, requirements;
- submission to the FDA of an IND, which must become effective before human clinical trials may begin;
- approval by an independent institutional review board, or IRB, at each clinical site before each trial may be initiated;
-

performance of adequate and well-controlled human clinical trials in accordance with good clinical practices, or GCP, to establish the safety and efficacy of the proposed drug product and the safety, potency and purity of a candidate biologic product for each indication;

- submission to the FDA of an NDA or an abbreviated new drug application, or ANDA, for a new drug product or BLA for a biological product, as applicable;
- satisfactory completion of an FDA advisory committee review, if applicable;
- satisfactory completion of an FDA inspection of the manufacturing facility or facilities at which the product is produced to assess compliance with cGMP requirements and to assure that the facilities, methods and controls are adequate to preserve the drug's identity, strength, quality and purity;
- FDA review and approval of the NDA or BLA; and
- compliance with any post-approval requirements, including the potential requirement to implement a Risk Evaluation and Mitigation Strategy program and the potential requirement to conduct post-approval studies.

We expect that all of our clinical product candidates will be subject to review as biological products under BLA standards. Although MM-310 contains both drug and biological components, we believe that this combination product would be subject to review as a biological product, pursuant to a BLA.

Preclinical studies and the IND process

Preclinical studies include laboratory evaluation of product chemistry and formulation, as well as in vitro and animal studies to assess the potential for adverse events and in some cases to establish a rationale for therapeutic use. The conduct of preclinical studies is subject to federal regulations and requirements, including GLP regulations. An IND sponsor must submit the results of the preclinical tests, together with manufacturing information, analytical data, any available clinical data or literature and a proposed protocol for clinical studies, among other things, to the FDA as part of an IND. An IND is an exemption from the FDCA that allows an unapproved product candidate to be shipped in interstate commerce for use in an investigational clinical trial and is a request for FDA authorization to administer such investigational product to humans. Such authorization must be secured prior to interstate shipment and administration of any product candidate that is not the subject of an approved application. Some long-term preclinical testing, such as animal tests of reproductive adverse events and carcinogenicity, may continue after the IND is submitted. An IND automatically becomes effective 30 days after receipt by the FDA, unless before that time the FDA raises concerns or questions related to one or more proposed clinical trials and places the trial on clinical hold. In such a case, the IND sponsor and the FDA must resolve any outstanding concerns before the clinical trial can begin. As a result, submission of an IND may not necessarily result in the FDA allowing clinical trials to commence.

Clinical trials

Clinical trials involve the administration of the investigational new drug to human subjects – healthy volunteers or patients – under the supervision of qualified investigators in accordance with GCP requirements, which include, among other things, the requirement that all research subjects provide their informed consent in writing before their participation in any clinical trial. Clinical trials are conducted under written study protocols detailing, among other things, the objectives of the study, the parameters to be used in monitoring safety and the effectiveness criteria to be evaluated. A protocol for each clinical trial and any subsequent protocol amendments must be submitted to the FDA as part of the IND. In addition, an IRB at each institution participating in the clinical trial must review and approve the plan for any clinical trial before it commences at that institution, and the IRB must conduct continuing review and reapprove the study at least annually. The IRB must review and approve, among other things, the study protocol and informed consent information to be provided to study subjects. An IRB may also require the clinical trial at the site to be halted, either temporarily or permanently, for failure to comply with the IRB's requirements, or may impose other conditions. For clinical trials involving an IND, an IRB must operate in compliance with FDA regulations. Additionally, some trials are overseen by an independent group of qualified experts organized by the trial sponsor, known as a data safety monitoring board, or DSMB. This group provides authorization as to whether or not a trial may move forward at designated check points based on access that only the DSMB maintains to available data from the study.

Human clinical trials are typically conducted in three sequential phases, which may overlap or be combined:

- Phase 1: The investigational drug or biological product is initially introduced into healthy human subjects or patients with the target disease or condition and tested for safety, side effects associated with increasing doses, pharmacological action, absorption, metabolism, distribution, excretion and, if possible, to gain an early indication of its effectiveness.
- Phase 2: The investigational drug or biological product is administered to a limited patient population to identify common adverse effects and safety risks, to preliminarily evaluate the efficacy of the product for specific targeted diseases and to determine dosage tolerance and optimal dosage. This phase may include

administration of the investigational drug to patients with concomitant disease conditions.

- Phase 3: The investigational drug or biological product is administered to an expanded patient population in adequate and well-controlled clinical trials, typically at geographically dispersed clinical trial sites, to generate sufficient data to statistically confirm the efficacy and safety of the product for approval, to permit the FDA to evaluate the overall risk-benefit profile of the product and to provide adequate information for the labeling of the product.

Progress reports detailing the results of clinical trials involving an IND must be submitted at least annually to the FDA and more frequently if serious adverse events occur. Phase 1, Phase 2 and Phase 3 clinical trials may not be completed successfully within any specified period, or at all. Furthermore, the FDA or the sponsor may suspend or terminate a clinical trial at any time on various grounds, including a finding that the research subjects are being exposed to an unacceptable health risk. Similarly, an IRB can suspend or terminate approval of a clinical trial at its institution if the clinical trial is not being conducted in accordance with the IRB's requirements or if the drug or biologic product has been associated with unexpected serious harm to patients.

In some cases, the FDA may approve an application for a product candidate but require the sponsor to conduct additional clinical trials to further assess the product candidate's safety and effectiveness after approval. Such post-approval trials are typically referred to as Phase 4 clinical trials. These studies are used to gain additional experience from the treatment of a larger number of patients in the intended treatment group and to further document a clinical benefit in the case of drugs approved under accelerated approval regulations.

Disclosure of clinical trial information

Sponsors of applicable clinical trials of FDA regulated products, including drugs, are required to register and disclose certain clinical trial information. Information related to the product, patient population, phase of investigation, study sites and investigators, and other aspects of the clinical trial is then made public on the ClinicalTrials.gov website as part of the registration. Sponsors are also obligated to disclose the results of their clinical trials after completion. Disclosure of the results of these trials can be delayed until the new product or new indication being studied has been approved. Competitors may use this publicly available information to gain knowledge regarding the progress of development programs.

Marketing approval

Assuming successful completion of the required clinical testing, the results of the preclinical and clinical studies, together with detailed information relating to the product's pharmacology chemistry, manufacture, controls and proposed labeling, among other things, are submitted to the FDA as part of an NDA or BLA requesting approval to market the product for one or more indications. FDA approval of the NDA or BLA is required before marketing of the product may begin in the United States. Under federal law, the submission of most NDAs and BLAs is subject to a substantial application user fee, currently $2,588,478 for an application requiring clinical data for fiscal year 2019, and the sponsor of an approved NDA or BLA is also subject to annual product or program fees, currently $309,915 per program. These fees may be increased or decreased annually.

The FDA conducts a preliminary review of all NDAs and BLAs within the first 60 days after receipt before accepting them for filing based on the agency's threshold determination that they are sufficiently complete to permit substantive review. The FDA may request additional information rather than accept an NDA or BLA for filing. In this event, the application must be resubmitted with the additional information, which would also be subject to review before the FDA accepts it for filing. Once the submission is accepted for filing, the FDA begins an in-depth substantive review. The FDA has agreed to specified performance goals in the review of NDAs and BLAs. Most such applications for non-priority products are reviewed within ten to twelve months after filing, and most applications for priority review products, that is, drugs and biologics that the FDA determines represent a significant improvement over existing therapy, are reviewed in six to eight months after filing. The review process may be extended by the FDA for three additional months to consider certain late-submitted information or clarification regarding information already provided in the submission. The FDA may also refer applications for novel drugs or biological products or products that present difficult questions of safety or efficacy to an advisory committee, typically a panel that includes clinicians and other experts, for review, evaluation and a recommendation as to whether the application should be approved. The FDA is not bound by the recommendations of an advisory committee, but it considers such recommendations carefully when making decisions.

Before approving an NDA or BLA, the FDA typically will inspect the facility or facilities where the product is manufactured. The FDA will not approve an application unless it determines that the manufacturing processes and facilities are in compliance with cGMP requirements and adequate to assure consistent production of the product within required specifications. In addition, before approving an NDA or BLA, the FDA will typically inspect one or more clinical sites to assure compliance with GCP and integrity of the clinical data submitted.

The testing and approval process requires substantial time, effort and financial resources, and each may take many years to complete. Data obtained from clinical activities are not always conclusive and may be susceptible to varying interpretations, which could delay, limit or prevent regulatory approval. We may encounter difficulties or unanticipated costs in our efforts to develop our product candidates and secure necessary governmental approvals, which could delay or preclude us from marketing our products.

After the FDA's evaluation of the NDA or BLA and inspection of the manufacturing facilities, the FDA may issue an approval letter or a complete response letter. An approval letter authorizes commercial marketing of the drug or biological product with specific prescribing information for specific indications. A complete response letter generally outlines the deficiencies in the submission and may require substantial additional testing or information in order for the FDA to reconsider the application. If and when those deficiencies have been addressed to the FDA's satisfaction in a resubmission of the NDA, the FDA will issue an approval letter. The FDA has committed to reviewing such resubmissions in two or six months depending on the type of information included. Even with submission of this additional information, the FDA ultimately may decide that the application does not satisfy the regulatory criteria for approval.

Even if the FDA approves a product, the agency may limit the approved indications for use for the product, require that contraindications, warnings or precautions be included in the product labeling, require that post-approval studies be conducted to further assess a drug's safety after approval, require testing and surveillance programs to monitor the product after commercialization, or impose other conditions, including distribution restrictions through a Risk Evaluation and Mitigation Strategy or other risk management mechanisms, which can materially affect the potential market and profitability of the product. The FDA may prevent or limit further marketing of a product based on the results of post-market studies or surveillance programs. After approval, some types of changes to the approved product, such as changes in indications, manufacturing changes and labeling, are subject to further testing requirements and FDA review and approval.

Fast track designation

The FDA is required to facilitate the development and expedite the review of drugs and biologics that are intended for the treatment of a serious or life-threatening disease or condition for which there is no effective treatment and which demonstrate the potential to address unmet medical needs for the condition. Under the fast track program, the sponsor of a new drug or biologic candidate may request the FDA to designate the product for a specific indication as a fast track product concurrent with or after the filing of the IND for the product candidate. The FDA must determine if the product candidate qualifies for fast track designation within 60 days after receipt of the sponsor's request.

In addition to other benefits, such as the ability to have more frequent interactions with the FDA, the FDA may initiate review of sections of a fast track product's NDA or BLA before the application is complete. This rolling review is available if the applicant provides and the FDA approves a schedule for the submission of the remaining information and the applicant pays applicable user fees. However, the FDA's time period goal for reviewing a fast track application does not begin until the last section of the NDA or BLA is submitted. In addition, the fast track designation may be withdrawn by the FDA if the FDA believes that the designation is no longer supported by data emerging in the clinical trial process.

Priority review

Under FDA priority review guidelines, a product candidate may be eligible for review within a six to eight month time frame from the time a complete application is accepted for filing. Products regulated by the FDA's Center for Drug Evaluation and Research, or CDER, are eligible for priority review if they provide a significant improvement compared to marketed products in the treatment, diagnosis or prevention of a disease. Products regulated by the FDA's Center for Biologics Evaluation and Research are eligible for priority review if they provide a significant improvement in the safety or effectiveness of the treatment, diagnosis or prevention of a serious or life-threatening disease. A fast track designated product candidate would ordinarily meet the FDA's criteria for priority review.

Accelerated approval

Under the FDA's accelerated approval regulations, the FDA may approve a drug or biologic for a serious or life-threatening illness that provides meaningful therapeutic benefit to patients over existing treatments based on a surrogate endpoint that is reasonably likely to predict clinical benefit. In clinical trials, a surrogate endpoint is a measurement of laboratory or clinical signs of a disease or condition that substitutes for a direct measurement of how a patient feels, functions or survives. Surrogate endpoints can often be measured more easily or more rapidly than clinical endpoints. A product candidate approved on this basis is subject to rigorous post-marketing compliance requirements, including the completion of Phase 4 or post-approval clinical trials to confirm the effect on the clinical endpoint. Failure to conduct required post-approval studies, or confirm a clinical benefit during post-marketing studies, would allow the FDA to withdraw the drug from the market on an expedited basis. All promotional materials for drug candidates approved under accelerated regulations are subject to prior review by the FDA.

Breakthrough therapy designation

The FDA is also required to expedite the development and review of the application for approval of drugs that are intended to treat a serious or life-threatening disease or condition where preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints. Under the breakthrough therapy program, the sponsor of a new drug candidate may request that the FDA designate the drug candidate for a specific indication as a breakthrough therapy concurrent with, or after, the filing of the IND for the drug candidate. The FDA must determine if the drug candidate qualifies for breakthrough therapy designation within 60 days of receipt of the sponsor’s request.

Orphan drugs

Under the Orphan Drug Act, the FDA may grant orphan drug designation to drugs or biologics intended to treat a rare disease or condition, which is generally defined as a disease or condition that affects fewer than 200,000 individuals in the United States. Orphan drug designation must be requested before submitting an NDA or BLA. After the FDA grants orphan drug designation, the generic identity of the drug or biologic and its potential orphan use are disclosed publicly by the FDA. Orphan drug designation is taken into consideration but generally does not convey any advantage in, or shorten the duration of, the regulatory review and approval process. The first NDA or BLA applicant to receive FDA approval for a particular active ingredient to treat a particular disease with FDA orphan drug designation is entitled to a seven-year exclusive marketing period in the United States for that product, for that indication. During the seven-year exclusivity period, the FDA may not approve any other applications to market the same drug or biologic for the same orphan indication, except in limited circumstances, such as a showing of clinical superiority to the product with orphan drug exclusivity in that it is shown to be safer, more effective or makes a major contribution to patient care. This is the case despite an earlier court opinion holding that the Orphan Drug Act unambiguously required the FDA to recognize orphan exclusivity regardless of a showing of clinical superiority. Orphan drug exclusivity does not prevent the FDA from approving a different drug or biologic for the same disease or condition, or the same drug or biologic for a different disease or condition. Among the other benefits of orphan drug designation are tax credits for certain research and a waiver of the NDA or BLA application user fee.

Pediatric information and exclusivity

Under the Pediatric Research Equity Act of 2003, an NDA, BLA or supplement to an NDA or BLA must contain data from pediatric studies that are adequate to assess the safety and effectiveness of the drug or biological product for the claimed indications in all relevant pediatric subpopulations, and to support dosing and administration for each pediatric subpopulation for which the product is safe and effective. The FDA may, on its own initiative or at the request of the applicant, grant deferrals for submission of some or all pediatric data until after approval of the product for use in adults, or full or partial waivers from the pediatric data requirements. Under the Food and Drug Administration Safety and Innovation Act, or FDASIA, the FDA has additional authority to take action against manufacturers not adhering to pediatric study requirements. Unless otherwise required by regulation, the pediatric data requirements do not apply to products with orphan drug designation.

Pediatric exclusivity is a type of non-patent exclusivity in the United States and, if granted, provides for the attachment of an additional six months of marketing protection to the term of any existing regulatory exclusivity or patent protection, including the non patent and orphan exclusivity. This six month exclusivity may be granted if an application sponsor submits pediatric data that fairly respond to a written request from the FDA for such data. The data do not need to show the product to be effective in the pediatric population studied; rather, if the clinical trial is deemed to fairly respond to the FDA’s request, the additional protection is granted.

The Hatch-Waxman Act

Abbreviated new drug applications

In seeking approval for a drug through an NDA, applicants are required to list with the FDA each patent that claims to cover the applicant’s product. Upon approval of a drug, each of the patents listed in the application for the drug is then published in the FDA’s Approved Drug Products with Therapeutic Equivalence Evaluations, commonly known as the Orange Book. Drugs listed in the Orange Book can, in turn, be cited by potential competitors in support of approval of an ANDA. Generally, an ANDA provides for marketing of a drug product that has the same active ingredients in the same strengths and dosage form as the listed drug and has been shown through bioequivalence testing to be therapeutically equivalent to the listed drug. Other than the requirement for bioequivalence testing, ANDA applicants

are not required to conduct or submit results of preclinical or clinical tests to prove the safety or effectiveness of their drug product. Drugs approved in this way are commonly referred to as “generic equivalents” to the listed drug, and can often be substituted by pharmacists under prescriptions written for the original listed drug.

The ANDA applicant is required to certify to the FDA concerning any patents listed for the approved product in the FDA’s Orange Book. Specifically, the applicant must certify that:

- the required patent information has not been filed;
- the listed patent has expired;
- the listed patent has not expired, but will expire on a particular date and approval is sought after patent expiration; or
- the listed patent is invalid or will not be infringed by the new product.

A certification that the new product will not infringe the already approved product's listed patents or that such patents are invalid is called a Paragraph IV certification. If the ANDA applicant does not challenge the listed patents, the ANDA will not be approved until all the listed patents claiming the referenced product have expired.

If the ANDA applicant has provided a Paragraph IV certification to the FDA, the applicant must also send notice of the Paragraph IV certification to the NDA and patent holders once the ANDA has been accepted for filing by the FDA. The NDA and patent holders may then initiate a patent infringement lawsuit in response to the notice of the Paragraph IV certification. The filing of a patent infringement lawsuit within 45 days after the receipt of a Paragraph IV certification automatically prevents the FDA from approving the ANDA until the earlier of a 30 month period, expiration of the patent, settlement of the lawsuit or a decision in the infringement case that the patent involved is deemed invalid or not infringed.

The ANDA also will not be approved until any applicable non-patent exclusivity, such as exclusivity for obtaining approval of a new chemical entity, listed in the Orange Book for the referenced product has expired. Federal law provides a period of five years following approval of a drug containing no previously approved active ingredients during which ANDAs for generic versions of those drugs cannot be received by the FDA, except that the application may be submitted in four years if it contains a Paragraph IV certification. If there is no listed patent in the Orange Book, there may not be a Paragraph IV certification, and thus, no ANDA may be filed before the expiration of the exclusivity period. Federal law provides for a period of three years of exclusivity following approval of a listed drug that contains previously approved active ingredients but is approved in a new dosage form, route of administration or combination, or for a new use, the approval of which was required to be supported by new clinical trials conducted by or for the sponsor, during which the FDA cannot grant effective approval of an ANDA based on that listed drug.

The FDA must establish a priority review track for certain generic drugs, requiring the FDA to review a drug application within eight (8) months for a drug that has three (3) or fewer approved drugs listed in the Orange Book and is no longer protected by any patent or regulatory exclusivities, or is on the FDA's drug shortage list. The FDA must also expedite review of ''competitor generic therapies'' or drugs with inadequate generic competition, including holding meetings with or providing advice to the drug sponsor prior to submission of the application.

Patent term extension

After NDA approval, owners of relevant drug patents may apply for up to a five year patent term extension. The allowable patent term extension is calculated as half of the drug's testing phase, based on the time between IND application and submission of the NDA, and all of the review phase, based on the time between the NDA submission and approval up to a maximum of five years. The time can be shortened if the FDA determines that the applicant did not pursue approval with due diligence. The total patent term after the extension may not exceed 14 years.

For patents that might expire during the application phase, the patent owner may request an interim patent term extension. An interim patent term extension increases the patent term by one year and may be renewed up to four times. For each interim patent term extension granted, the post-approval patent term extension is reduced by one year. The director of the U.S. Patent and Trademark Office must determine that approval of the drug covered by the patent for which a patent term extension is being sought is likely. Interim patent term extensions are not available for a drug for which an NDA has not been submitted.

Section 505(b)(2) new drug applications

Most drug products obtain FDA marketing approval pursuant to an NDA or an ANDA. A third alternative is a special type of NDA, commonly referred to as a Section 505(b)(2) NDA, which enables the applicant to rely, in part, on the FDA's previous approval of a similar product, or published literature, in support of its application.

Section 505(b)(2) NDAs often provide an alternate path to FDA approval for new or improved formulations or new uses of previously approved products. Section 505(b)(2) permits the filing of an NDA where at least some of the information required for approval comes from studies not conducted by or for the applicant and for which the applicant has not obtained a right of reference. If the Section 505(b)(2) applicant can establish that reliance on the FDA's previous approval is scientifically appropriate, it may eliminate the need to conduct certain preclinical or clinical studies of the new product. The FDA may also require companies to perform additional studies or measurements to support the change from the approved product. The FDA may then approve the new product for all or some of the label indications for which the referenced product has been approved, as well as for any new indication sought by the Section 505(b)(2) applicant.

To the extent that the Section 505(b)(2) applicant is relying on studies conducted for an already approved product, the applicant is required to certify to the FDA concerning any patents listed for the approved product in the Orange Book to the same extent that an ANDA applicant would. As a result, approval of a Section 505(b)(2) NDA can be stalled until all the listed patents claiming the referenced product have expired, until any non-patent exclusivity, such as exclusivity for obtaining approval of a new chemical entity, listed in the Orange Book for the referenced product has expired, and, in the case of a Paragraph IV certification and subsequent patent infringement suit, until the earlier of a 30 month period, settlement of the lawsuit or a decision in the infringement case that the patent involved is deemed invalid or not infringed.

Combination products

A combination product is a product comprised of (i) two or more regulated components (i.e., drug/device, biologic/device, drug/biologic or drug/device/biologic) that are physically, chemically, or otherwise combined or mixed and produced as a single entity; (ii) two or more separate products packaged together in a single package or as a unit and comprised of drug and device products, device and biological products, or biological and drug products; (iii) a drug, device, or biological product packaged separately that according to its investigational plan or proposed labeling is intended for use only with an approved individually specified drug, device, or biological product where both are required to achieve the intended use, indication, or effect and where, upon approval of the proposed product, the labeling of the approved product would need to be changed (e.g., to reflect a change in intended use, dosage form, strength, route of administration, or significant change in dose); or (iv) any investigational drug, device, or biological product packaged separately that according to its proposed labeling is for use only with another individually specified investigational drug, device, or biological product where both are required to achieve the intended use, indication, or effect.

The FDA is divided into various branches, or Centers, by product type. Different Centers typically review drug, biologic or device applications. In order to review an application for a combination product, the FDA must decide which Center should be responsible for the review. FDA regulations require that the FDA determine the combination product's primary mode of action, or PMOA, which is the single mode of a combination product that provides the most important therapeutic action of the combination product. The Center that regulates that portion of the product that generates the PMOA or that has expertise in the relevant therapeutic area becomes the lead evaluator. If there are two independent modes of action, neither of which is subordinate to the other, the FDA makes a determination as to which Center to assign the product based on consistency with other combination products raising similar types of safety and effectiveness questions or to the Center with the most expertise in evaluating the most significant safety and effectiveness questions raised by the combination product. When evaluating an application, a lead Center may consult other Centers but still retain complete reviewing authority, or it may collaborate with another Center, by which the lead Center assigns review of a specific section of the application to another Center, delegating its review authority for that section. Typically, the FDA requires a single marketing application submitted to the Center selected to be the lead evaluator, although the agency has the discretion to require separate applications to more than one Center. One reason to submit multiple evaluations is if the applicant wishes to receive some benefit that accrues only from approval under a particular type of application, like new drug product exclusivity. If multiple applications are submitted, each application may be evaluated by a different lead Center.

Biosimilars law

The Biologics Price Competition and Innovation Act of 2009, or BPCIA, amended the PHSA to create a new licensure framework for biosimilar products, which could ultimately subject our biological products to competition. Under the BPCIA, a manufacturer may submit an application for licensure of a biologic product that is "biosimilar to" or "interchangeable with" a referenced, branded biologic product. Previously, there had been no licensure pathway for such biosimilar or interchangeable products. For purposes of the BPCIA, a reference product is defined as the single

biological product licensed under a full BLA against which a biological product is evaluated in an application submitted under a follow-on BLA. Biosimilarity sufficient to reference a prior FDA-approved product requires that there be no differences in conditions of use, route of administration, dosage form, and strength, and no clinically meaningful differences between the biological product and the reference product in terms of safety, purity, and potency. Biosimilarity must be shown through analytical studies, animal studies, and at least one clinical trial, absent a waiver by the Secretary of the U.S. Department of Health & Human Services. A biosimilar product may be deemed interchangeable with a prior approved product if it meets the higher hurdle of demonstrating that it can be expected to produce the same clinical results as the reference product and, for products administered multiple times, the biologic and the reference biologic may be switched after one has been previously administered without increasing safety risks or risks of diminished efficacy relative to exclusive use of the reference biologic.

The BPCIA also created a 12-year period of reference product exclusivity, which can be extended to 12½ years with pediatric exclusivity. The 12-year exclusivity period begins on the date of first licensure of the reference product under the PHSA and during which the licensure of a follow-on application for a biosimilar or interchangeable product cannot be made effective. During the first four years (or four and one-half years with pediatric exclusivity) of the 12-year period, an application for a biosimilar or interchangeable version of the reference product cannot be submitted to the FDA.

The BPCIA includes limits on obtaining 12-year reference product exclusivity for certain changes or modifications to the reference product. A separate 12-year reference product exclusivity period does not apply to:

- a BLA supplement for the product that is the reference product;
- a subsequent BLA filed by the same reference product sponsor or manufacturer (or a licensor, predecessor in interest, or other related entity) for a change (not including a modification to the structure of the biological product) that results in a new indication, route of administration, dosing schedule, dosage form, delivery system, delivery device or strength; or
- a modification to the structure of the biological product that does not result in a change in safety, purity or potency.

The FDA has not yet issued proposed regulations setting forth its interpretation of the BPCIA's provisions but has issued guidance documents and draft guidance documents related to BPCIA implementation concerning biosimilarity and interchangeability, BLA submission requirements, exclusivity, clinical pharmacology, statistics, labeling and naming. As of February 1, 2019, the FDA has approved 17 biosimilar products for use in the United States. No interchangeable biosimilars have been approved.

In addition to creating a 12-year period of reference product exclusivity, the BPCIA clarifies the interaction of that exclusivity with orphan drug exclusivity, such that the licensure of a biosimilar or interchangeable version of a reference product that was designated and approved as an orphan drug may only occur after the later of the expiration of any applicable seven-year orphan drug exclusivity or the 12-year reference product exclusivity (or seven and one-half years and 12½ years with pediatric exclusivity).

Like pediatric exclusivity applicable to drug products approved under the FDCA, pediatric exclusivity applicable to biological reference products is subject to an exception. Pediatric exclusivity will not apply to either the 12-year reference product or the seven-year orphan drug exclusivity periods if the FDA determines later than nine months prior to the expiration of such period that the study reports a BLA sponsor submitted in response to a written request for pediatric studies met the terms of that request.

Our investigational biological products, if approved, could be considered reference products entitled to 12-year exclusivity. Even if our products are considered to be reference products eligible for exclusivity, another company could market a competing version of any of our biological products if the FDA approves a full BLA for such product containing the sponsor's own preclinical data and data from adequate and well-controlled clinical trials to demonstrate the safety, purity and potency of their product.

The BPCIA also sets forth a complex mechanism for resolving patent disputes that involves a step-wise exchange of information prior to the initiation of a patent infringement lawsuit against a biosimilar or interchangeable product sponsor. Unlike the Hatch-Waxman Act, the BPCIA provides no automatic stay on approval of a biosimilar or interchangeable product application.

Overview of FDA regulation of companion diagnostics

We are developing in vitro diagnostics for use in selecting the patients that we believe will respond to our cancer therapeutics.

The FDA published final guidance in July 2014 that addresses issues critical to developing in vitro companion diagnostics. The guidance provides that in vitro companion diagnostics that are essential for the safe and effective use of a corresponding therapeutic product must be approved contemporaneously with that therapeutic in most circumstances. Based on the guidance and the FDA's past treatment of companion diagnostics, we believe that the FDA will likely require one or more of our in vitro diagnostics to obtain premarket approval, or PMA, in conjunction with approval of the associated therapeutic, which will involve coordination of review by CDER and by the FDA's

Center for Devices and Radiological Health Office of In Vitro Diagnostics and Radiological Health.

Diagnostic tests determined by the FDA to be useful, but not essential, for the safe and effective use of a corresponding therapeutic product are also subject to the same medical device pathways, but their clearance or approval would not be subject to a coordinated review of the diagnostic test and the therapeutic product.

The FDA classifies medical devices into one of three classes. Devices deemed to pose lower risk are placed in either Class I or II, which requires the manufacturer to submit to the FDA a premarket notification requesting permission for commercial distribution. Some low risk devices are exempt from this requirement. Devices deemed by the FDA to pose the greatest risk, such as life-sustaining, life-supporting or implantable devices, or devices deemed not substantially equivalent to a previously cleared 510(k) device, are placed in Class III, requiring a PMA. A medical device, including an in vitro diagnostic, or IVD, to be commercially distributed in the United States must receive either 510(k) clearance or PMA (or be a Class I exempt device that does not require pre-market review) from the FDA prior to marketing. The FDA has previously required in vitro companion diagnostics intended to select the patients who will respond to the product candidate to obtain a PMA simultaneously with approval of the product candidate.

510(k) clearance pathway

If any of the diagnostic products under development were determined by FDA not to be essential to the safe and effective prescription of a corresponding therapeutic product, it is possible that the diagnostic test could require 510(k) clearance. The FDA's 510(k) clearance pathway usually takes from three to twelve months, but it can take significantly longer. The FDA may require additional information, including clinical data, to make a determination regarding substantial equivalence.

After a device receives 510(k) clearance, any modification that could significantly affect its safety or effectiveness, or that would constitute a new or major change in its intended use, would require a new 510(k) clearance or, depending on the modification, a PMA. The FDA requires each manufacturer to determine whether the proposed change requires submission of a 510(k) notice or a PMA, but the FDA can review any such decision and can disagree with a manufacturer's determination. If the FDA disagrees with a manufacturer's determination, the FDA can require the manufacturer to cease marketing and/or recall the modified device until 510(k) clearance or a PMA is obtained. If the FDA requires us to seek 510(k) clearance or a PMA for any modifications to a previously cleared product, we may be required to cease marketing or recall the modified device until we obtain this clearance or approval. Also, in these circumstances, we may be subject to significant regulatory fines or penalties.

PMA pathway

Devices deemed by the FDA to pose the greatest risk, such as life-sustaining, life supporting or implantable devices, or devices deemed not substantially equivalent to a previously 510(k) cleared device or a preamendment Class III device for which PMA applications have not been called, are placed in Class III, requiring PMA. The PMA pathway requires proof of the safety and effectiveness of the device to the FDA's satisfaction. The PMA pathway generally takes from one to three years or longer from submission of the application. Most companion diagnostic tests have been classified as Class III devices subject to the PMA pathway.

A PMA application for an IVD must provide extensive preclinical and clinical trial data. Preclinical data for an IVD includes many different tests, including how reproducible the results are when the same sample is tested multiple times by multiple users at multiple laboratories. The clinical data need to establish that the test is sufficiently safe, effective and reliable in the intended use population. In addition, the FDA must be convinced that a device has clinical utility, meaning that an IVD provides information that is clinically meaningful. A biomarker's clinical significance may be obvious, or the applicant may be able to rely upon published literature or submit data to show clinical utility.

A PMA application also must provide information about the device and its components regarding, among other things, device design, manufacturing and labeling. PMA applications are subject to an application fee; for fiscal year 2019, the standard fee for review of a PMA is $322,147 and the small business fee for review of a PMA is $80,537.

As part of the PMA review, the FDA will typically inspect the manufacturer's facilities for compliance with Quality System Regulation, or QSR, requirements, which impose elaborate design control, testing, manufacturing, control, documentation and other quality assurance procedures.

Upon submission, the FDA determines if the PMA application is sufficiently complete to permit a substantive review, and, if so, the FDA accepts the application for filing. The FDA then commences an in-depth review of the PMA application. The entire process typically takes one to three years, but may take longer. The review time is often significantly extended as a result of the FDA asking for more information or clarification of information already provided. The FDA also may respond with a not approvable determination based on deficiencies in the application and require additional clinical trials that are often expensive and time-consuming and can substantially delay approval. During the review period, an FDA advisory committee, typically a panel of clinicians, likely will be convened to

review the application and recommend to the FDA whether, or upon what conditions, the device should be approved. Although the FDA is not bound by the advisory panel decision, the panel's recommendation is important to the FDA's overall decision making process.

If the FDA's evaluation of the PMA application is favorable, the FDA typically issues an approvable letter requiring the applicant's agreement to specific conditions, such as changes in labeling, or specific additional information, such as submission of final labeling, in order to secure final approval of the PMA. If the FDA concludes that the applicable criteria have been met, the FDA will issue a PMA for the approved indications, which can be more limited than those originally sought by the manufacturer. The PMA can include post-approval conditions that the FDA believes necessary to ensure the safety and effectiveness of the device, including, among other things, restrictions on labeling, promotion, sale and distribution. Failure to comply with the conditions of approval can result in material adverse enforcement action, including the loss or withdrawal of the approval.

Even after approval of a PMA, a new PMA or PMA supplement may be required in the event of a modification to the device, its labeling or its manufacturing process. Supplements to a PMA often require the submission of the same type of information required for an original PMA, except that the supplement is generally limited to the information needed to support the proposed change from the product covered by the original PMA.

Clinical trials

A clinical trial is almost always required to support a PMA application. All clinical trials of investigational devices must be conducted in compliance with the FDA's requirements. If an investigational device could pose a significant risk to patients pursuant to FDA regulations, the FDA must approve an Investigational Device Exemption, or IDE, application prior to initiation of investigational use. IVD trials usually do not require an IDE, as the FDA does not judge them to be a significant risk, either because the results do not affect the patients in the study or because obtaining a sample from the patient is not by means of a high risk or invasive procedure. However, for a trial where the IVD result directs the therapeutic care of patients with cancer (companion diagnostics) or the IVD sampling is invasive, we believe that the FDA would consider the investigation to present significant risk and require an IDE.

An IDE application must be supported by appropriate data, such as laboratory test results, showing that it is safe to test the device in humans and that the testing protocol is scientifically sound. The FDA typically grants IDE approval for a specified number of patients. A nonsignificant risk device does not require FDA approval of an IDE. Both significant risk and nonsignificant risk investigational devices require approval from IRBs at the study centers where the device will be used.

During the trial, the sponsor must comply with the FDA's IDE requirements for investigator selection, trial monitoring, reporting and record keeping. The investigators must obtain patient informed consent, rigorously follow the investigational plan and study protocol, control the disposition of investigational devices and comply with all reporting and record keeping requirements. Prior to granting PMA, the FDA typically inspects the records relating to the conduct of the study and the clinical data supporting the PMA application for compliance with applicable requirements.

Although the QSR does not fully apply to investigational devices, the requirement for controls on design and development does apply. The sponsor also must manufacture the investigational device in conformity with the quality controls described in the IDE application and any conditions of IDE approval that the FDA may impose with respect to manufacturing.

Post-market

After a device is on the market, numerous regulatory requirements apply. These requirements include: the QSR, labeling regulations, the FDA's general prohibition against promoting products for unapproved or "off label" uses, the Medical Device Reporting regulation, which requires that manufacturers report to the FDA if their device may have caused or contributed to a death or serious injury or malfunctioned in a way that would likely cause or contribute to a death or serious injury if it were to recur, and the Reports of Corrections and Removals regulation, which requires manufacturers to report recalls and field actions to the FDA if initiated to reduce a risk to health posed by the device or to remedy a violation of the FDCA.

The FDA enforces these requirements by inspection and market surveillance. If the FDA finds a violation, it can institute a wide variety of enforcement actions, ranging from a public warning letter to more severe sanctions such as: fines, injunctions and civil penalties; recall or seizure of products; operating restrictions, partial suspension or total shutdown of production; refusing requests for PMA of new products; withdrawing PMAs already granted; and criminal prosecution.

Other regulatory requirements

Any drug or biological products manufactured or distributed by us pursuant to FDA approvals are subject to pervasive and continuing regulation by the FDA, including, among other things, requirements relating to recordkeeping, periodic reporting, product sampling and distribution, advertising and promotion and reporting of adverse drug experiences. After approval, most changes to the approved product, such as adding new indications or other labeling claims are subject to prior FDA review and approval.

The FDA may impose a number of post-approval requirements as a condition of approval of an NDA or BLA. For example, the FDA may require post-marketing testing, including Phase 4 clinical trials, and surveillance to further assess and monitor the product's safety and effectiveness after commercialization. Regulatory approval of oncology products often requires that patients in clinical trials be followed for long periods to determine the overall survival benefit of the drug or biologic.

In addition, drug and biologic manufacturers and other entities involved in the manufacture and distribution of approved drugs and biological products are required to register their establishments with the FDA and state agencies, and are subject to periodic unannounced inspections by the FDA and these state agencies for compliance with cGMP requirements. The FDA was also granted new inspection authorities under FDASIA. Changes to the manufacturing process are strictly regulated and often require prior FDA approval before being implemented. FDA regulations also require investigation and correction of any deviations from cGMP and impose reporting and documentation requirements upon us and any third-party manufacturers that we may decide to use. Accordingly, manufacturers must continue to expend time, money and effort in the areas of production and quality control to maintain cGMP compliance.

Once an approval is granted, the FDA may withdraw the approval if compliance with regulatory requirements and standards is not maintained or if problems occur after the product reaches the market. Later discovery of previously unknown problems with a product, including adverse events of unanticipated severity or frequency, or with manufacturing processes, or failure to comply with regulatory requirements, may result in revisions to the approved labeling to add new safety information, imposition of post-market studies or clinical trials to assess new safety risks or imposition of distribution or other restrictions under a Risk Evaluation and Mitigation Strategy program. Other potential consequences include, among other things:

- restrictions on the marketing or manufacturing of the product, complete withdrawal of the product from the market or product recalls;
- fines, untitled and warning letters or holds on post-approval clinical trials;
- refusal of the FDA to approve pending applications or supplements to approved applications, or suspension or revocation of product license approvals;
    - product seizure or detention, or refusal to permit the import or export of products; or
- consent decrees, injunctions or the imposition of civil or criminal prosecution.

The FDA strictly regulates marketing, labeling, advertising and promotion of products that are placed on the market. Drugs and biologics may be promoted only for the approved indications and in accordance with the provisions of the approved label. The FDA and other agencies actively enforce the laws and regulations prohibiting the promotion of off label uses, and a company that is found to have improperly promoted off label uses may be subject to significant liability. If a company is found to have promoted off-label uses, it may become subject to adverse public relations and administrative and judicial enforcement by the FDA, the Department of Justice or the Office of the Inspector General of the Department of Health and Human Services, as well as state authorities. This could subject a company to a range of penalties that could have a significant commercial impact, including civil and criminal fines and agreements that materially restrict the manner in which a company promotes or distributes drug products.

Additional provisions

Anti-kickback and false claims laws

In addition to FDA restrictions on marketing of pharmaceutical products, pharmaceutical companies that participate in federal healthcare programs like Medicare or Medicaid are subject to various U.S. federal and state laws that may restrict certain marketing practices. These laws include but are not limited to anti-kickback statutes and false claims statutes. The federal anti-kickback statute prohibits, among other things, knowingly and willfully offering, paying, soliciting or receiving remuneration to induce or in return for purchasing, leasing, ordering or arranging for the purchase, lease or order of any healthcare item or service reimbursable under Medicare, Medicaid or other federally financed healthcare programs. The Patient Protection and Affordable Care Act as amended by the Health Care Education and Reconciliation Act of 2010, collectivel