CorMedix Inc.
Form 10-K
March 16, 2017

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
WASHINGTON, DC 20549

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FORM 10-K

ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934

For the fiscal year ended: December 31, 2016

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: 001-34673

CORMEDIX INC.
(Exact name of Registrant as Specified in Its Charter)

Delaware	20-5894890
(State or Other Jurisdiction ofIncorporation or Organization)	(I.R.S. EmployerIdentification No.)

1430 US Highway 206, Suite 200, Bedminster, NJ	07921
(Address of Principal Executive Offices)	(Zip Code)

Registrant's telephone number, including area code: (908) 517-9500

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

Title of each class	Name of each exchange on which registered
Common Stock, $0.001 Par Value	NYSE MKT LLC

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 and posted on its corporate Web site, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T during the preceding 12 months (or for such shorter period that the registrant was required to submit and post such files).

Yes No

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulations S-K is not contained herein, and will not be contained, to the best of the 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 or a smaller reporting company. See the definitions of "large accelerated filer," "accelerated filer" and "smaller reporting company" in Rule 12b-2 of the Exchange Act. (Check one):

Large accelerated filer Accelerated filer

Non-accelerated filer Smaller reporting company

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Act).

Yes No

The aggregate market value of the registrant's voting and non-voting common equity held by non-affiliates of the registrant, based upon the closing price of the registrant's common stock on the last business day of the registrant's most recently completed second fiscal quarter was approximately $72.6 million. Solely for the purpose of this calculation, shares held by directors and executive officers of the registrant have been excluded. Such exclusion should not be deemed a determination or an admission by the registrant that such individuals are, in fact, affiliates of the registrant.

The number of outstanding shares of the registrant's common stock was 40,720,838 as of March 14, 2017.

DOCUMENTS INCORPORATED BY REFERENCE

Certain portions of the registrant's definitive Proxy Statement for its 2017 Annual Meeting of Stockholders are incorporated herein by reference, as indicated in Part III.

CORMEDIX INC.

Neutrolin® is our registered trademark. All other trade names, trademarks and service marks appearing in this report are the property of their respective owners. We have assumed that the reader understands that all such terms are source-indicating. Accordingly, such terms, when first mentioned in this report, appear with the trade name, trademark or service mark notice and then throughout the remainder of this report without trade name, trademark or service mark notices for convenience only and should not be construed as being used in a descriptive or generic sense.

PART I

Forward-Looking Statements

This report contains "forward-looking statements" that involve risks and uncertainties, as well as assumptions that, if they never materialize or prove incorrect, could cause our results to differ materially from those expressed or implied by such forward-looking statements. The statements contained in this report that are not purely historical are forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended (the "Securities Act"), and Section 21E of the Securities Exchange Act of 1934, as amended (the "Exchange Act"). Forward-looking statements are often identified by the use of words such as, but not limited to, "anticipate," "believe," "can," "continue," "could," "estimate," "expect," "intend," "may," "will," "plan," "project," "seek," "should," "target," "will," expressions or variations intended to identify forward-looking statements. These statements are based on the beliefs and assumptions of our management based on information currently available to management. Such forward-looking statements are subject to risks, uncertainties and other important factors that could cause actual results and the timing of certain events to differ materially from future results expressed or implied by such forward-looking statements. Factors that could cause or contribute to such differences include, but are not limited to, those identified below in the section titled "Item 1A. Risk Factors." Furthermore, such forward-looking statements speak only as of the date of this report. Except as required by law, we undertake no obligation to update any forward-looking statements to reflect events or circumstances after the date of such statements.

Item 1.
Business

Overview

We are a biopharmaceutical company focused on developing and commercializing therapeutic products for the prevention and treatment of infectious and inflammatory diseases.

Our primary focus is on the development of our lead product candidate, Neutrolin® (also known as CRMD003), for potential commercialization in the United States ("U.S.") and other key markets. We have in-licensed the worldwide rights to develop and commercialize Neutrolin®. Neutrolin is a novel anti-infective solution (a formulation of taurolidine, citrate and heparin 1000 u/ml) for the reduction and prevention of catheter-related infections and thrombosis in patients requiring central venous catheters in clinical settings such as dialysis, critical/intensive care, and oncology. Infection and thrombosis represent key complications among critical care / intensive care and cancer patients with central venous catheters. These complications can lead to treatment delays and increased costs to the healthcare system when they occur due to hospitalizations, need for IV antibiotic treatment, long-term anticoagulation therapy, removal/replacement of the central venous catheter, related treatment costs and increased mortality. We believe Neutrolin addresses a significant unmet medical need and a potential large market opportunity.

Neutrolin – United States

The U.S. Food and Drug Administration, or FDA, has designated Neutrolin as a Qualified Infectious Disease Product, or QIDP, for prevention of catheter related blood stream infections in patients with end stage renal disease receiving hemodialysis through a central venous catheter. Catheter-related blood stream infections and clotting can be life-threatening. The QIDP designation provides an additional five years of market exclusivity in addition to the five years granted for a New Chemical Entity. In addition, in January 2015, the FDA granted Fast Track designation to Neutrolin Catheter Lock Solution, pursuant to the Food and Drug Administration Safety Innovation Act, or FDASIA, highlighting the large unmet need to prevent infections in the U.S. healthcare system. The Fast Track designation of Neutrolin provides us with the opportunity to meet with the FDA on a more frequent basis during the development process, and also ensures eligibility to request priority review of the marketing application.

In late 2013, we met with the FDA to determine the pathway for U.S. marketing approval of Neutrolin. Based on those discussions, we determined to conduct two pivotal trials to demonstrate safety and effectiveness of Neutrolin to secure marketing approval in the U.S. We initiated a Phase 3 clinical trial in hemodialysis patients with a central venous catheter in December 2015 and are currently planning to initiate a Phase 3 trial in oncology patients with catheters.

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We launched the Phase 3 clinical trial in hemodialysis catheters in the U.S. in December 2015. The clinical trial, named Catheter Lock Solution Investigational Trial, or LOCK-IT-100, is a prospective, multicenter, randomized, double-blind, placebo-controlled, active control trial which aims to demonstrate the efficacy and safety of Neutrolin in preventing catheter-related bloodstream infections, or CRBSI, in subjects receiving hemodialysis therapy as treatment for end stage renal disease. The primary endpoint for the trial is time to CRBSI. The trial will evaluate whether Neutrolin is superior to the active control heparin by documenting the incidence of CRBSI and the time until the occurrence of CRBSI. Key secondary endpoints are catheter patency which is defined as required use of tissue plasminogen activating factor (tPA) or removal of catheter due to dysfunction or for any reason. We now project to complete enrollment in the fourth quarter of 2017, subject to funding requirements.

We are in discussions with the FDA to develop the design of a Phase 3 clinical trial in oncology patients with catheters, or LOCK-IT-200. This trial also is subject to funding requirements (see “Management’s Discussion and Analysis of Financial Condition and Results of Operations - Liquidity and Capital Resources - Funding and Capital Requirements” in Part II, Item 7 of this report).

Neutrolin – International

In July 2013, we received CE Mark approval for Neutrolin. As a result, in December 2013, we commercially launched Neutrolin in Germany for the prevention of catheter-related bloodstream infections (“CRBSI”), and maintenance of catheter patency in hemodialysis patients using a tunneled, cuffed central venous catheter for vascular access. To date, Neutrolin is registered and may be sold in certain European Union and Middle Eastern countries for such treatment.

In September 2014, the TUV-SUD and The Medicines Evaluation Board of the Netherlands granted a label expansion for Neutrolin for these same expanded indications for the European Union (“EU”). In December 2014, we received approval from the Hessian District President in Germany to expand the label to include use in oncology patients receiving chemotherapy, IV hydration and IV medications via central venous catheters. The expansion also adds patients receiving medication and IV fluids via central venous catheters in intensive or critical care units (cardiac care unit, surgical care unit, neonatal critical care unit, and urgent care centers). An indication for use in total parenteral nutrition was also approved.

Additional Development Possibilities

We are evaluating opportunities for the possible expansion for taurolidine as a platform. Patent applications have been filed in: wound closure, surgical meshes, wound management, and osteoarthritis, including visco-supplementation. There exists a need to control and protect against surgical site infections upon wound closure. We believe taurolidine can also offer benefits not currently available in marketed antimicrobial medical devices. It can also provide a significant advantage in devices for burn victims and use in less sterile environments. We are also involved in a pre-clinical research collaboration for the use of taurolidine as a possible treatment for rare orphan pediatric tumors.

Neutrolin

Market Opportunity

Central venous catheters and peripherally inserted central catheters are an important and frequently used method for accessing the vasculature in hemodialysis (a form of dialysis where the patient’s blood is circulated through a dialysis filter), administering chemotherapy and basic fluids (total parenteral nutrition) in cancer patients and for cancer chemotherapy, long term antibiotic therapy, total parenteral nutrition (complete or partial dietary support via intravenous nutrients) and critical care/intensive care patients.

The treatment of patients undergoing hemodialysis requires access to their vascular system on a recurring basis. According to the 2015 United States Renal Disease System, there were 660,000 patients on hemodialysis. It has been reported by Hemodialysis National Kidney Foundation that patients requiring a catheter represent over 63 million catheter/dialysis treatment days per year. In the United States, 5.7 million intensive care patients were admitted annually according to the Society of Critical Care Medicine, which is estimated to represent 28.5 million catheter days associated with ICU stays alone. As of 2014, there were over 14.5 million patients in the United States living with cancer, with an estimated 7.7 million having had a long-term central venous catheter. When stages of disease and types of chemotherapy regime are considered, the number of catheter days per year are 90 million. Infections and thrombosis represent key complications among cancer patients with central venous catheters. One of the major and common complications for all patients requiring central venous catheters is catheter related blood stream infections, or CRBSIs, and the clinical complications associated with them. There are an estimated 250,000 CRBSIs each year. The U.S. Centers for Disease Control and Prevention stated in the Journal of American Medicine that the total annual cost in the United States of treating all CRBI episodes and their complications would amount to approximately $6 billion.

Biofilm build up is the pathogenesis of both infections and thrombotic complications in central venous catheters. Prevention of CRBIs and inflammatory complications requires both decontamination of the internal surface of the catheter to prevent the systemic dissemination of organisms contained within the biofilm as well as an anticoagulant to retain patency. Biofilm forms when bacteria adhere to surfaces in aqueous environments and begin to excrete a slimy, glue-like substance that can anchor them to various types of materials, including intravenous catheters. The presence of biofilm has many adverse effects, including the ability to release bacteria into the blood stream. The current standard of catheter care is to instill a heparin lock solution at a concentration of 1,000 u/mL into each catheter lumen immediately following treatment, in order to prevent clotting between dialysis treatments. However, a heparin lock solution provides no protection from the risk of infection.

Currently, there are no pharmacologic agents approved in the U.S. for the prevention of CRBIs in central venous catheters. As noted above, we received the CE Mark approval for Neutrolin from the Medical Evaluation Board, or MEB, at the EU in July 2013.

We believe there is a significant need for prevention of CRBIs in the hemodialysis patient population as well as for other patient populations utilizing central venous catheters and peripherally inserted central catheters, such as oncology/chemotherapy, total parenteral nutrition and intensive care unit patients.

Neutrolin is a broad-spectrum antimicrobial/antifungal and anticoagulant combination that is active against common microbes including antibiotic-resistant strains and in addition may prevent biofilm formation. We believe that using Neutrolin as an anti-infective solution will significantly reduce the incidence of catheter-related blood stream infections, thus reducing the need for local and systemic antibiotics while prolonging catheter life.

Initially, we expect to sell Neutrolin directly to hospitals and also to key dialysis center operators. We anticipate that Medicare reimbursement could be available for Neutrolin in other catheter indications in intensive care, oncology and total parenteral nutrition through relevant hospital inpatient diagnosis-related groups (DRGs) or outpatient ambulatory payment classifications (APCs), the End-Stage Renal Disease Prospective Payment System (ESRD PPS) base payment, or under the Durable Medical Equipment, Prosthetics, Orthotics, and Supplies (DMEPOS) Fee Schedule, depending on the setting of care. We also plan to seek separate reimbursement as a drug, where available under Medicare, through mechanisms such as pass-through status under the Hospital Outpatient Prospective Payment System, the transitional drug add-on payment adjustment under the ESRD PPS, or reimbursement as a drug used with a DME infusion pump. We cannot fully anticipate changes in reimbursement requirements and mechanisms in the coming years, however, and we cannot be certain that Neutrolin will be granted separate reimbursement under any of these mechanisms.

Furthermore, we anticipate that the U.S. Centers for Medicare & Medicaid Services (CMS), and private payers will increasingly demand that manufacturers demonstrate the cost effectiveness of their product as part of the reimbursement review and approval process. With this in mind, we have incorporated health economic evaluations into our ongoing clinical studies to support this review in the context of the prospective use of Neutrolin in dialysis, the ICU and oncology settings. Our studies might not be sufficient to support coverage or reimbursement at levels that allow providers to use Neutrolin.

Competitive Landscape

The drug and medical device industries are highly competitive and subject to rapid and significant technological change. Neutrolin’s current and future competitors include large as well as specialty pharmaceutical and biotechnology companies. Many of our competitors have substantially greater financial, technical and human resources than we do and significantly more experience in the development and commercialization of drugs and medical devices. Further, the development of new treatment methods could render Neutrolin non-competitive or obsolete.

We believe that the key competitive factors that will affect the development and commercial success of Neutrolin are efficacy and safety, as well as pricing and reimbursement.

Drug:

To the best of our knowledge, the following product candidates have been recognized for the prevention and treatment of catheter-related blood stream infections.

TauroLock, manufactured by Tauro-Implant (Winsen, Germany). TauroLock has received a CE Mark and is distributed in 25 countries. It has anti-microbial and anti-coagulant activity and contains a combination of citrate 4% with (cyclo)-taurolidine and heparin or urokinase TauroLock has four formulations: TauroLock, Tauro_lock Heparin 100, TauroLock Heparin 500 and TauroLock Urokinase 2500IU.

Zuragen, being developed by Ash Access Technology (Lafayette,IN). It has antimicrobial and anticoagulant activity and contains methylene blue, parabens and 7% citrate.

B-Lock, being developed by Great Lakes Pharmaceuticals Inc. (Cleveland, OH). It has anti-microbial, anti-coagulant and anti-fungal activity and contains trimethoprim, EDTA and ethanol combinations. Initiated study in 2012 in Poland and Hungary to support CE Mark in European Union.

DuraLock-C, manufactured by Medical Components, Inc. (Harleysville,PA). DuraLock-C received a CE Mark and is distributed in a number of European Union countries. It has anti-microbial and anti-thrombosis activity and contains trisodium citrate in 46.7%, 30% and 4% concentrations.

IntraLock, manufactured by Fresenius Medical Care AG & Co. (Bad Homburg, Germany). IntraLock received a CE Mark and is distributed in a number of European Union countries. It is an anticoagulant solution to prevent thrombus formation in catheters. IntraLock contains citrate (4%) for anticoagulation and a small amount of polyhexanide for preservation.

TauroSept, manufactured by Geistlich Pharma (Wolhusen, Switzerland). TauroSept received Class 3 CE Mark and is distributed in a number of European Union countries. TauroSept contains 2% taurolidine solution, 5% polyvinylpyrrolidone and traces of HCl and NaOH to adjust pH. It contains no anticoagulant substances.

Medical Devices:

Tego® Needlefree Connector, manufactured by ICU Medical Inc. (California, USA) Tego Needlefree Connector received 510(k) clearance from the FDA. The Tego connector creates a mechanical and microbiology closed system when attached to the hub of the catheter and works with all hemodialysis CVC related applications.

Curos® (Luer-lock caps twist on, stay on) disinfecting port protectors designed specifically for Tego Needlefree Connectors, manufactured by Ivera Medical Corporation. Curos received 510 (k) clearance from the FDA. Curos for Tego Needlefree Connectors contains 70% isopropyl alcohol-saturated, sponge-like foam that disinfects ports in three minutes and keeps ports clean for seven days.

ClearGuard® HD End Caps for Hemodialysis Catheters, manufactured by Pursuit Vascular, Inc. ClearGuard HD End Caps received 510 (k) clearance from the FDA. The ClearGuard HD End Cap consists of 1) a copolyester polymer plug, which has a rod extending from the tier region that is coated with the antimicrobial agent chlorhexidine acetate (CHA) and 2) a nylon lock ring with threads that are also coated with CHA.

BioFlo DuraMax Dialysis Catheter with Endexo Technology, manufactured by AngioDynamics. The product received 510(k) clearance by the FDA. The BioFlo DuraMax chronic dialysis catheter features Endexo Technology, a catheter material more resistant to thrombus accumulation. Endexo technology is permanent, non-eluting polymer “blended” into the polyurethane from which the catheter is made.

Some device companies have launched antibiotic or antimicrobial-coated catheters as short-term prevention of catheter infection. We believe these are not effective for hemodialysis catheters due to the long term use and high

blood flow associated with hemodialysis.

Manufacturing

All of our manufacturing processes currently are, and we expect them to continue to be, outsourced to third parties. We rely on third-party manufacturers to produce sufficient quantities of drug product for use both commercially and in clinical trials. We intend to continue this practice in the future.

In April 2015, we entered into a Preliminary Services Agreement with [RC]2 Pharma Connect LLC ("RC2"), pursuant to which RC2 coordinates certain manufacturing services related to taurolidine, which is a key ingredient in Neutrolin. Specifically, RC2 undertook a critical parameters evaluation for our manufacturing needs and to coordinate the cGMP processes set forth in the agreement that we believe are necessary for the submission of our planned new drug application for Neutrolin to the FDA, as well as any foreign regulatory applications. The total cost for RC2's services under the preliminary services agreement is approximately $1.7 million which is expected to be incurred under the terms of this agreement through the first quarter of 2017. Since inception through December 31, 2016, RC2 completed and we recognized expense of approximately $1,505,000 for its services related to this agreement.

We are also working with RC2 under several service agreements for an aggregate amount of $7.6 million for the manufacture of clinical supplies to support our ongoing and planned Phase 3 clinical trials. During the years ended December 31, 2016 and 2015, we recognized research and development expense of approximately $2,359,000 and $1,348,000, respectively, related to these agreements. We may terminate these agreements upon 30 days written notice and are only obligated for project costs and reasonable project shut down costs provided through the date of termination.

Navinta LLC, a U.S.-based active pharmaceutical ingredient, or API, developer, provides API manufacturing (manufactured in India at an FDA-compliant facility) and a Drug Master File for Neutrolin, pursuant to a supply agreement dated December 7, 2009 (the "Navinta Agreement"). On March 24, 2015, we and Navinta LLC entered into an amendment to the Navinta Agreement to extend the term of the Navinta Agreement to March 31, 2016 and to lower the price per kilogram of API that we purchase from Navinta LLC under the Navinta Agreement. We also agreed to purchase a minimum amount of product from Navinta LLC during 2015, which replaced the prior minimum purchase requirement. The Navinta Agreement was terminable by either party upon 30 days written notice. The Navinta Agreement expired in accordance with its terms without delivery of the minimum purchase requirement and without any further obligations by either party.

We are confident that there exist a sufficient number of potential alternate sources for the drug substances required to produce our products, as well as third-party manufacturers, that we will be able to find alternate suppliers and third-party manufacturers in the event that our relationship with any supplier or third-party manufacturer deteriorates.

United States Government Regulation

The research, development, testing, manufacture, labeling, promotion, advertising, distribution, and marketing, among other things, of our products are extensively regulated by governmental authorities in the United States and other countries. Our products may be classified by the FDA as a drug or a medical device depending upon the indications for use or claims. Because certain of our product candidates are considered as medical devices and others are considered as drugs for regulatory purposes, we intend to submit applications to regulatory agencies for approval or clearance of both medical devices and pharmaceutical product candidates.

In the United States, the FDA regulates drugs and medical devices under the Federal Food, Drug, and Cosmetic Act and the agency's implementing regulations. If we fail to comply with the applicable United States requirements at any time during the product development process, clinical testing, and the approval process or after approval, we may become subject to administrative or judicial sanctions. These sanctions could include the FDA's refusal to approve pending applications, license suspension or revocation, withdrawal of an approval, warning letters, adverse publicity, product recalls, product seizures, total or partial suspension of production or distribution, injunctions, fines, civil penalties or criminal prosecution, among other actions. Any agency enforcement action could have a material adverse effect on us.

Drug Approval Process

The research, development, and approval process in the United States and elsewhere is intensive and rigorous and generally takes many years to complete. The typical process required by the FDA before a therapeutic drug may be marketed in the United States includes:

preclinical laboratory and animal tests performed under the FDA's Good Laboratory Practices, or GLP, regulations;

submission to the FDA of an investigational new drug application, or IND, which must become effective before human clinical trials may commence;

human clinical studies to evaluate the drug's safety and effectiveness for its intended uses;

FDA review of whether the facility in which the drug is manufactured, processed, packaged, or held meets standards designed to assure the product's continued quality and FDA review of clinical trial sites to determine whether the clinical trials were conducted in accordance with Good Clinical Practices, or GCPs; and

submission of a new drug application, or NDA, to the FDA, and approval of the application by the FDA to allow sales of the drug.

During preclinical testing, studies are performed with respect to the chemical and physical properties of candidate formulations. These studies are subject to GLP requirements. Biological testing is typically done in animal models to demonstrate the activity of the compound against the targeted disease or condition and to assess the apparent effects of the new product candidate on various organ systems, as well as its relative therapeutic effectiveness and safety. An IND application must be submitted to the FDA and become effective before studies in humans may commence.

Clinical trial programs in humans generally follow a three-phase process. Typically, Phase 1 studies are conducted in small numbers of healthy volunteers or, on occasion, in patients afflicted with the target disease. Phase 1 studies are conducted to determine the metabolic and pharmacological action of the product candidate in humans and the side effects associated with increasing doses, and, if possible, to gain early evidence of effectiveness. In Phase 2, studies are generally conducted in larger groups of patients having the target disease or condition in order to validate clinical endpoints, and to obtain preliminary data on the effectiveness of the product candidate and optimal dosing. This phase also helps determine further the safety profile of the product candidate. In Phase 3, large-scale clinical trials are generally conducted in patients having the target disease or condition to provide sufficient data for the statistical proof of effectiveness and safety of the product candidate as required by United States and foreign regulatory agencies. Typically two Phase 3 trials are required for marketing approval.

In the case of products for certain serious or life-threatening diseases, the initial human testing may be done in patients with the disease rather than in healthy volunteers. Because these patients are already afflicted with the target disease or condition, it is possible that such studies will also provide results traditionally obtained in Phase 2 studies. These studies are often referred to as “Phase 1/2” studies. However, even if patients participate in initial human testing and a Phase 1/2 study is carried out, the sponsor is still responsible for obtaining all the data usually obtained in both Phase 1 and Phase 2 studies.

Before proceeding with a study, sponsors may seek a written agreement known as a Special Protocol Assessment, or SPA, from the FDA regarding the design, size, and conduct of a clinical trial. Among other things, SPAs can cover clinical studies for pivotal trials whose data will form the primary basis to establish a product’s efficacy. SPAs help establish up-front agreement with the FDA about the adequacy of a clinical trial design to support a regulatory approval, but the agreement is not binding on the FDA if new circumstances arise. An SPA may only be modified with the agreement of the FDA and the trial sponsor or if the director of the FDA reviewing division determines that a substantial scientific issue essential to determining the safety or efficacy of the drug was identified after the testing began. There is no guarantee that a study will ultimately be adequate to support an approval even if the study is subject to an SPA.

Additionally, some clinical trials are overseen by an independent group of qualified experts organized by the clinical trial sponsor, known as a data safety monitoring board or committee. This group regularly reviews accumulated data and advises the study sponsor regarding the continuing safety of trial subjects, and the continuing validity and scientific merit of the clinical trial. The data safety monitoring board receives special access to unblinded data during the clinical trial and may advise the sponsor to halt the clinical trial if it determined there is an unacceptable safety risk for subjects or on other grounds, such as no demonstration of efficacy.

The manufacture of investigational drugs for the conduct of human clinical trials is subject to current Good Manufacturing Practice, or cGMP, requirements. Investigational drugs and active pharmaceutical ingredients imported into the United States are also subject to regulation by the FDA relating to their labeling and distribution. Further, the export of investigational drug products outside of the United States is subject to regulatory requirements of the receiving country as well as U.S. export requirements under the Federal Food, Drug, and Cosmetic Act, or FDCA.

IND sponsors are also required to submit a number of reports to the FDA during the course of a development program. For instance, sponsors are required to make annual reports to the FDA concerning the progress of their clinical trial programs as well as more frequent reports for certain serious adverse events. Sponsors must submit a protocol for each clinical trial, and any subsequent protocol amendments to the FDA. Investigators must also provide certain information to the clinical trial sponsors to allow the sponsors to make certain financial disclosures to the FDA. Information about certain clinical trials, including a description of the study and study results, must be submitted within specific timeframes to the National Institutes of Health, or NIH, for public dissemination on their clinicaltrials.gov website. Moreover, under the 21st Century Cures Act, manufacturers or distributors of investigational drugs for the diagnosis, monitoring, or treatment of one or more serious diseases or conditions must

have a publicly available policy concerning expanded access to investigational drugs.

United States law requires that studies conducted to support approval for product marketing be “adequate and well controlled.” In general, this means that either a placebo or a product already approved for the treatment of the disease or condition under study must be used as a reference control. The recently passed 21st Century Cures Act, however, provides for FDA acceptance of new kinds of data such as such as patient experience data, real world evidence, and, for appropriate indications sought through supplemental marketing applications, data summaries. Studies must also be conducted in compliance with good clinical practice requirements, and informed consent must be obtained from all study subjects.

In addition, under the Pediatric Research Equity Act, or PREA, an NDA or supplement to an NDA for a new active ingredient, indication, dosage form, dosage regimen, or route of administration must contain data that are adequate to assess the safety and effectiveness of the drug 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.

The FDA also may require submission of a risk evaluation and mitigation strategy, or REMS, to ensure that the benefits of the drug outweigh the risks of the drug. The REMS plan could include medication guides, physician communication plans, and elements to assure safe use, such as restricted distribution methods, patient registries, or other risk minimization tools. An assessment of the REMS must also be conducted at set intervals. Following product approval, a REMS may also be required by the FDA if new safety information is discovered and the FDA determines that a REMS is necessary to ensure that the benefits of the drug outweigh the risks of the drug.

The clinical trial process for a new compound can take ten years or more to complete. The FDA may prevent clinical trials from beginning or may place clinical trials on hold at any point in this process if, among other reasons, it concludes that study subjects are being exposed to an unacceptable health risk. Trials may also be prevented from beginning or may be terminated by institutional review boards, or IRBs, who must review and approve all research involving human subjects and amendments thereto. The IRB must continue to oversee the clinical trial while it is being conducted. This includes the IRBs receiving information concerning unanticipated problems involving risk to subjects. Side effects or adverse events that are reported during clinical trials can delay, impede, or prevent marketing authorization. Similarly, adverse events that are reported after marketing authorization can result in additional limitations being placed on a product’s use and, potentially, withdrawal of the product from the market.

Following the completion of a clinical trial, the data are analyzed by the sponsoring company to determine whether the trial successfully demonstrated safety and effectiveness and whether a product approval application may be submitted. In the United States, if the product is regulated as a new drug, an NDA must be submitted and approved before commercial marketing may begin. The NDA must include a substantial amount of data and other information concerning the safety and effectiveness of the compound from laboratory, animal, and human clinical testing, as well as data and information on manufacturing, product quality and stability, and proposed product labeling.

Each domestic and foreign manufacturing establishment, including any contract manufacturers that we may decide to use, must be listed in the NDA and must be registered with the FDA. The application generally will not be approved until the FDA conducts a manufacturing inspection, approves the applicable manufacturing process for the drug product, and determines that the facility is in compliance with current cGMP requirements. Moreover, FDA will also typically inspect one or more clinical trial sites to confirm that the applicable clinical trials were conducted in accordance with GCPs.

Under the Prescription Drug User Fee Act, as amended, the FDA receives fees for reviewing an NDA, as well as annual fees for commercial manufacturing establishments and for approved products. These fees can be significant. Fee waivers or reductions are available in certain circumstances. One basis for a waiver of the application user fee is if the applicant employs fewer than 500 employees, including employees of affiliates, the applicant does not have an approved marketing application for a product that has been introduced or delivered for introduction into interstate commerce, and the applicant, including its affiliates, is submitting its first marketing application. Product candidates that are designated as orphan drugs, which are further described below, are also not subject to application user fees unless the application includes an indication other than the orphan indication. Under certain circumstances, orphan products may also be exempt from product and establishment fees.

Each NDA submitted for FDA approval is usually reviewed for administrative completeness and reviewability. Following this review, the FDA may request additional information rather than accept an NDA for filing. In this event, the application must be resubmitted with the additional information. The resubmitted application is also subject to review before the FDA accepts it for filing.

Once accepted for filing, the FDA's review of an application may involve review and recommendations by an independent FDA advisory committee. The FDA must refer applications for drugs that contain active ingredients, including any ester or salt of the active ingredients that have not previously been approved by the FDA to an advisory committee or provide in an action letter a summary for not referring it to an advisory committee. The FDA may also refer drugs to advisory committees when it is determined that an advisory committee's expertise would be beneficial to the regulatory decision-making process, including the evaluation of novel products and the use of new technology. An advisory committee is typically a panel that includes clinicians and other experts, which review, evaluate, and make a recommendation as to whether the application should be approved and under what conditions. The FDA is not bound by the recommendations of an advisory committee, but it considers such recommendations carefully when making decisions.

After evaluating the NDA and all related information, including the advisory committee recommendation, if any, and inspection reports regarding the manufacturing facilities and clinical trial sites, the FDA may issue an approval letter, or, in some cases, a Complete Response Letter, or CRL. If a CRL is issued, the applicant may either resubmit the NDA, addressing all of the deficiencies identified in the letter; withdraw the application; or request an opportunity for a hearing. A CRL indicates that the review cycle of the application is complete and the application is not ready for approval and describes all of the specific deficiencies that the FDA identified in the NDA. A CRL generally contains a statement of specific conditions that must be met in order to secure final approval of the NDA, and may require additional clinical or preclinical testing in order for the FDA to reconsider the application. The deficiencies identified may be minor, for example, requiring labeling changes; or major, for example, requiring additional clinical trials. Even with submission of this additional information, the FDA ultimately may decide that the application does not satisfy the regulatory criteria for approval. If and when those conditions have been met to the FDA's satisfaction, the FDA may issue an approval letter. An approval letter authorizes commercial marketing of the drug with specific prescribing information for specific indications.

Even if the FDA approves a product, it may limit the approved therapeutic uses for the product as described in the product labeling, require that warning statements be included in the product labeling, require that additional studies be conducted following approval as a condition of the approval, impose restrictions and conditions on product distribution, prescribing, or dispensing in the form of a REMS or otherwise limit the scope of any approval.

Special FDA Expedited Review and Approval Programs

The FDA has various programs, including Fast Track designation, priority review and breakthrough designation, that are intended to expedite or simplify the process for the development and FDA review of certain drug products that are intended for the treatment of serious or life threatening diseases or conditions, and demonstrate the potential to address unmet medical needs or present a significant improvement over existing therapy. The purpose of these programs is to provide important new drugs to patients earlier than under standard FDA review procedures.

To be eligible for a Fast Track designation, the FDA must determine, based on the request of a sponsor, that a product is intended to treat a serious or life threatening disease or condition and demonstrates the potential to address an unmet medical need. The FDA will determine that a product will fill an unmet medical need if the product will provide a therapy where none exists or provide a therapy that may be potentially superior to existing therapy based on efficacy, safety, or public health factors. If Fast Track designation is obtained, drug sponsors may be eligible for more frequent development meetings and correspondence with the FDA. In addition, the FDA may initiate review of sections of an NDA before the application is complete. This "rolling review" is available if the applicant provides and the FDA approves a schedule for the remaining information. A Fast Track product is also eligible to apply for accelerated approval and priority review.

The FDA may give a priority review designation to drugs that are intended to treat serious conditions and, if approved, would provide significant improvements in the safety or effectiveness of the treatment, diagnosis, or prevention of serious conditions. A priority review means that the goal for the FDA is to review an application within six months, rather than the standard review of ten months under current PDUFA guidelines, of the 60-day filing date for new molecular entities.

Moreover, under the provisions of the Food and Drug Administration Safety and Innovation Act, or FDASIA, enacted in 2012, a sponsor can request designation of a product candidate as a "breakthrough therapy." A breakthrough therapy is defined as a drug that is intended, alone or in combination with one or more other drugs, to treat a serious or life-threatening disease or condition, and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. Drugs designated as breakthrough therapies are eligible for the Fast Track designation features as described above, intensive guidance on an efficient drug development program

beginning as early as Phase 1 trials, and a commitment from the FDA to involve senior managers and experienced review staff in a proactive collaborative, cross-disciplinary review.

Even if a product qualifies for one or more of these programs, the FDA may later decide that the product no longer meets the conditions for qualification or decide that the time period for FDA review or approval will not be shortened.

A final new program to expedite the development of drug products is the limited population pathway for antibacterial and antifungal drugs, which was passed as part of the recent enacted 21st Century Cures Act. Under this program, a sponsor can request drug approval under this new pathway for an antibacterial or antifungal drug if the drug is intended to treat a serious or life-threatening infection in a limited population of patients with unmet needs. Under this program, the FDA's determination of safety and effectiveness would reflect the risk-benefit profile of the drug in the intended limited population, taking into account the severity, rarity, or prevalence of the infection and the availability of alternative treatments in the limited population. The drug may be approved for the limited population notwithstanding a lack of evidence to fully establish a favorable benefit-risk profile in a broader population. Under this program, the FDA must provide prompt advice to sponsors seeking approval under this pathway to enable them to plan a development program. If approved under this pathway, certain post-marketing requirements would apply, such as required labeling and advertising statements and pre-distribution submission of promotional materials to FDA. If after approval for a limited population, a product receives a broader approval, the FDA may remove such post-marketing restrictions. While a drug may only be approved for a limited population under this program, the 21st Century Cures Act states that it is not intended to restrict the prescribing of antimicrobial drugs or other products by healthcare professionals.

Exclusivity

For approved drug products, market exclusivity provisions under the FDCA provide periods of regulatory exclusivity, which gives the holder of an approved NDA limited protection from new competition in the marketplace for the innovation represented by its approved drug.

Section 505 of the FDCA describes three types of marketing applications that may be submitted to the FDA to request marketing authorization for a new drug. A Section 505(b)(1) NDA is an application that contains full reports of investigations of safety and efficacy. A Section 505(b)(2) NDA is an application in which the applicant, in part, relies on investigations that were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted. Section 505(j) establishes an abbreviated approval process for a generic version of approved drug products through the submission of an Abbreviated New Drug Application, or ANDA. An ANDA provides for marketing of a generic drug product that has the same active ingredients, dosage form, strength, route of administration, labeling, performance characteristics, and intended use, among other things, to a previously approved product. Limited changes must be pre-approved by the FDA via a suitability petition.

Five years of exclusivity are available to New Chemical Entities, or NCEs. A NCE is a drug that contains no active moiety that has been approved by the FDA in any other NDA. An active moiety is the molecule or ion, excluding those appended portions of the molecule, that cause the drug to be an ester, salt, including a salt with hydrogen or coordination bonds, or other noncovalent derivatives, such as a complex, chelate, or clathrate, of the molecule, responsible for the therapeutic activity of the drug substance. During the exclusivity period, the FDA may not accept for review and make an ANDA or a 505(b)(2) NDA approval effective for an application submitted by another company that contains the previously approved active moiety. An ANDA or 505(b)(2) application, however, may be submitted one year before NCE exclusivity expires if the applicant submits a certification stating that the patents listed by the NCE sponsor in FDA's list of Approved Drug Products with Therapeutic Equivalence Evaluations, or Orange Book, are invalid or will not be infringed by the manufacture, use, or sale of the drug product for which approval is sought. Five-year exclusivity will also not delay the submission or approval of a full NDA; however, an applicant submitting a full NDA would be required to conduct or obtain a right of reference to all of the preclinical studies and adequate and well-controlled clinical trials necessary to demonstrate safety and efficacy.

Pediatric exclusivity is another type of non-patent marketing 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, including the non-patent exclusivity period described above. This six-month exclusivity may be granted if

an NDA 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. If reports of requested pediatric studies are submitted to and accepted by the FDA within the required time frames, whatever statutory or regulatory periods of exclusivity or Orange Book listed patent protection cover the drug are extended by six months. Moreover, pediatric exclusivity attaches to all formulations, dosage forms, and indications for products with existing marketing exclusivity or patent life that contain the same active moiety as that which was studied.

The Orphan Drug Act also provides incentives for the development of drugs intended to treat rare diseases or conditions, which generally are diseases or conditions affecting fewer than 200,000 individuals annually in the United States, or affecting more than 200,000 in the United States and for which there is no reasonable expectation that the cost of developing and making the drug available in the United States will be recovered from sales in the United States. Additionally, sponsors must present a plausible hypothesis for clinical superiority to obtain orphan designation if there is a drug already approved by the FDA that is intended for the same indication and that is considered by the FDA to be the same drug as the already approved drug. This hypothesis must be demonstrated to obtain orphan drug exclusivity. If granted, prior to product approval, Orphan Drug Designation entitles a party to financial incentives such as opportunities for grant funding towards clinical study costs, tax advantages, and user-fee waivers. In addition, if a product receives FDA approval for the indication for which it has orphan designation, the product is generally entitled to orphan drug exclusivity, which means the FDA may not approve any other application to market the same drug for the same indication for a period of seven years, except in limited circumstances, such as a showing of clinical superiority over the product with orphan exclusivity.

For certain infectious disease products, the above discussed exclusivity period