OPKO HEALTH, INC.

FORM 10-K
(Annual Report)

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UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
WASHINGTON, DC 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, 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 001-33528

OPKO Health, Inc.

(Exact Name of Registrant as Specified in Its Charter)

Delaware	**75-2402409**
(State or Other Jurisdiction of Incorporation or Organization)	**(I.R.S. Employer Identification No.)**

4400 Biscayne Blvd., Miami, FL 33137
(Address of Principal Executive Offices) (Zip Code)

(Registrant ' s Telephone Number, Including Area Code): (305) 575-4100

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

Title of Each Class	Name of Each Exchange on Which Registered
Common Stock, $.01 par value per share	**NASDAQ Global Select 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 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 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, 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.

(in Rule 12b-2 of the Exchange Act) (Check one):

Large accelerated filer	☒	Accelerated filer	☐
Non-accelerated filer	☐ (Do not check if a smaller reporting company)	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 voting and non-voting common equity held by non-affiliates computed by reference to the price at which the common equity was last sold, as of the last business day of the registrant's most recently completed second fiscal quarter was: $3,048,418,845.

As of February 20, 2017 , the registrant had 558,221,985 shares of Common Stock outstanding.

Documents Incorporated by Reference

Portions of the registrant's definitive proxy statement for its 2017 Annual Meeting of Stockholders are incorporated by reference in Items 10, 11, 12, 13, and 14 of Part III of this Annual Report on Form 10-K.

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CAUTIONARY STATEMENT REGARDING FORWARD-LOOKING STATEMENTS

This Annual Report on Form 10-K contains "forward-looking statements," as that term is defined under the Private Securities Litigation Reform Act of 1995 ("PSLRA"), Section 27A of the Securities Act of 1933, as amended, and Section 21E of the Securities Exchange Act of 1934, as amended. Forward-looking statements include statements about our expectations, beliefs or intentions regarding our product development efforts, business, financial condition, results of operations, strategies or prospects. You can identify forward-looking statements by the fact that these statements do not relate strictly to historical or current matters. Rather, forward-looking statements relate to anticipated or expected events, activities, trends or results as of the date they are made. Because forward-looking statements relate to matters that have not yet occurred, these statements are inherently subject to risks and uncertainties that could cause our actual results to differ materially from any future results expressed or implied by the forward-looking statements. Many factors could cause our actual activities or results to differ materially from the activities and results anticipated in forward-looking statements. These factors include those described below and in "Item 1A-Risk Factors" of this Annual Report on Form 10-K. We do not undertake an obligation to update forward-looking statements. We intend that all forward-looking statements be subject to the safe-harbor provisions of the
PSLRA. These forward-looking statements are only predictions and reflect our views as of the date they are made with respect to future events and financial performance.

Risks and uncertainties, the occurrence of which could adversely affect our business, include the following:

- we have a history of losses and may not generate sustained positive cash flow sufficient to fund our operations and research and development programs;
- the risks inherent in developing, obtaining regulatory approvals for and commercializing new, commercially viable and competitive products and treatments;
- our research and development activities may not result in commercially viable products;
- that earlier clinical results of effectiveness and safety may not be reproducible or indicative of future results;
- that we may fail to obtain regulatory approval for hGH-CTP or successfully commercialize *Rayaldee* and hGH-CTP;
- that we may not generate profits or cash flow from our laboratory operations or substantial revenue from our pharmaceutical and diagnostic products;
- that currently available over-the-counter and prescription products, as well as products under development by others, may prove to be as or more effective than our products for the indications being studied;
- our ability to build a successful pharmaceutical sales and marketing infrastructure;
- our ability and our distribution and marketing partners' ability to comply with regulatory requirements regarding the sales, marketing and manufacturing of our products and product candidates and the operation of our laboratories;
- the performance of our third-party distribution partners, licensees and manufacturers over which we have limited control;
- our success is dependent on the involvement and continued efforts of our Chairman and Chief Executive Officer;
- integration challenges for Transition Therapeutics, Bio-Reference, EirGen and other acquired businesses;
- changes in regulation and policies in the United States and other countries, including increasing downward pressure on health care reimbursement;
- our ability to manage our growth and our expanded operations;
- increased competition, including price competition;
- changing relationships with payers, including the various state and multi-state Blues programs, suppliers and strategic partners;
- efforts by third-party payors to reduce utilization and reimbursement for clinical testing services;
- failure to timely or accurately bill for our services;
- failure in our information technology systems, including cybersecurity attacks or other data security incidents;
- failure to obtain and retain new clients and business partners, or a reduction in tests ordered or specimens submitted by existing clients;
- failure to establish, and perform to, appropriate quality standards to assure that the highest level of quality is observed in the performance of our testing services;
- failure to maintain the security of patient-related information;
- our ability to obtain and maintain intellectual property protection for our products;
- our ability to defend our intellectual property rights with respect to our products;
- our ability to operate our business without infringing the intellectual property rights of others;
- our ability to attract and retain key scientific and management personnel;
- our need for, and ability to obtain, additional financing;
- adverse results in material litigation matters or governmental inquiries;
- failure to obtain and maintain regulatory approval outside the U.S.;
- legal, economic, political, regulatory, currency exchange, and other risks associated with international operations; and

- our ability to finance and successfully complete construction of a research, development and manufacturing center in Waterford, Ireland.

PART I

Unless the context otherwise requires, all references in this Annual Report on Form 10-K to the "Company", "OPKO", "we", "our", "ours", and "us" refer to OPKO Health, Inc., a Delaware corporation, including our wholly-owned subsidiaries.

ITEM 1. BUSINESS

OVERVIEW

We are a diversified healthcare company that seeks to establish industry-leading positions in large and rapidly growing medical markets. Our diagnostics business includes Bio-Reference Laboratories ("Bio-Reference"), the nation's third-largest clinical laboratory with a core genetic testing business and a 400-person sales and marketing team to drive growth and leverage new products, including the *4Kscore* prostate cancer test and the *Claros 1* in-office immunoassay platform (in development). Our pharmaceutical business features *Rayaldee* , an FDA-approved treatment for secondary hyperparathyroidism ("SHPT") in adults with stage 3 or 4 chronic kidney disease ("CKD") and vitamin D insufficiency (launched in November 2016), and VARUBI™ for chemotherapy-induced nausea and vomiting (oral formulation launched by partner TESARO in November 2015 and pending approval for IV formulation), TT401, a once or twice weekly oxyntomodulin for type 2 diabetes and obesity which is a clinically advanced drug candidate among the new class of GLP-1 glucagon receptor dual agonists, and TT701, an androgen receptor modulator for androgen deficiency indications which we intend to study for benign prostate hypertrophy (BPH). Our pharmaceutical business also features hGH-CTP, a once-weekly human growth hormone injection (in Phase 3 for growth hormone deficiency and partnered with Pfizer), and a long-acting Factor VIIa drug for hemophilia (Phase 2a). In addition to our pharmaceutical and diagnostic development programs, we own established pharmaceutical platforms in Ireland, Chile, Spain and Mexico which generate revenue and which we expect to facilitate future market entry for our products currently in development. We have a development and commercial supply pharmaceutical company, as well as a global supply chain operation and holding company in Ireland, which we expect will play an important role in the development, manufacturing, distribution and approval of a wide variety of drugs with an emphasis on high potency products. We also own a specialty active pharmaceutical ingredients ("APIs") manufacturer in Israel, which we expect will facilitate the development of our pipeline of molecules and compounds for our proprietary molecular diagnostic and therapeutic products.

We have a highly experienced management team that we believe has demonstrated an ability to successfully build and manage pharmaceutical and healthcare businesses. Based on their experience in the industry, we believe that our management team has extensive development, regulatory and commercialization expertise and relationships that provide access to commercial opportunities.

All product or service marks appearing in type form different from that of the surrounding text are trademarks or service marks owned, licensed to, promoted or distributed by OPKO, its subsidiaries or affiliates, except as noted. All other trademarks or services marks are those of their respective owners.

GROWTH STRATEGY

We expect our future growth to come from leveraging our commercial infrastructure, proprietary technology and development strengths, and by opportunistically pursuing complementary, accretive, or strategic acquisitions and investments.

We launched our first pharmaceutical product, *Rayaldee,* in the U.S. market in the fourth quarter of 2016. We have under development a broad and diversified portfolio of diagnostic tests, small molecules, and biologics targeting a broad range of unmet medical needs. We also operate the third largest full service clinical laboratory in the U.S. We intend to continue to leverage our proprietary technology and our strengths in all phases of research and development to further develop and commercialize our portfolio of proprietary pharmaceutical and diagnostic products. In support of our strategy, we intend to:

- continue to enhance our commercialization capability in the U.S. and internationally;
- develop and commercialize *Rayaldee* for new indications, including the treatment of SHPT in patients with vitamin D insufficiency and stage 5 CKD requiring regular hemodialysis;
- obtain requisite regulatory approval and compile clinical data for our most advanced product candidates; and
- expand into other medical markets that provide significant opportunities and that we believe are complementary to and synergistic with our business.

In addition, we expect to leverage the Bio-Reference business and infrastructure to drive rapid and widespread uptake of our diagnostic products, including the *4Kscore* test and the *Claros 1* in-office immunoassay platform. We also intend to

leverage the genetic and genomic data generated and accumulated through Bio-Reference's genetic sequencing laboratory to enhance drug discovery and clinical trial programs.

We have and expect to continue to be opportunistic and to pursue complementary or strategic acquisitions, licenses and investments. Our management team has significant experience in identifying, executing and integrating these transactions. We expect to use well-timed, carefully selected acquisitions, licenses and investments to continue to drive our growth, including:

- *Products and technologies.* We intend to continue to pursue product and technology acquisitions and licenses that will complement our existing businesses and provide new product and market opportunities, enhance our profitability, leverage our existing assets, and contribute to our own organic growth.
- *Commercial businesses.* We intend to continue to pursue acquisitions of commercial businesses that will both drive our growth and provide geographically diverse sales and distribution opportunities.
- *Early stage investments.* We have and may continue to make investments in early stage companies that we perceive to have valuable proprietary technology and significant potential to create value for OPKO as a shareholder.

CORPORATE INFORMATION

We were originally incorporated in Delaware in October 1991 under the name Cytoclonal Pharmaceutics, Inc., which was later changed to eXegenics, Inc. ("eXegenics"). On March 27, 2007, we were part of a three-way merger with Froptix Corporation ("Froptix") and Acuity Pharmaceuticals, Inc. ("Acuity"), both research and development companies. On June 8, 2007, we changed our name to OPKO Health, Inc. Our shares are publicly traded on the NASDAQ Stock Market under the ticker "OPK" and on the Tel Aviv Stock Exchange. Our principal executive offices are located in leased office space in Miami, Florida.

We currently manage our operations in two reportable segments: diagnostics and pharmaceuticals. The pharmaceutical segment consists of the pharmaceutical operations we acquired in Chile, Mexico, Ireland, Israel and Spain and our pharmaceutical research and development operations. The diagnostics segment primarily consists of the clinical laboratory operations we acquired through the acquisitions of Bio-Reference and our point-of-care operations. There are no significant inter-segment sales. We evaluate the performance of each segment based on operating profit or loss. There is no inter-segment allocation of interest expense and income taxes. Refer to Note 16 for financial information about the segments and geographic areas.

CURRENT PRODUCTS AND SERVICES AND RELATED MARKETS

Diagnostics

Bio-Reference Laboratories

Through Bio-Reference, the third largest full service clinical laboratory in the United States, we now offer comprehensive laboratory testing services utilized by healthcare providers in the detection, diagnosis, evaluation, monitoring, and treatment of diseases, including esoteric testing, molecular diagnostics, anatomical pathology, genetics, women's health and correctional healthcare. We market and sell these services to physician offices, clinics, hospitals, employers and governmental units nationally, with the largest concentration of business in the larger metropolitan areas across New York, New Jersey, Maryland, Pennsylvania, Delaware, Washington DC, Florida, California, Texas, Illinois and Massachusetts. Bio-Reference has an approximately 400-person sales and marketing team and operates a network of approximately 275 patient service centers or in-office phlebotomy stations for collection of patient specimens.

Our Bio-Reference laboratory testing business consists of routine testing and esoteric testing. Routine tests measure various health parameters, such as the functions of the heart, kidney, liver, thyroid and other organs, including such tests as blood cell counts, cholesterol levels, pregnancy, substance abuse and urinalysis. We typically operate 24 hours per day, 365 days per year and perform and report most routine test results within 24 hours.

The esoteric tests we perform require sophisticated equipment and materials, highly skilled personnel and professional attention. Esoteric tests are ordered less frequently than routine tests and typically are priced higher than routine tests. Esoteric tests include tests related to endocrinology, genetics and genomics, immunology, microbiology, HIV tests, molecular diagnostics, next generation sequencing, oncology, serology, and toxicology.

Through Bio-Reference, we operate in the following highly specialized laboratory divisions:

- *Bio-Reference Laboratories.* Bio-Reference constitutes our core clinical testing laboratory offering automated, high volume routine testing services, STAT testing, informatics, HIV, Hep C and other molecular tests.
- *GenPath (Oncology).* National oncology presence with expertise in cancer pathology and diagnostics, as well as molecular diagnostics. Core tests include FLOW, IHC, MicroArray, FISH, ISH, Morphology, and full service oncology.
- *GenPath (Women's Health).* Innovative technology platform for sexually transmitted infections has enabled expansion nationally with specimens coming from 41 states, including Image Directed Paps analysis, HPV Plus, and STI Testing.
- *GeneDx.* Industry leading national laboratory for testing rare and ultra-rare genetic diseases with international reach, performing testing on specimens from more than 50 countries.
- *Laboratorio Bueno Salud* . National testing laboratory dedicated to serving the Spanish-speaking population in the United States, where all business is conducted in Spanish including patient and physician interaction.

We have one of the largest marketing staffs of any laboratory in the country with sales and marketing groups dedicated to urology, oncology, women's health, genetic testing and correctional health, as well as cross-over groups selling to large institutions. All of our sales and marketing personnel operate in a dual capacity, as both marketing and client support representatives, which we believe provides better customer service and a strong connection with our customers.

We expect the clinical laboratory testing industry will continue to experience growth in testing volumes due to aging of the population in the U.S., patient awareness of the value of laboratory tests, a decrease in the cost of tests, the development of sophisticated and specialized tests for detection and management of disease, increased recognition of early detection and prevention as a means of reducing healthcare costs, and ongoing research and development in genetics and genomics and personalized medicine. Our mission is to be recognized by our clients as the premier provider of clinical laboratory testing, information and related services.

Bio-Reference provides us with a significant diagnostics commercial infrastructure for marketing and sales that reached more than 11 million patients in 2016. In addition, its large team of managed care experts complement our efforts to ensure that payors recognize the value of our diagnostic and laboratory tests for reimbursement purposes. We continue to leverage the national marketing, sales and distribution resources of Bio-Reference, along with its 400-person sales and marketing team, to enhance sales of and reimbursement for our *4Kscore* test, a laboratory developed blood test that provides a personalized risk score for aggressive prostate cancer. We plan to continue to leverage the Bio-Reference commercial infrastructure and capabilities, as well as its extensive relationships with payers, to commercialize OPKO's other diagnostic products under development, including the *Claros 1* .

4Kscore Test

We offer the *4Kscore* test through our Bio-Reference laboratory located in Elmwood Park, New Jersey. We began selling the *4Kscore* test in the U.S. in March 2014 and in Europe and Mexico in September 2014 and January 2015, respectively. The *4Kscore* test is a laboratory developed test that measures the blood plasma levels of four different prostate-derived kallikrein proteins: Total PSA, Free PSA, Intact PSA and Human Kallikrein-2 ("hK2"). These biomarkers are then combined with a patient's age, DRE status (nodule / no nodule), and prior negative biopsy status (yes / no) using a proprietary algorithm to calculate the risk (probability) of finding a Gleason Score 7 or higher prostate cancer. The four kallikrein panel of biomarkers utilized in the *4Kscore* test is based on decades of research conducted by scientists at Memorial Sloan-Kettering Cancer Center and leading European institutions. Investigators at the Lund University, Sweden, University of Turku, Finland and Memorial Sloan Kettering Cancer Center, New York, have also demonstrated that the *4Kscore tes* t can predict the 20-year risk for development of prostate metastases in men who present at age 50 or 60 years old with an elevated PSA.

The *4Kscore* test was developed by OPKO and validated in 2014 in a prospective, blinded study of 1,012 men in collaboration with 26 urology centers across the U.S. Results showed that the *4Kscore* test was highly accurate for predicting the presence of high-grade cancer (Gleason score 7 or higher) prior to prostate biopsy. The full data from the blinded, prospective U.S. clinical validation study were published in European Urology (Eur Urol. 2015 Sep;68(3):464-70. doi: 10.1016/j.eururo.2014.10.021. Epub 2014 Oct 27.).

The clinical data demonstrated the ability of the *4Kscore* test to discriminate between men with high-grade, aggressive prostate cancer and those men who had no findings of cancer or had low-grade or indolent form of the disease. The discrimination, measured by Area Under the Curve ("AUC") analysis, was 0.82 and was significantly higher than previously developed tests. Furthermore, the *4Kscore* test demonstrated excellent risk calibration, indicating the accuracy of the result for

an individual patient. The high value of AUC and the excellent risk calibration make the *4Kscore* test result valuable information for the shared decision-making between the urologist and patient on whether or not to perform a prostate biopsy.

A separate clinical study indicated that the *4Kscore* test led to 64.6% fewer biopsies. The study, " *The 4Kscore® Test Reduces Prostate Biopsy Rates in Community and Academic Urology Practices",* published in the January 2016 edition of Reviews in Urology, which included 611 patients seen by 35 academic and community urologists across the U.S., evaluated the influence of the *4Kscore* test on urologist-patient decisions about whether to perform a biopsy in men who had an abnormal PSA and or DRE result. Test results for patients were stratified into low risk (< 7.5%), intermediate risk (7.5%-19.9%) and high risk (≥20%) for developing aggressive prostate cancer. Nearly half (49.3%) of the men were categorized as low risk; 25.7% and 25.0% fell into the intermediate-risk and high-risk categories, respectively. Notably, the *4Kscore* test results influenced biopsy decisions in 88.7% of the men. In the three risk groups, a biopsy was avoided in 94.0%, 52.9%, and 19.0% of men in the low, intermediate, and high-risk categories, respectively.

The value of the *4Kscore* test has been demonstrated in 12 peer-reviewed clinical studies involving more than 22,000 patients and we have been granted a Category I CPT code by the AMA for our *4Kscore* test, which was published in August 2016 and effective January 1, 2017. CPT codes are used by insurance companies and government payers to describe health care services and procedures, and having a Category I CPT code is critical to facilitate reimbursement in government programs such as Medicare and Medicaid, as well as private insurance programs. We believe having the Category I CPT code will help facilitate obtaining broader coverage from payers for the *4Kscore* test and allow greater access to the test for a broader group of patients across the U.S.

The National Comprehensive Cancer Network ("NCCN") included the *4Kscore* test as a recommended test in their 2015 and 2016 Guidelines for Prostate Cancer Early Detection. The panel making this recommendation concluded that the *4Kscore* test is indicated for use prior to a first prostate biopsy, or after a negative biopsy, to assist patients and physicians in further defining the probability of high-grade cancer. In addition, the European Association of Urology (EAU) Prostate Cancer Guidelines Panel included the *4Kscore* test in the 2016 EAU Guidelines for Prostate Cancer, concluding that the *4Kscore* , as a blood test with greater specificity over the PSA test, is indicated for use prior to a first prostate biopsy or after a negative biopsy to assist patients and physicians in further defining the probability of high-grade cancer.

We have and will continue to commit substantial efforts to obtaining broad reimbursement coverage for the *4Kscore* test. We have obtained a positive coverage decision from at least one national private payer and pricing agreements from several regional payers. Novitas Solutions, the local Medicare Administrative Contractor, or MAC, for our laboratory in New Jersey, has been and continues to pay for the majority of our *4Kscore* Medicare submissions. Although Novitas initially issued a positive draft local coverage determination (LCD) in May 2016, the coverage determination was retired due to a conflicting LCD issued by Palmetto, another MAC. We are working diligently to address concerns raised by Palmetto pertaining primarily to clinical utility and believe we have supplied sufficient scientific and clinical data to support a positive coverage determination by any Medicare contractor. We expect to significantly expand our efforts to obtain broad reimbursement for the *4Kscore* test throughout 2017 and beyond.

Point-of-Care Diagnostics

OPKO Diagnostics, LLC ("OPKO Diagnostics"), formerly Claros Diagnostics, Inc., is developing a novel diagnostic instrument system to provide rapid, high performance blood test results and enable tests to be run in point-of-care settings. The instrument, a microfluidics-based diagnostic test system consisting of a credit card-sized disposable test cassette that works with a small but sophisticated desktop analyzer, provides high performance quantitative blood test results within minutes and permits the transition of complex immunoassays from the centralized reference laboratory to the physician's office, hospital nurses station, or other decentralized location. The technology only requires a finger stick drop of blood introduced into the test cassette which can then run a quantitative test.

We commenced a multi-center clinical trial for the PSA test in January 2017 and expect to submit our application to the FDA for a pre-marketing authorization ("PMA") for the PSA test upon completion of the trial. We also intend to commence a clinical trial of a testosterone diagnostic test for our point-of-care system. We expect to fully leverage Bio-Reference's marketing, sales and distribution resources for the launch of the *Claros 1* system and associated diagnostic tests in the U.S after FDA clearance or approval.

We are also presently working to add additional tests for our point-of-care system, including vitamin D, and we believe that there are many more applications for the technology, including infectious disease, cardiology, women's health, and companion diagnostics.

Pharmaceutical Business

We currently have one commercial stage pharmaceutical product and several pharmaceutical compounds and technologies in various stages of research and development for a broad range of indications and conditions, including the following:

Renal Products

We launched *Rayaldee* , our lead renal product, in the U.S. market in November 2016. In June 2016, the FDA approved *Rayaldee* extended release capsules for the treatment of secondary hyperparathyroidism (SHPT) in adults with stage 3 or 4 chronic kidney disease (CKD) and serum total 25-hydroxyvitamin D levels less than 30 ng/mL. *Rayaldee* is a patented extended release product containing 30 mcg of a prohormone called calcifediol (25-hydroxyvitamin D_3).

We have a 50-person highly specialized sales and marketing team dedicated to the launch and commercialization of *Rayaldee* , and we expect to increase our sales and marketing efforts in the second half of 2017. Efforts are underway to obtain broad commercial and Part D insurance coverage for *Rayaldee.* The Company has contracted for commercial and Part D coverage for more than sixty percent (60%) of U.S. covered lives and expects that number to reach seventy percent (70%) by mid-2017.

In connection with the launch of *Rayaldee* , the Company has also engaged in a comprehensive ongoing market education campaign highlighting the unmet need in treating SHPT, including by leveraging key opinion leaders in community outreach programs such as speakers' bureaus and patient advocacy programs.

In May 2016, we entered into a collaboration with Vifor Fresenius Medical Care Renal Pharma (VFMCRP) for the development and commercialization of *Rayaldee* in Europe, Canada, Mexico, Australia, South Korea and certain other international markets for the treatment of SHPT in patients with stage 3 or 4 CKD and vitamin D insufficiency. Under the terms of the agreement, OPKO received an upfront payment of $50 million, and will receive up to $232 million in regulatory and sales based milestones. In addition, VFMCRP will pay OPKO tiered, double digit royalties on sales of the product. OPKO and VFMCRP will also collaborate to develop and commercialize a new dosage form of *Rayaldee* for the treatment of SHPT in hemodialysis patients. OPKO granted VFMCRP an option to acquire rights to this dosage form for the U.S. market; if exercised, OPKO will receive up to $555 million in additional milestones and double digit royalties.

The FDA approval for *Rayaldee* was supported by successful top-line results from two pivotal phase 3 trials of *Rayaldee* that were identical randomized, double-blind, placebo-controlled, multi-site studies which established the safety and efficacy of *Rayaldee* as a new treatment for SHPT in adults with stage 3 or 4 CKD and vitamin D insufficiency.

Vitamin D insufficiency arises in CKD due to the abnormal upregulation of CYP24A1, an enzyme that destroys vitamin D and its metabolites. Studies in CKD patients have demonstrated that currently available over-the-counter and prescription vitamin D products cannot reliably raise blood vitamin D prohormone levels and effectively treat SHPT, a condition commonly associated with CKD in which the parathyroid glands secrete excessive amounts of parathyroid hormone (“PTH”). Prolonged elevation of blood PTH causes excessive calcium and phosphorus to be released from bone, leading to elevated serum calcium and phosphorus levels, softening of the bones (osteomalacia) and calcification of vascular and renal tissues. SHPT affects 40-82% of patients with stage 3 or 4 CKD and approximately 95% of patients with stage 5 CKD.

The completed pivotal trials for *Rayaldee* successfully met all primary efficacy and safety endpoints. The primary efficacy endpoint was a responder analysis in which “responder” was defined as any treated subject who demonstrated an average 30% decrease in PTH from pre-treatment baseline during the last six weeks of the 26-week treatment period. A significantly higher response rate was observed with *Rayaldee* which steadily increased with treatment duration. The response rate with *Rayaldee* was similar in CKD stages 3 and 4. Safety and tolerability data were comparable in both treatment groups. Patients completing the two pivotal trials were treated, at their election, for an additional six months with *Rayaldee* during an open-label extension study. Data from the extension study indicated that the PTH lowering response rates steadily increased with duration of *Rayaldee* treatment without deterioration in safety profile. In addition to SHPT in CKD patients, we also are developing *Rayaldee* for other indications, including for SHPT in patients with vitamin D insufficiency and stage 5 CKD requiring regular hemodialysis. A phase 2 study is expected to commence in 2017 in hemodialysis patients. In August 2014, we also announced the submission of an IND to the FDA to evaluate *Rayaldee* as an adjunctive therapy for the prevention of skeletal-related events in patients with bone metastases undergoing anti-resorptive therapy. We commenced a phase 1 dose escalation study in the fourth quarter of 2014 in breast and prostate cancer patients with bone metastases who are receiving anti-resorptive therapy. The study is evaluating safety, markers of vitamin D and mineral metabolism and tumor progression. We are currently evaluating interim data from the study.

Our second most advanced renal product, *Alpharen* (Fermagate Tablets), is a new and potent non-absorbed phosphate binder to treat hyperphosphatemia in Stage 5 CKD patients requiring regular hemodialysis. *Alpharen* (Fermagate Tablets) has been shown to be safe and effective in treating hyperphosphatemia in phase 2 and 3 trials in stage 5 CKD patients undergoing

chronic hemodialysis. Hyperphosphatemia, or elevated serum phosphorus, is common in dialysis patients and tightly linked to the progression of SHPT and vascular calcification, both of which drive morbidity and mortality. The kidneys provide the primary route of excretion for excess phosphorus absorbed from ingested food. As kidney function worsens, serum phosphorus levels increase and directly stimulate PTH secretion. Stage 5 CKD patients requiring dialysis must reduce their dietary phosphate intake and usually require regular treatment with orally administered phosphate binding agents to lower serum phosphorus to meet the recommendations of the Kidney Disease Improving Global Outcomes ("KDIGO") Clinical Practice Guidelines that elevated serum phosphorus levels should be lowered toward the normal range. Hyperphosphatemia contributes to soft tissue mineralization and affects approximately 90% of dialysis patients. Dialysis patients require ongoing phosphate binder treatment to maintain controlled serum phosphorus levels. We are currently preparing to conduct a single additional Phase 3 clinical trial intended to support marketing approvals in North America and in Europe.

We believe the CKD patient population is large and growing as a result of obesity, hypertension and diabetes; therefore this patient population represents a significant market opportunity. According to the National Kidney Foundation, CKD afflicts over 26 million people in the U.S., including more than 20 million patients with stage 3 or 4 CKD. In stage 5 CKD, kidney function is minimal to absent and most patients require regular dialysis or a kidney transplant for survival. An estimated 71-97% of CKD patients have vitamin D insufficiency which can lead to SHPT and its debilitating consequences. CKD continues to be associated with poor outcomes, reflecting the inadequacies of the current standard of care. Vitamin D insufficiency, hyperphosphatemia and SHPT, when inadequately treated, are major contributors to poor CKD outcomes. We intend to develop and commercialize *Rayaldee* and *Alpharen* to constitute part of the foundation for a new and markedly improved standard of care for CKD patients having SHPT and/or hyperphosphatemia.

SARM

Through the acquisition of Transition Therapeutics, a Toronto-based biotechnology company, we acquired TT701, an orally administered selective androgen receptor modulator (SARM) which we are developing for the treatment of patients who will benefit from its effects on increasing muscle and bone strength and decreasing body fat mass. The selective and antagonistic properties of TT701 appear to be well suited to provide anabolic therapeutic benefits to specific patient populations, while potentially avoiding, or even reducing, prostate hypertrophy.

A Phase 2 study of 350 male subjects for another indication showed significantly increased lean body mass and muscle strength and significant fat mass reduction with no change in lower PSA levels. TT701 is currently being studied in a Phase 2 study in prostate cancer patients who have undergone radical prostatectomy, and a Phase 2b study is planned to determine the optimal dose to treat patients with Benign Prostatic Hypertrophy (BPH).

Biologics

Our biologics business focuses on developing and commercializing longer-acting proprietary versions of already approved therapeutic proteins. One of our innovative platform technologies uses a short, naturally-occurring amino acid sequence (carboxl terminal peptide or “CTP”) that has the effect of slowing the removal from the body of the therapeutic protein to which it is attached. This CTP can be readily attached to a wide array of existing therapeutic proteins, stabilizing the therapeutic protein in the bloodstream and extending its life span without additional toxicity or loss of desired biological activity. We are using the CTP technology to develop new, proprietary versions of certain existing therapeutic proteins that have longer life spans than therapeutic proteins without CTP. We believe that our products will have greatly improved therapeutic profiles and distinct market advantages.

There are two existing biopharmaceuticals on the market that currently utilize CTP technology. The first product is human chorionic gonadotropin (“hCG”), of which CTP is naturally a part. Besides being present normally in high amounts during pregnancy, it is also given therapeutically to women or men as a fertility treatment (sold by Merck-Serono, Merck & Co. and Ferring). The second product is ELONVA® (FSH-CTP), which is sold by Merck & Co. The data from the clinical and therapeutic use of these products gave us confidence that the CTP technology is able to address the major problems faced by the other attempted approaches to increase protein lifespan. Clinical and therapeutic data from these products also reassured us that CTP can be used safely and that it is effective in extending the serum lifetime and activity. We are the exclusive licensee for the utilization of CTP technology in all therapeutic proteins, peptides and their modified forms except for human FSH, LH, TSH and hCG.

hGH-CTP

Our lead product candidate utilizing CTP, hGH-CTP, is a recombinant human growth hormone product under development for the treatment of growth hormone deficiency (“GHD”), which is a pituitary disorder resulting in short stature in children and other physical ailments in both children and adults.

In December 2014, we entered into an exclusive worldwide agreement with Pfizer for the development and commercialization of hGH-CTP for the treatment of GHD in adults and children, as well as for the treatment of growth failure

in children born SGA. In connection with the transaction, we granted Pfizer an exclusive license to commercialize hGH-CTP worldwide, and we received non-refundable and non-creditable upfront payments of $295 million and are eligible to receive up to an additional $275 million upon the achievement of certain regulatory milestones. In addition, we are eligible to receive initial tiered royalty payments associated with the commercialization of hGH-CTP for Adult GHD with percentage rates ranging from the high teens to mid-twenties. Upon the launch of hGH-CTP for Pediatric GHD in certain major markets, the royalties will transition to regional, tiered gross profit sharing for both hGH-CTP and Pfizer's Genotropin®.

Pursuant to our agreement with Pfizer, we will lead the clinical development activities for the hGH-CTP program and will be responsible for funding the development programs for the key indications, which includes Adult and Pediatric GHD and Pediatric SGA. Pfizer will be responsible for all development costs for additional indications as well as all post-marketing studies. In addition, Pfizer will fund the commercialization activities for all indications and lead the manufacturing activities covered by the global development plan.

GHD occurs when the production of growth hormone, secreted by the pituitary gland, is disrupted. Since growth hormone plays a critical role in stimulating body growth and development, and is involved in the production of muscle protein and in the breakdown of fats, a decrease in the hormone affects numerous body processes. hGH is used for the long-term treatment of children and adults with inadequate secretion of endogenous growth hormone. The primary indications it treats in children are GHD, SGA, kidney disease, Prader-Willi Syndrome and Turner's Syndrome. In adults, the primary indications are replacement of endogenous growth hormone and the treatment of AIDS-induced weight loss. Patients using hGH receive daily injections six or seven times a week. This is particularly burdensome for pediatric patients. We believe a significant market opportunity exists for a longer-lasting version of hGH that would require fewer injections.

In December 2016, we announced preliminary topline data from our Phase 3, double blind, placebo controlled study of hGH-CTP in adults with GHD. The multinational, multi-center study, which utilized a 2:1 randomization between hGH-CTP and placebo, enrolled 203 subjects, 198 of whom received at least one dose of study treatment. Treatment was administered through a weekly injection. The topline results showed:

- The active group had a mean change in trunk fat mass of -0.4kg and placebo group was 0;
- There was no statistically significant difference (≤ 0.05 (p value)) between the active and placebo group;
- 97% of hGH-CTP vs 6% of placebo group showed IGF-1 normalization; and
- The safety profile of hGH-CTP is consistent with that observed with those treated with daily growth hormone

Although there was no statistically significant difference between hGH-CTP and placebo on the primary endpoint of change in trunk fat mass from baseline to 26 weeks, after unblinding the study, we identified an exceptional value of trunk fat mass reduction in the placebo group that may have affected the primary outcome. We believe the exceptional data point warrants an outlier sensitivity analysis of the primary endpoint and related secondary endpoints. Upon completion of the data sensitivity analysis, we plan to discuss the study results and outlier analysis with the regulatory authorities to determine next steps in obtaining regulatory approval.

We are continuing as planned with our development of hGH-CTP, including our Phase 3 trial of hGH-CTP in pediatric patients which we initiated in December 2016. The global study is a 220 patient study in pediatric GHD patients designed to evaluate weekly treatment with hGH-CTP versus daily injections of Genotropin. The hGH-CTP will be delivered in a pen device in this multi-regional study. In addition to the Phase 3 pediatric study, we have continued without interruption our ongoing Phase 3 adult and Phase 2 pediatric open label extension studies for hGH-CTP, for which we plan to switch patients to the disposable pen device. We also expect to initiate a 44 patient study in pediatric GHD patients in Japan and are planning to commence a global study for SGA. hGH-CTP has orphan drug designation in the U.S. and Europe for both adults and children with GHD.

Factor VII

In addition to hGH-CTP, we are developing a product to extend the life span of Factor VIIa (hemophilia) using the CTP technology. In February 2013, the FDA granted orphan drug designation to our longer-acting version of clotting Factor VIIa, Factor VIIa-CTP, for the treatment of bleeding episodes in patients with hemophilia A or B with inhibitors to Factor VIII or Factor IX. These patients are currently being treated by commercially-available Factor VIIa, with estimated 2013 worldwide sales of $1.7 billion. Currently, Factor VIIa therapy is available only as an intravenous (IV) formulation which, due to Factor VIIa's short half-life, requires multiple infusions to treat a bleeding episode. In addition, frequent infusions are onerous when used as preventative prophylactic therapy, especially for children.

Pre-clinical studies of IV and subcutaneous formulations of our product in hemophilic animal models demonstrated its duration of action and significantly increased survival. In February 2016, we commenced a Phase 2a dose escalation study to

determine safety and explore efficacy endpoints of our long acting Factor VIIa-CTP for the treatment of bleeding episodes in hemophilia A or B patients with inhibitors to Factor VIII or Factor IX. Factor VIIa-CTP has been granted orphan designation in Europe as well as the U.S.

We believe that the CTP technology may also be broadly applicable to other best-selling therapeutic proteins in the market and provide several key advantages over our competitor's existing products: significant reduction in the number of injections required to achieve the same or superior therapeutic effect from the same dosage; faster commercialization with greater chance of success and lower costs than those typically associated with a new therapeutic protein; and manufacturing using industry-standard biotechnology-based protein production processes.

Oxyntomodulin

In addition to hGH-CTP and Factor VII-CTP, our internal product development program is currently focused on developing a once weekly administered oxyntomodulin for type 2 diabetes and obesity. Our most advanced oxyntomodulin product candidate, TT401, a once-weekly administered peptide for the treatment of type 2 diabetes and associated obesity, is a dual agonist of the GLP-1 (Glucagon-Like Peptide-1) and glucagon receptors. The receptors play an integral role in regulating appetite, food intake, satiety and energy utilization in the body. Stimulating both of the receptors, TT401 has the potential to regulate blood glucose.

TT401 has been evaluated in a Phase 2 study enrolling 420 type 2 diabetes subjects in a 24 week study consisting of a 12-week randomized blinded stage followed by a 12-week open-label stage. The study included four once-weekly dose arms of TT401 (10mg, 15mg, 30mg, 50mg), a placebo arm, and an active comparator arm (exenatide extended release – 2mg). The study was completed in February, 2016. Subjects receiving the highest dose of TT401 peptide once weekly in the study demonstrated significantly superior weight loss compared with currently approved extended release exenatide and placebo after 12 and 24 weeks of treatment. TT401 also provided a reduction in HbA1c, a marker of sugar metabolism, similar to exenatide at weeks 12 and 24. TT401 strengthens OPKO's existing pipeline of oxyntomodulin drug candidates for the treatment of type 2 diabetes and obesity.

OPKO's MOD-6031, currently in a phase 1 study, is a once weekly oxyntomodulin with a proprietary delivery system to slowly release the natural oxyntomodulin, which allows the molecule to penetrate the blood brain barrier. The potential of MOD-6031 to interact with CNS, as well as peripheral receptors, is expected to mimic the natural effect of oxyntomodulin for its effects on satiety and weight loss. MOD-6031 is a long-acting oxyntomodulin comprising oxyntomodulin linked at its N-terminus to a polyethylene glycol ("PEG") linear chain through a proprietary bi-functional hydrolysable linker. Administration of the conjugate into the blood results in slow release of the non-modified natural oxyntomodulin. Our preclinical studies have shown that a single weekly injection of our compound in development significantly inhibited food intake and reduced body weight in obese and diabetic animal models, as well as improving the lipid profile by reducing cholesterol levels in obese and diabetic mice. We initiated a phase 1 study of MOD-6031 in the first quarter of 2016.

We believe oxyntomodulin has potential to be a safe, long term therapy for obese and diabetes type II patients, representing significant market opportunities. More than 380 million are living with diabetes worldwide, of which approximately 90% have type II diabetes. According to the World Health Organization, there are more than 500 million severely overweight or obese people.

APIs

FineTech Pharmaceutical, Ltd. ("FineTech"), is our Israeli-based subsidiary that develops and produces high value, high potency specialty APIs. Through its FDA registered facility in Nesher, Israel, FineTech currently manufactures commercial APIs for sale or license to pharmaceutical companies in the U.S., Canada, Europe and Israel. We believe that FineTech's significant know-how and experience with analytical chemistry and organic syntheses, together with its production capabilities, may play a valuable role in the development of our pipeline of proprietary molecules and compounds for diagnostic and therapeutic products, while providing revenues and profits from its existing API business.

Oligonucleotide Therapeutics

OPKO CURNA, LLC ("CURNA"), previously CURNA Inc., is engaged in the discovery of new drugs for the treatment of a wide variety of illnesses, including cancer, heart disease, metabolic disorders and a range of genetic anomalies. CURNA's broad platform technology utilizes a short, single strand oligonucleotide and is based on the up-regulation of protein production through interference with non-coding RNA's, or natural antisense. This strategy contrasts with established approaches which down-regulate protein production. CURNA has designed a novel type of therapeutic modality, termed AntagoNAT, and has initially demonstrated this approach for up-regulation of several therapeutically relevant proteins in *in vitro* and animal models. We believe that this short, single strand oligonucleotide can be delivered intravenously or subcutaneously without the drug delivery or cell penetration complications typically associated with double stranded siRNA therapeutics. CURNA has identified and developed compounds which increase the production of over 80 key proteins involved in a large number of individual diseases. We have ongoing pre-clinical studies for several of these compounds, with an initial focus on orphan diseases including Dravet Syndrome, Rett Syndrome and MPS-1.

NK-1 Program

We acquired rolapitant and other neurokinin-1 ("NK-1") assets from Merck & Co. In December 2010, we exclusively out-licensed the development, manufacture and commercialization of our lead NK-1 candidate, VARUBI™ (rolapitant), to TESARO. VARUBI™, a potent and selective competitive antagonist of the NK-1 receptor, had successfully completed phase 2 clinical testing for prevention of chemotherapy induced nausea and vomiting, or CINV, and post-operative induced nausea and vomiting. TESARO's NDA for oral VARUBI™ was approved by the FDA in September 2015, and in November 2015, TESARO commenced the commercial launch of VARUBI™ in the United States. TESARO's IV formulation of VARUBI™ is pending FDA approval.

Under the terms of the license, we received a $6.0 million upfront payment from TESARO and are eligible to receive milestone payments of up to $30.0 million upon achievement of certain regulatory and commercial sale milestones (of which $20.0 million has been paid to date) and additional commercial milestone payments of up to $85.0 million if specified levels of annual net sales are achieved. TESARO is also obligated to pay us tiered royalties on annual net sales achieved in the United States and Europe at percentage rates that range from the low double digits to the low twenties, and outside of the United States and Europe at low double-digit percentage rates. TESARO assumed responsibility for clinical development and commercialization of licensed products at its expense. Under the agreement, we will continue to receive royalties on a county-by-country and product-by-product basis until the later of the date that all of the patents rights licensed from us and covering rolapitant expire, are invalidated or are not enforceable, and 12 years from the date of the first commercial sale of the product.

If TESARO elects to develop and commercialize VARUBI™ in Japan through a third-party licensee, TESARO will share equally with us all amounts it receives in connection with such activities, subject to certain exceptions and deductions. The term of the license will remain in force until the expiration of the royalty term unless we terminate the license earlier for TESARO's material breach of the license or bankruptcy. TESARO has a right to terminate the license during the term for any reason on three month's written notice.

We are currently developing an additional NK-1 compound acquired from Merck for pruritis.

Asthma and COPD

In May 2010, we acquired worldwide rights to a novel heparin-derived oligosaccharide which has significant potential in treating asthma and chronic obstructive pulmonary disease ("COPD"). Over 22 million people in the U.S. live with asthma, including nearly 6 million children. Additionally, there are more than 12 million people in the U.S. who have COPD. Currently available therapies often include unwanted side effects and may have limited efficacy. We believe that our product may have an improved efficacy and side effect profile. Our initial studies have demonstrated anti-inflammatory and anti-allergic activity when administered orally or inhaled with inhalers or nebulizers in sheep and mice asthma models. We have also successfully completed human feasibility studies in asthma.

To complement our portfolio of respiratory products, we acquired Inspiro Medical Ltd., a medical device firm developing a new platform to deliver small molecule drugs like corticosteroids and beta agonists or larger molecules to treat respiratory disease. Inspiro's *Inspiromatic* is a "smart" easy-to-use dry powder inhaler with several advantages over existing devices. In a First In Man double blinded clinical study conducted in 30 asthmatic children comparing *Inspiromatic* to a market leading dry powder inhaler, *Inspiromatic* demonstrated superior pulmonary delivery of the active drug.

Commercial Operations

We also intend to continue to leverage our global commercialization expertise to pursue acquisitions of commercial

businesses that will both drive our growth and provide geographically diverse sales and distribution opportunities. During 2015, we acquired EirGen, a growing, profitable and cash flow positive specialty pharmaceutical company based in Ireland. EirGen is focused on the development and commercial supply of high potency, high barrier to entry, pharmaceutical products. Through its facility in Waterford, Ireland, EirGen currently manufactures high potency pharmaceutical products and exports to over 40 countries all over the world. High potency drugs such as those used for cancer chemotherapy are typically unsuitable for manufacture in normal multi-product facilities due to cross contamination risks.

To date, EirGen and its commercial partners have filed several product applications with the FDA in Europe and in Japan. EirGen has a strong research and development portfolio of high barrier to entry drugs and we expect to rapidly expand its drug portfolio. We believe EirGen will play an important role in the development, manufacturing, distribution and approval of a wide variety of drugs in a variety of dosage forms with an emphasis on high potency products.

OPKO Health Europe (previously Farmadiet Group Holding, S.L.) operates primarily in Spain and has more than 20 years of experience in the development, manufacture, marketing, and sale of pharmaceutical, nutraceutical, and veterinary products in Europe.

OPKO Mexico (previously Pharmacos Exakta S.A. de C.V.), is engaged in the manufacture, marketing, sale, and distribution of ophthalmic and other pharmaceutical products to private and public customers in Mexico. OPKO Mexico manufacturers and sells products primarily in the generics market in Mexico, although it also has some proprietary products as well.

OPKO Chile (previously Pharma Genexx, S.A.) markets, sells and distributes pharmaceutical and natural products to the private, hospital, pharmacy and public institutional markets in Chile for a wide range of indications, including, cardiovascular products, vaccines, antibiotics, gastro-intestinal products, and hormones, among others. ALS Distribuidora Limitada ("ALS") is engaged in the business of importation, commercialization and distribution of pharmaceutical products for private markets in Chile. ALS started operations in 2009 as the exclusive product distributor of Arama Laboratorios y Compañía Limitada ("Arama"), a company with more than 20 years of experience in the pharmaceutical products market. In connection with the acquisition of ALS, OPKO acquired all of the product registrations and trademarks previously owned by Arama, as well as the Arama name.

Strategic Investments

We have and may continue to make investments in other early stage companies that we perceive to have valuable proprietary technology and significant potential to create value for OPKO as a shareholder.

RESEARCH AND DEVELOPMENT EXPENSES

During the years ended December 31, 2016 , 2015, and 2014, we incurred $111.2 million , $99.5 million , and $83.6 million , respectively, of research and development expenses related to our various product candidates. During the years ended December 31, 2016 , 2015 and 2014, our research and development expenses primarily consisted of OPKO Biologics and OPKO Renal development programs including, expenses related to the development of hGH-CTP and phase 3 clinical trials for *Rayaldee* .

INTELLECTUAL PROPERTY

We believe that technology innovation is driving breakthroughs in healthcare. We have adopted a comprehensive intellectual property strategy which blends the efforts to innovate in a focused manner with the efforts of our business development activities to strategically in-license intellectual property rights. We develop, protect, and defend our own intellectual property rights as dictated by the developing competitive environment. We value our intellectual property assets and believe we have benefited from early and insightful efforts at understanding diagnostics, as well as the disease and the molecular basis of potential pharmaceutical intervention.

We actively seek, when appropriate and available, protection for our products and proprietary information by means of U.S. and foreign patents, trademarks, trade secrets, copyrights, and contractual arrangements. Patent protection in the pharmaceutical and diagnostic fields, however, can involve complex legal and factual issues. There can be no assurance that any steps taken to protect such proprietary information will be effective.

We own or license-in over a thousand U.S. and foreign patents and applications for our products, product candidates and our outlicensed product candidates. These patents cover pharmaceuticals, diagnostics and other products and their uses, pharmaceutical and diagnostic compositions and formulations and product manufacturing processes. Our patents are filed in various locations worldwide as is appropriate to the particular patent and its use.

Rayaldee

We have multiple U.S. patent families relating to *Rayaldee* . These patents are also filed in multiple countries worldwide. One patent family claims a sustained release oral dosage formulation and a method of treating 25-hydroxy vitamin D insufficiency or deficiency and will not expire until at least February 2027. A second patent family claims a method of administering 25-hydroxy vitamin D_3 by controlled release, a formulation for controlled release of a vitamin D compound, a controlled release oral dosage formulation of a vitamin D compound and a method of treatment, and will not expire until at least April 2028. We also have additional patent applications pending relating to the sustained release formulation and its use which will expire in 2034 and have licensed patents covering the capsule shell. The patents issued in the U.S. covering *Rayaldee* are listed in the Approved Drug Products with Therapeutic Equivalents Evaluations, or the Orange Book.

Rolapitant

The rolapitant line of patents, licensed to TESARO, includes multiple patent families that cover anti-nausea treatment for chemotherapy patients. These U.S. patents are also filed and granted in many countries around the world. One patent family covers the chemical composition of rolapitant and related compounds and expires in December 2023 (with the patent term adjustment.) A patent term extension request was submitted to the USPTO in October 2015 to obtain an additional 1,716 days which will, upon approval, extend the rolapitant compound patent expiration date to August 2028.The second patent family covers pharmaceutical formulations, including a capsule formulation with a related method of use and expires in April of 2027. The third patent family covers particular aspects of the chemical composition of rolapitant as well as certain methods of treating delayed onset nausea and expires in April 2027. The fourth patent family covers a powdered pharmaceutical composition of a crystalline salt of rolapitant and expires in March 2028. The current line of rolapitant patents are approved for oral treatment. Patent applications directed towards IV formulation of rolapitant are currently pending. In addition to the patents covering rolapitant, OPKO has an additional patent family granted worldwide covering another NK-1 antagonist (SCH900978) that is in development for the treatment of pruritus.

hGH-CTP

The hGH-CTP line of patents, which is currently licensed to Pfizer, Inc., includes two main patent families that cover modified human grown hormone treatment. These U.S. patents are also filed in multiple countries around the world. One patent family covers certain CTP modified hGH polypeptides relating to growth hormones and their method of use and expires in February of 2027 (with the exception of two US patents, namely US 8304386 and US 8097435, which expire in Jan 2028 and April 2027, respectively, due to Patent Term Adjustment for each). The second patent family covers cytokine-based polypeptides relating to human growth hormone treatment and expires in 2027. In addition to the CTP patents and applications licensed to Pfizer, OPKO has multiple patent families covering similar biologicals with patents and applications pending in the U.S. and internationally.

TT401 and TT701

In 2016, we acquired Transition Therapeutics, Inc. which is developing multiple drug candidates that include TT401 (a long acting oxyntomodulin) and TT701 (a selective androgen receptor modulator (SARM)), each of which are licensed from Eli Lilly and have granted patents worldwide covering the compounds and their use in their respective indications. U.S. Pat. No. 8367607 covers TT401 and expires in December 2030, without extension. U.S. Pat. No. 7968587 covers TT701 and expires, without extension, in November 2027. In addition, Transition and its affiliates have patented compounds (scyllo-inositol) in development for the treatment of Alzheimer’s disease. The patents are pending or granted in many countries of the world. We and/or our affiliates will seek all available patent term extensions for our product candidates and products.

Because the patent positions of pharmaceutical, biotechnology, and diagnostics companies are highly uncertain and involve complex legal and factual questions, the patents owned and licensed by us, or any future patents, may not prevent other companies from developing similar or therapeutically equivalent products or ensure that others will not be issued patents that may prevent the sale of our products or require licensing and the payment of significant fees or royalties. Furthermore, to the extent that any of our future products or methods are not patentable, that such products or methods infringe upon the patents of third parties, or that our patents or future patents fail to give us an exclusive position in the subject matter claimed by those patents, we will be adversely affected. We may be unable to avoid infringement of third party patents and may have to obtain a license, defend an infringement action, or challenge the validity of the patents in court. A license may be unavailable on terms and conditions acceptable to us, if at all. Patent litigation is costly and time consuming, and we may be unable to prevail in any such patent litigation or devote sufficient resources to even pursue such litigation.

LICENSES AND COLLABORATIVE RELATIONSHIPS

Our strategy is to develop a portfolio of product candidates through a combination of internal development, acquisition, and external partnerships. Collaborations are key to our strategy and we continue to build relationships and forge partnerships in various areas where unmet medical need and commercial opportunities exist. In May 2016, we entered into a license and collaboration with VFMCRP for the development and commercialization of *Rayaldee* in Europe, Canada, Mexico, Australia, South Korea and certain other international markets for the treatment of SHPT in adults with CKD and vitamin D insufficiency. In December 2014, we entered into an exclusive agreement with Pfizer for the development and commercialization of our long-acting hGH-CTP for the treatment of GHD in adults and children, as well as for the treatment of growth failure in children born small for gestational age. Previously, we (or entities we have acquired) have completed strategic licensing transactions with the University of Texas Southwestern Medical Center at Dallas, the President and Fellows of Harvard College, Academia Sinica, The Scripps Research Institute, TESARO, INEOS Healthcare, and Arctic Partners, among others.

COMPETITION

The pharmaceutical and diagnostic testing industries are highly competitive and require an ongoing, extensive search for technological innovation. The industries are characterized by rapidly advancing technologies, intense competition and a strong emphasis on proprietary products. They also require, among other things, the ability to effectively discover, develop, test and obtain regulatory approvals for products, as well as the ability to effectively commercialize, market and promote approved products.

Numerous companies, including major pharmaceutical companies, specialty pharmaceutical companies and specialized biotechnology companies, are engaged in the development, manufacture and marketing of pharmaceutical products competitive with those that we are or intend to commercialize ourselves and through our partners. Competitors to our diagnostics business include major diagnostic companies, reference laboratories, molecular diagnostic firms, universities and research institutions. Most of these companies have substantially greater financial and other resources, larger research and development staffs and more extensive marketing and manufacturing organizations than ours. This enables them, among other things, to make greater research and development investments and efficiently utilize their research and development costs, as well as their marketing and promotion costs, over a broader revenue base. This also provides our competitors with a competitive advantage in connection with the highly competitive product acquisition and product in-licensing process, which may include auctions in which the highest bidder wins. Our competitors may also have more experience and expertise in obtaining marketing approvals from the FDA and other regulatory authorities. In addition to product development, testing, approval, and promotion, other competitive factors in the pharmaceutical and diagnostics industry include industry consolidation, product quality and price, product technology, reputation, customer service, and access to technical information.

In our clinical laboratory operations, we compete with three types of providers in a highly fragmented and competitive industry: hospital laboratories, physician-office laboratories and other independent clinical laboratories. Our major competitors in the New York metropolitan area are two of the largest national laboratories, Quest Diagnostics and Laboratory Corporation of America. Although we are much smaller than these national laboratories, we believe that we compete successfully with them in our region due to our innovative testing services and our level of service. We believe our responses to medical consultation are faster and more personalized than those of the national laboratories. Our client service staff deals only with basic technical questions and those that have medical or scientific significance are referred directly to our senior scientists and medical staff.

We are seeking to commercialize our *4Kscore* product in the U.S., Europe and Mexico in a laboratory setting and to capitalize on near-term commercialization opportunities for our proprietary diagnostic point-of-care system by transitioning laboratory-based tests, including the *4Kscore* , PSA, testosterone and other tests to our point-of-care system. We expect to leverage Bio-Reference's national marketing, sales and distribution resources, along with its 400-person sales and marketing team to support commercialization of the *4Kscore* and *Claros 1* products. Competitors to our diagnostics business are many and include major diagnostic companies, molecular diagnostic firms, universities, and research institutions.

Our ability to commercialize our pharmaceutical and diagnostic test product candidates and compete effectively will depend, in large part, on:

- our ability to meet all necessary regulatory requirements to advance our product candidates through clinical trials and the regulatory approval process in the U.S. and abroad;
- the perception by physicians and other members of the health care community of the safety, efficacy, and benefits of our products compared to those of competing products or therapies;
- our ability to manufacture products we may develop on a commercial scale;
- the effectiveness of our sales and marketing efforts;

- the willingness of physicians to adopt a new diagnostic or treatment regimen represented by our technology;
- our ability to secure reimbursement for our product candidates;
- the price of the products we may develop and commercialize relative to competing products;
- our ability to accurately forecast and meet demand for our product candidates if regulatory approvals are achieved;
- our ability to develop a commercial scale infrastructure either on our own or with a collaborator, which would include expansion of existing facilities, including our manufacturing facilities, development of a sales and distribution network, and other operational and financial systems necessary to support our increased scale;
- our ability to maintain a proprietary position in our technologies; and
- our ability to rapidly expand the existing information technology infrastructure and configure existing operational, manufacturing, and financial systems (on our own or with third party collaborators) necessary to support our increased scale, which would include existing or additional facilities and or partners.

GOVERNMENT REGULATION

The U.S. government regulates healthcare through various agencies, including but not limited to the following: (i) the FDA, which administers the Federal Food, Drug and Cosmetic Act ("FDCA"), as well as other relevant laws; (ii) the Centers for Medicare & Medicaid Services ("CMS"), which administers the Medicare and Medicaid programs; (iii) the Office of Inspector General ("OIG"), which enforces various laws aimed at curtailing fraudulent or abusive practices, including by way of example, the Anti-Kickback Statute, the Physician Self-Referral Law, commonly referred to as the Stark law, the Civil Monetary Penalty Law (including the beneficiary inducement prohibition) ("CMP"), and the laws that authorize the OIG to exclude healthcare providers and others from participating in federal healthcare programs; and (iv) the Office of Civil Rights, which administers the privacy aspects of the Health Insurance Portability and Accountability Act of 1996. All of the aforementioned are agencies within the Department of Health and Human Services ("HHS"). Healthcare is also provided or regulated, as the case may be, by the Department of Defense through its TriCare program, the Department of Veterans Affairs, especially through the Veterans Health Care Act of 1992, the Public Health Service within HHS under Public Health Service Act § 340B (42 U.S.C. § 256b), the Department of Justice through the Federal False Claims Act and various criminal statutes, and state governments under the Medicaid and other state sponsored or funded programs and their internal laws regulating all healthcare activities.

The testing, manufacture, distribution, advertising, and marketing of drug and diagnostic products and medical devices, as well as the performance of clinical testing services, are subject to extensive regulation by federal, state, and local governmental authorities in the U.S., including the FDA, and by similar agencies in other countries. Any drug, diagnostic, or device product that we develop must receive all relevant regulatory approvals or clearances, as the case may be, before it may be marketed in a particular country.

Clinical Laboratory Operations

Our clinical laboratory operations are subject to regulations, which are designed to ensure the quality and reliability of clinical laboratories by mandating specific standards in the areas of personnel qualifications, administration and participation in proficiency testing, patient test management, quality control, quality assurance and inspections. Laboratories must undergo on-site surveys at least every two years, which may be conducted by the Federal Clinical Laboratory Improvement Amendments ("CLIA") program or by a private CMS approved accrediting agency. The sanction for failure to comply with CLIA requirements may be suspension, revocation or limitation of a laboratory's CLIA certificate, which is necessary to conduct business, as well as significant fines and/or criminal penalties. We are also subject to regulation of laboratory operations under state clinical laboratory laws. State clinical laboratory laws may require that laboratories and/or laboratory personnel meet certain qualifications, specify certain quality controls or require maintenance of certain records. Certain states, such as New York, California, Maryland, Pennsylvania, Rhode Island and Florida, each require that we obtain licenses to test specimens from patients residing in those states and additional states may require similar licenses in the future. Only Washington and New York State are exempt under CLIA, as these states have established laboratory quality standards at least as stringent as CLIA's. Potential sanctions for violation of these statutes and regulations include significant fines and the suspension or loss of various licenses, certificates and authorizations.

Our clinical laboratory operations are subject to complex laws, regulations and licensure requirements relating to billing and payment for laboratory services, sales and marketing interactions with ordering physicians and other health care providers, security and confidentiality of health information, and environmental and occupational safety, among others. Changes in regulations often increase the cost of testing or processing claims. Also, these laws may be interpreted or applied by a

prosecutorial, regulatory or judicial authority in a manner that could require us to make changes in our operations, including in our pricing, billing and/or marketing practices in a manner that could adversely affect operations.

Drug Development

The regulatory process, which includes overseeing preclinical studies and clinical trials of each pharmaceutical compound to establish its safety and efficacy and confirmation by the FDA that good laboratory, clinical, and manufacturing practices were maintained during testing and manufacturing, can take many years, requires the expenditure of substantial resources, and gives larger companies with greater financial resources a competitive advantage over us. Delays or terminations of clinical trials that we undertake would likely impair our development of product candidates. Delays or terminations could result from a number of factors, including stringent enrollment criteria, slow rate of enrollment, size of patient population, having to compete with other clinical trials for eligible patients, geographical considerations, and others.

Although accelerated pathways for approval exist for certain drugs, generally, FDA review processes can be lengthy and unpredictable, and we may encounter delays or rejections of our applications when submitted. Generally, in order to gain FDA approval, we must first conduct preclinical studies in a laboratory and in animal models to obtain preliminary information on a compound and to identify any safety problems. The results of these studies are submitted as part of an IND application that the FDA must review before human clinical trials of an investigational drug can commence.

Clinical trials are normally done in three sequential phases and generally take two to five years or longer to complete. Phase 1 consists of testing the drug product in a small number of humans, normally healthy volunteers, to determine preliminary safety and tolerable dose range. Phase 2 usually involves studies in a limited patient population to evaluate the effectiveness of the drug product in humans having the disease or medical condition for which the product is indicated, determine dosage tolerance and optimal dosage, and identify possible common adverse effects and safety risks. Phase 3 consists of additional controlled testing at multiple clinical sites to establish clinical safety and effectiveness in an expanded patient population of geographically dispersed test sites to evaluate the overall benefit-risk relationship for administering the product and to provide an adequate basis for product labeling. Phase 4 clinical trials may be conducted- and are sometimes required - after approval to gain additional experience from the treatment of patients in the intended therapeutic indication. There are also certain situations when drugs and biologics are eligible for one of FDA's expedited approval programs, designed to shorten review and development time.

After completion of clinical trials of a new drug product, FDA and foreign regulatory authority marketing approval must be obtained. Assuming that the clinical data support the product's safety and effectiveness for its intended use, a Biologics License Application (BLA) or an NDA is submitted to the FDA for its review. Generally, it takes one to three years to obtain approval. If questions arise during the FDA review process, approval may take a significantly longer period of time. The testing and approval processes require substantial time and effort and we may not receive approval on a timely basis, if at all, or the approval that we receive may be for a narrower indication than we had originally sought, potentially undermining the commercial viability of the product. Even if regulatory approvals are obtained, a marketed product is subject to continual review, and later discovery of previously unknown problems or failure to comply with the applicable regulatory requirements may result in restrictions on the marketing of a product or withdrawal of the product from the market as well as possible civil or criminal sanctions. For marketing outside the U.S., we also will be subject to foreign regulatory requirements governing human clinical trials and marketing approval for pharmaceutical products. The requirements governing the conduct of clinical trials, product licensing, pricing, and reimbursement vary widely from country to country.

Other than *Rayaldee* , none of our pharmaceutical products under development have been approved for marketing in the U.S. or elsewhere. We may not be able to obtain regulatory approval for any such products under development in a timely manner, if at all. Failure to obtain requisite governmental approvals or failure to obtain approvals of the scope requested will delay or preclude us, or our licensees or marketing partners, from marketing our products, or limit the commercial use of our products, and thereby would have a material adverse effect on our business, financial condition, and results of operations. See "Risk Factors — The results of pre-clinical trials and previous clinical trials for our products may not be predictive of future results, and our current and planned clinical trials may not satisfy the requirements of the FDA or other non-U.S. regulatory authorities."

Device Development

Medical devices are subject to varying levels of premarket regulatory control, the most comprehensive of which requires human clinical trials be conducted before a device receives approval for commercial distribution. The FDA classifies medical devices into one of three classes based upon their risk profile (both to the patient and provider): Class I devices are relatively simple "low risk" technologies, and can be manufactured and distributed with general controls without a premarket clearance or approval from the FDA; Class II devices are somewhat more complex "moderate risk" devices, and require greater scrutiny from the agency, requiring a premarket clearance from the FDA before market entry; Class III devices are "high risk"

technologies inserted or implanted in the body, intended to treat life sustaining functions. These Class III technologies require a premarket approval from the FDA before market entry.

In the U.S., a company generally can obtain permission to distribute a new device in one of two ways. The first applies to a Class II device that is substantially equivalent to a device first marketed prior to May 1976, or to another device marketed after that date, but which was substantially equivalent to a pre-May 1976 device. To obtain FDA permission to distribute the device, a company generally must submit a section 510(k) premarket notification, and receive an FDA order finding substantial equivalence to a predicate device (pre-May 1976 or post-May 1976 device that was substantially equivalent to a pre-May 1976 device) and permitting commercial distribution of that device for its intended use. A 510(k) submission must provide information supporting a claim of substantial equivalence to the predicate device. If clinical data from human experience are required to support the 510(k) submission, these data must be gathered in compliance with investigational device exemption ("IDE"), regulations for investigations performed in the U.S. The 510(k) process is normally used for products of the type that the Company proposes distributing. The FDA review process for premarket notifications submitted pursuant to section 510(k) takes, on average, about 90 days, but it can take substantially longer if the FDA has concerns, and there is no guarantee that the FDA will "clear" the device for marketing, in which case the device cannot be distributed in the U.S. There is also no guarantee that the FDA will deem the applicable device subject to the 510(k) process, as opposed to the more time-consuming, resource-intensive and problematic, PMA process described below.

The second, more comprehensive, PMA process, which can take a year or longer, applies to a new device that is not substantially equivalent to a pre-1976 product or that is to be used in supporting or sustaining life or preventing impairment. These devices are normally Class III devices. For example, most implantable devices are subject to the approval process. Two steps of FDA approval are generally required before a company can market a product in the U.S. that is subject to approval, as opposed to clearance. First, a company must comply with IDE regulations in connection with any human clinical investigation of the device. These regulations permit a company to undertake a clinical study of a "non-significant risk" device without formal FDA approval. Prior express FDA approval is required if the device is a significant risk device. Second, the FDA must review the company's PMA application, which contains, among other things, clinical information acquired under the IDE. The FDA will approve the PMA application if it finds there is reasonable assurance that the device is safe and effective for its intended use. The PMA process takes substantially longer than the 510(k) process and it is conceivable that the FDA would not agree with our assessment that a device that we propose to distribute should be a Class I or Class II device. If that were to occur we would be required to undertake the more complex and costly PMA process. However, for either the 510(k) or the PMA process, the FDA could require us to run clinical trials, which would pose all of the same risks and uncertainties associated with the clinical trials of drugs, described above.

Even when a clinical study has been approved by the FDA or deemed approved, the study is subject to factors beyond a manufacturer's control, including, but not limited to the fact that the institutional review board at a given clinical site might not approve the study, might decline to renew approval which is required annually, or might suspend or terminate the study before the study has been completed. Also, the interim results of a study may not be satisfactory, leading the sponsor to terminate or suspend the study on its own initiative or the FDA may terminate or suspend the study. There is no assurance that a clinical study at any given site will progress as anticipated; there may be an insufficient number of patients who qualify for the study or who agree to participate in the study or the investigator at the site may have priorities other than the study. Also, there can be no assurance that the clinical study will provide sufficient evidence to assure the FDA that the product is safe and effective, a prerequisite for FDA approval of a PMA, or substantially equivalent in terms of safety and effectiveness to a predicate device, a prerequisite for clearance under 510(k). Even if the FDA approves or clears a device, it may limit its intended uses in such a way that manufacturing and distributing the device may not be commercially feasible. For marketing outside the U.S., we also will be subject to foreign regulatory requirements governing clinical trials and marketing approval for medical devices. The requirements governing the conduct of clinical trials, device clearance/approval, pricing, and reimbursement vary widely from country to country. In addition to the regulatory clearance and approval processes described herein, the FDA periodically issues draft guidance documents designed to provide additional detail on or reform aspects of the 510(k) and PMA clearance and approval processes. To the extent the FDA finalizes and implements these documents, the average 510(k) and PMA submission requirements and review times may change and devices that might previously have been cleared under the 510(k) process may require approval under the PMA process (and vice-versa). Additionally, the Medical Device User Fee Amendments of 2012 authorized the FDA to collect user fees for the review of certain premarket submissions received on or after October 1, 2012, including 510(k) and PMA applications. These fees are intended to improve the device review process, but it is still too early to assess the actual impact on the industry.

After clearance or approval to market is given, the FDA and foreign regulatory agencies, upon the occurrence of certain events, are authorized under various circumstances to withdraw the clearance or approval or require changes to a device, its manufacturing process or its labeling or additional proof that regulatory requirements have been met.

A manufacturer of a device approved through the PMA is not permitted to make changes to the device, which affects its safety or effectiveness without first submitting a supplement application to its PMA and obtaining FDA approval for that supplement. In some instances, the FDA may require clinical trials to support a supplement application. A manufacturer of a device cleared through the 510(k) process must submit another premarket notification if it intends to make a change or modification in the device that could significantly affect the safety or effectiveness of the device, such as a significant change or modification in design, material, chemical composition, energy source or manufacturing process. Any change in the intended uses of a PMA device or a 510(k) device requires an approved PMA supplement or a cleared premarket notification. Exported devices are subject to the regulatory requirements of each country to which the device is exported, as well as certain FDA export requirements.

A company that intends to manufacture medical devices is required to register with the FDA before it begins to manufacture the device for commercial distribution. As a result, we and any entity that manufactures products on our behalf will be subject to periodic inspection by the FDA for compliance with the FDA's Quality System Regulation requirements and other regulations. In the European Community, we will be required to maintain certain International Organization for Standardization ("ISO"), certifications in order to sell products and we or our manufacturers undergo periodic inspections by notified bodies to obtain and maintain these certifications. These regulations require us or our manufacturers to manufacture products and maintain documents in a prescribed manner with respect to design, manufacturing, testing and control activities. Further, we are required to comply with various FDA and other agency requirements for labeling and promotion. The Medical Device Reporting regulations require that we provide information to the FDA whenever there is evidence to reasonably suggest that a device may have caused or contributed to a death or serious injury or, if a malfunction were to occur, could cause or contribute to a death or serious injury. In addition, the FDA prohibits us from promoting a medical device for unapproved indications.

Diagnostic Products

Certain of our diagnostic products in development are subject to regulation by the FDA and similar international health authorities. For these products, we have an obligation to adhere to the FDA's cGMP regulations. Additionally, we are subject to periodic FDA inspections, quality control procedures, and other detailed validation procedures. If the FDA finds deficiencies in the validation of our manufacturing and quality control practices, they may impose restrictions on marketing specific products until corrected.

Regulation by governmental authorities in the U.S. and other countries may be a significant factor in how we develop, test, produce and market our diagnostic test products. Diagnostic tests like ours may not fall squarely within the regulatory approval process for pharmaceutical or device products as described above, and the regulatory pathway is not as clear. Although the FDA regulates in vitro diagnostic devices, some companies have successfully commercialized diagnostic tests for various conditions and disease states without seeking clearance or approval for such tests through a 510(k) or PMA approval process. These tests are known as laboratory developed tests ("LDTs") and are designed, manufactured, and used within a single laboratory that is certified under the Clinical Laboratory Improvement Amendments of 1988 ("CLIA"). CLIA is a federal law that regulates clinical laboratories that perform testing on specimens derived from humans for the purpose of providing information for diagnostic, preventative or treatment purpose. Such LDT testing is currently under the purview of CMS and state agencies that provide oversight of the safe and effective use of LDTs.

However, the FDA has consistently asserted that it has the regulatory authority to regulate LDTs despite historically exercising enforcement discretion. In furtherance of that position, the FDA issued two draft guidance documents in October 2014: (1) Framework for Regulatory Oversight of Laboratory Developed Tests (the "Framework Guidance"); and (2) FDA Notification and Medical Device Reporting for Laboratory Developed Tests (the "Notification Guidance"). The Framework Guidance outlines the FDA's plan to adopt over time a risk-based approach to regulating LDTs whereby different classifications of LDTs would be subject to different levels of FDA oversight and enforcement, including, for example, prohibitions on adulteration and misbranding, establishment registration and device listing, premarket notification, banned devices, records and reports, good manufacturing practices, adverse event reporting, premarket review of safety, effectiveness, and clinical validity, and quality system requirements. The Notification Guidance is intended to explain how clinical laboratories should notify the FDA of the LDTs they develop and how to satisfy Medical Device Reporting requirements. However, the FDA indicated in November 2016 that it would delay implementation of the Framework Guidance and the Notification Guidance, and seek additional input from industry. In addition, on January 13, 2017, the FDA published a synthesis of feedback on the Framework Guidance and Notification Guidance titled, Discussion Paper on Laboratory Developed Tests (the "Discussion Paper"). The Discussion Paper provided notice that the FDA would not issue a final guidance on the oversight of LDTs to allow for further public discussion on appropriate oversight approach, and to give congressional authorizing committees the opportunity to develop a legislative solution.

If finalized in the October 2014 format, the Framework Guidance and the Notification Guidance may have a materially adverse effect on the time, cost, and risk associated with the Company's development and commercialization of LDTs for the U.S. market, and there can be no assurance that clearances or approvals sought by the Company will be granted and maintained. However, the FDA's authority to regulate LDTs continues to be challenged, the FDA has indicated that it will continue dialogue with the industry, and the timeline and process for finalizing the draft guidance documents is unknown. We will continue to monitor changes to all domestic and international LDT regulatory policy so as to ensure compliance with the current regulatory scheme.

Impact of Regulation

The FDA in the course of enforcing the FDCA may subject a company to various sanctions for violating FDA regulations or provisions of the FDCA, including requiring recalls, issuing Warning Letters, seeking to impose civil money penalties, seizing devices that the agency believes are non-compliant, seeking to enjoin distribution of a specific type of device or other product, seeking to revoke a clearance or approval, seeking disgorgement of profits and seeking to criminally prosecute a company and its officers and other responsible parties.

The levels of revenues and profitability of biopharmaceutical companies may be affected by the continuing efforts of government and third party payers to contain or reduce the costs of health care through various means. For example, in certain foreign markets, pricing or profitability of therapeutic and other pharmaceutical products is subject to governmental control. In the U.S., there have been, and we expect that there will continue to be, a number of federal and state proposals to implement similar governmental control. In addition, in the U.S. and elsewhere, sales of therapeutic and other pharmaceutical products are dependent in part on the availability and adequacy of reimbursement from third party payers, such as the government or private insurance plans. Third party payers are increasingly challenging established prices, and new products that are more expensive than existing treatments may have difficulty finding ready acceptance unless there is a clear therapeutic benefit. On April 1, 2014, the Protecting Access to Medicare Act of 2014 ("PAMA") was enacted into law. Under PAMA, Medicare payment for clinical diagnostic laboratory tests will be established by calculating a weighted mean of private payer rates with new rates to be effective January 1, 2018. Further, applicable laboratories will be required to report payment rates for covered tests starting in 2016 (to establish the payment rates that will be effective January 1, 2018). Failure to report such data may result in a civil money penalty in an amount of up to $10,000 per day. It is anticipated that the market-based payment system will result in lower reimbursement rates for clinical diagnostic laboratory tests. Even though the permitted annual decrease will be capped through 2023, the cap does not apply to new tests or new advanced diagnostic tests. We cannot assure you that any of our products will be considered cost effective, or that reimbursement will be available or sufficient to allow us to sell them competitively and profitably.

State and Federal Security and Privacy Regulations

The privacy and security regulations under the Health Insurance Portability and Accountability Act of 1996, as amended by the Health Information Technology for Economic and Clinical Health Act of 2009 (the "HITECH Act", and collectively, "HIPAA"), establish comprehensive federal standards with respect to the uses and disclosures of protected health information, or PHI, by health plans and health care providers, in addition to setting standards to protect the confidentiality, integrity and availability of electronic PHI. The regulations establish a complex regulatory framework on a variety of subjects, including:

- the circumstances under which uses and disclosures of PHI are permitted or required without a specific authorization by the patient, including but not limited to treatment purposes, to obtain payments for services and health care operations activities;
- a patient's rights to access, amend and receive an accounting of certain disclosures of PHI;
- the content of notices of privacy practices for PHI; and
- administrative, technical and physical safeguards required of entities that use or receive PHI electronically.

The final omnibus rule implementing the HITECH Act took effect on March 26, 2013. The rule is broad in scope, but certain provisions are particularly significant in light of our business operations. For example, the final "omnibus" rule implementing the HITECH Act:

- Makes clear that situations involving impermissible access, acquisition, use or disclosure of protected health information are now presumed to be a breach unless the covered entity or business associate is able to demonstrate that there is a low probability that the information has been compromised;
- Defines the term "business associate" to include subcontractors and agents that receive, create, maintain or transmit protected health information on behalf of the business associate;

- Establishes new parameters for covered entities and business associates on uses and disclosures of PHI for fundraising and marketing; and
- Establishes clear restrictions on the sale of PHI without patient authorization.

As a provider of clinical laboratory services and as we launch commercial diagnostic tests, we must continue to implement policies and procedures related to compliance with the HIPAA privacy and security regulations, as required by law. The privacy and security regulations provide for significant fines and other penalties for wrongful use or disclosure of PHI, including potential civil and criminal fines and penalties.

Anti-Kickback Laws, Physician Self-Referral Laws, False Claims Act, Civil Monetary Penalties

We are also subject to various federal, state, and international laws pertaining to health care "fraud and abuse," including anti-kickback laws and false claims laws. The federal Anti-Kickback Statute prohibits anyone from knowingly and willfully soliciting, receiving, offering, or paying any remuneration with the intent to refer, or to arrange for the referral or order of, services or items payable under a federal health care program, including the purchase or prescription of a particular drug or the use of a service or device. Recognizing that the Anti-Kickback Statute is broad and may technically prohibit many innocuous or beneficial arrangements, Congress authorized the U.S. Department of Health and Human Services Office of Inspector General, or OIG, to issue a series of regulations, known as "safe harbors." These safe harbors set forth requirements that, if met in their entirety, will assure health care providers and other parties that they will not be prosecuted under the Anti-Kickback Statute. The failure of a transaction or arrangement to fit precisely within one or more safe harbors does not necessarily mean that it is illegal, or that prosecution will be pursued. However, conduct and business arrangements that do not fully satisfy each applicable safe harbor may result in increased scrutiny by government enforcement authorities, such as the OIG.

Violations of the Anti-Kickback Statute are punishable by the imposition of criminal fines, civil money penalties, treble damages, and/or exclusion from participation in federal health care programs. Many states have also enacted similar anti-kickback laws. The Anti-Kickback Statute and similar state laws and regulations are expansive. If the government were to allege against or convict us of violating these laws, there could be a material adverse effect on our business, results of operations, financial condition, and our stock price. Even an unsuccessful challenge could cause adverse publicity and be costly to respond to, which could have a materially adverse effect on our business, results of operations and financial condition. We will consult counsel concerning the potential application of these and other laws to our business and our sales, marketing and other activities and will make good faith efforts to comply with them. However, given the broad reach of federal and state anti-kickback laws and the increasing attention given by law enforcement authorities, we are unable to predict whether any of our activities will be challenged or deemed to violate these laws.

We are also subject to the physician self-referral laws, commonly referred to as the Stark law, which is a strict liability statute that generally prohibits physicians from referring Medicare patients to providers of "designated health services," including clinical laboratories, with whom the physician or the physician's immediate family member has an ownership interest or compensation arrangement, unless an applicable exception applies. Moreover, many states have adopted or are considering adopting similar laws, some of which extend beyond the scope of the Stark law to prohibit the payment or receipt of remuneration for the prohibited referral of patients for designated healthcare services and physician self-referrals, regardless of the source of the payment for the patient's care. If it is determined that certain of our practices or operations violate the Stark law or similar statutes, we could become subject to civil and criminal penalties, including exclusion from the Medicare programs and loss of government reimbursement. The imposition of any such penalties could harm our business.

Another development affecting the health care industry is the increased use of the federal civil False Claims Act and, in particular, actions brought pursuant to the False Claims Act's "whistleblower" or "qui tam" provisions. The False Claims Act, as amended by the Fraud Enforcement and Recovery Act of 2009 and the Patient Protection and Affordable Care Act of 2010 ("Affordable Care Act"), imposes liability on any person or entity who, among other things, knowingly presents, or causes to be presented, a false or fraudulent claim for payment by a federal health care program. We submit claims for services performed at our laboratories. The qui tam provisions of the False Claims Act allow a private individual to bring actions on behalf of the federal government alleging that the defendant has submitted a false claim to the federal government, and to share in any monetary recovery. In recent years, the number of suits brought by private individuals has increased dramatically. In addition, various states have enacted false claim laws analogous to the False Claims Act. Many of these state laws apply where a claim is submitted to any third-party payor and not merely a federal health care program. When an entity is determined to have violated the False Claims Act, it may be required to pay up to three times the actual damages sustained by the government, plus civil penalties for each separate false claim. There are many potential bases for liability under the False Claims Act. Liability arises, primarily, when an entity knowingly submits, or causes another to submit, a false claim for reimbursement to the federal government. The False Claims Act has been used to assert liability on the basis of inadequate care, kickbacks and other improper referrals, improper use of Medicare numbers when detailing the provider of services, and allegations as to misrepresentations with respect to the services rendered. Our activities relating to the sale and marketing of

our products may be subject to scrutiny under these laws. We are unable to predict whether we would be subject to actions under the False Claims Act or a similar state law, or the impact of such actions. However, the costs of defending such claims, as well as any sanctions imposed, could significantly adversely affect our financial performance.

Further, the beneficiary inducement prohibition of the federal Civil Monetary Penalty Law prohibits any entity from offering or transferring to a Medicare or Medicaid beneficiary any remuneration that the entity knows or should know is likely to influence the beneficiary's selection of a particular provider, practitioner or supplier of Medicare or Medicaid payable items or services, including waivers of copayments and deductible amounts (or any part thereof) and transfers of items or services for free or for other than fair market value. On December 7, 2016, the OIG released amendments to the CMP. Some of the amendments may impact our business, such as allowing certain remuneration to financially needy individuals. Entities found in violation may be liable for civil monetary penalties of up to $10,000 for each wrongful act. Although we believe that our sales and marketing practices are in material compliance with all applicable federal and state laws and regulations, relevant regulatory authorities may disagree and violation of these laws, or, our exclusion from such programs as Medicaid and other governmental programs as a result of a violation of such laws, could have a material adverse effect on our business, results of operations, financial condition and cash flows.

Sunshine Act

With the launch of *Rayaldee* , we are now subject to the federal Physician Payments Sunshine Act under the Affordable Care Act, and its implementing regulations (the "Sunshine Act"). The Sunshine Act requires manufacturers of drugs, devices, biological and medical supplies covered by Medicare, Medicaid or the Children's Health Insurance Program, to report information related to certain payments or other transfers of value made or distributed to physicians and teaching hospitals, or to entities or individuals at the request of, or designated on behalf of, the physicians and teaching hospitals. Manufacturers must also report, on an annual basis, certain ownership and investment interests held by physicians and their immediate family members and payments or other "transfers of value" made to such physician owners. A failure to report each payment, other transfer of value, or ownership/investment interest in a timely, accurate, and complete manner may result in civil monetary penalties of up to $150,000 annually. Further, the "knowing" failure to report each payment, other transfer of value, or ownership/investment interest may result in a one million dollar annual penalty. Several other states and a number of countries worldwide have adopted or are considering the adoption of similar transparency laws. Any failure by us to implement proper procedures to track and report on a timely basis transfers of value to physicians and teaching hospitals could result in substantial penalties.

Foreign Corrupt Practices Act

We are also subject to the U.S. Foreign Corrupt Practices Act ("FCPA"), which prohibits corporations and individuals from paying, offering to pay, or authorizing the payment of anything of value to any foreign government official, government staff member, political party, or political candidate in an attempt to obtain or retain business or to otherwise influence a person working in an official capacity. The FCPA also requires public companies to make and keep books and records that accurately and fairly reflect their transactions and to devise and maintain an adequate system of internal accounting controls. Our international activities create the risk of unauthorized payments or offers of payments by our employees, consultants, sales agents or distributors, even though they may not always be subject to our control. We discourage these practices by our employees and agents. However, our existing safeguards and any future improvements may prove to be less than effective, and our employees, consultants, sales agents or distributors may engage in conduct for which we might be held responsible. Any failure by us to adopt appropriate compliance procedures and ensure that our employees and agents comply with the FCPA and applicable laws and regulations in foreign jurisdictions could result in substantial penalties or restrictions on our ability to conduct business in certain foreign jurisdictions.

MANUFACTURING AND QUALITY

Other than our facilities in Waterford, Ireland, Guadalajara, Mexico, Nesher, Israel, and Banyoles, Spain, we currently have no pharmaceutical manufacturing facilities. We have entered into agreements with various third parties for the formulation and manufacture of our pharmaceutical clinical supplies. These suppliers and their manufacturing facilities must comply with FDA regulations, current good laboratory practices ("cGLPs") and current good manufacturing practices ("cGMPs"). We plan to outsource the manufacturing and formulation of our clinical supplies.

The FDA and similar regulatory bodies may inspect our facilities and the facilities of those who manufacture on our behalf worldwide. If the FDA or similar regulatory bodies inspecting our facilities or the facilities of our suppliers find regulatory violations in manufacturing and quality control practices or procedures they may require us to cease partial or complete manufacturing operations until the violations are corrected. They may also impose restrictions on distribution of specific products until the violations are corrected.

Our point-of-care diagnostic system consists of a disposable test cassette and an analyzer. We prepare all necessary test reagents and assemble and package the disposable cassettes at our facility in Woburn, Massachusetts. We rely on third parties for the manufacture of the analyzer.

We are committed to providing high quality products to our customers, and we plan to meet this commitment by working diligently to continue implementing updated and improved quality systems and concepts throughout our organization.

SALES & MARKETING

Our diagnostics business includes Bio-Reference's 400-person sales and marketing team in the U.S. to drive growth and leverage new products, including the *4Kscore* prostate cancer test and the *Claros 1* in-office immunoassay platform. We have a highly specialized, field based 50-person sales and marketing team in the U.S. dedicated to the launch and commercialization of *Rayaldee* . We also have limited sales and marketing personnel in Ireland, Chile, Spain, Mexico and Israel.

EMPLOYEES

As of December 31, 2016 , we had 6,041 full-time employees worldwide. None of our employees are represented by a collective bargaining agreement.

Code of Ethics

We have adopted a Code of Business Conduct and Ethics. We require all employees, including our principal executive officer and principal accounting officer and other senior officers and our employee directors, to read and to adhere to the Code of Business Conduct and Ethics in discharging their work-related responsibilities. Employees are required to report any conduct that they believe in good faith to be an actual or apparent violation of the Code of Business Conduct and Ethics. The Code of Business Conduct and Ethics is available on our website at http://www.OPKO.com.

Available Information

We make available free of charge on or through our web site, at www.opko.com, our Annual Reports on Form 10-K, Quarterly Reports on Form 10-Q, Current Reports on Form 8-K and all amendments to those reports as soon as reasonably practicable after such material is electronically filed with the SEC. Additionally, the public may read and copy any materials we file with the SEC at the SEC's Public Reference Room at 100 F Street, NE, Room 1580, Washington, D.C., 20549. Information regarding operation of the Public Reference Room is available by calling the SEC at 1-800-SEC-0330. Information that we file with the SEC is also available at the SEC's Web-site at www.sec.gov.

ITEM 1A. RISK FACTORS.

You should carefully consider the risks described below, as well as other information contained in this report, including the consolidated financial statements and the notes thereto and "Management's Discussion and Analysis of Financial Condition and Results of Operations." The occurrence of any of the events discussed below could significantly and adversely affect our business, prospects, results of operations, financial condition, and cash flows.

RISKS RELATED TO OUR BUSINESS

We have a history of operating losses and may not become profitable in the near future.

We are not profitable and have incurred losses since our inception. We may not generate substantial revenue from the sale of proprietary pharmaceutical products or certain of our diagnostic products for some time and we have generated only limited revenue from our pharmaceutical operations in the United States, Chile, Mexico, Israel, Spain, and Ireland, and from sale of the *4Kscore* test. We may not successfully leverage the national marketing, sales and distribution resources of Bio-Reference to enhance sales of, and reimbursement for, our *4Kscore* test and our other diagnostic products under development, which would adversely impact our ability to generate substantial revenue from the sale of these products for some time. *Rayaldee* is our only pharmaceutical product that has been approved for marketing, other than those products sold by our Chilean, Mexican, Israeli, Spanish, and Irish subsidiaries. We continue to incur substantial research and development and general and administrative expenses related to our operations and, to date, we have devoted most of our financial resources to research and development, including our pre-clinical development activities and clinical trials. We may incur losses from our operations for the foreseeable future and these losses could increase as we continue our research activities and conduct development of, and seek regulatory approvals and clearances for, our product candidates, and prepare for and begin to commercialize any approved or cleared products, particularly if we are unable to generate profits and cash flow from Bio-Reference and our other commercial businesses. If we are unable to generate profits and cash flow from Bio-Reference and our other commercial businesses, our product candidates fail in clinical trials or do not gain regulatory approval or clearance, or if our approved products and product candidates do not achieve market acceptance, we may never become profitable. In particular, if we are unable to successfully commercialize *Rayaldee* , we may never generate substantial revenues from *Rayaldee* or achieve profitability. In addition, if we are required by the U.S. Food and Drug Administration ("FDA"), to perform studies in addition to those we currently anticipate, our expenses will increase beyond current expectations and the timing of any potential product approval may be delayed. Even if we achieve profitability in the future, we may not be able to sustain profitability in subsequent periods.

We may require substantial additional funding, which may not be available to us on acceptable terms, or at all.

As of December 31, 2016 , we have cash and cash equivalents of $168.7 million . We believe we have sufficient cash and cash equivalents on hand or available to us from operations or through lines of credit to meet our anticipated cash requirements for operations and debt service beyond the next 12 months. We have based this estimate on assumptions that may prove to be wrong or subject to change, and we may be required to use our available capital resources sooner than we currently expect or curtail aspects of our operations in order to preserve our capital. Because of the numerous risks and uncertainties associated with the development and commercialization of our products and product candidates, the success of our relationship with Pfizer and VFMCRP and the success of our integration of Bio-Reference and Transition Therapeutics, we are unable to estimate the amounts of increased capital outlays and operating expenditures associated with our current and anticipated clinical trials and our expanded commercial operations. Our future capital requirements will depend on a number of factors, including the successful commercialization of *Rayaldee* , our relationship with Pfizer and VFMCRP, cash flow generated by Bio-Reference and costs associated with the integration of the Bio-Reference and Transition Therapeutics operations, the continued progress of our research and development of product candidates, the timing and outcome of clinical trials and regulatory approvals, the costs involved in preparing, filing, prosecuting, maintaining, defending, and enforcing patent claims and other intellectual property rights, the status of competitive products, the availability of financing, and our success in developing markets for our products and product candidates.

Until we can generate a sufficient amount of product and service revenue to finance our cash requirements for research, development and operations, we will need to finance future cash needs primarily through public or private equity offerings, debt financings, or strategic collaborations. Our ability to obtain additional capital may depend on prevailing economic conditions and financial, business and other factors beyond our control. Disruptions in the U.S. and global financial markets may adversely impact the availability and cost of credit, as well as our ability to raise money in the capital markets. Economic conditions have been, and continue to be, volatile. Continued instability in these market conditions may limit our ability to

replace, in a timely manner, maturing liabilities and access the capital necessary to fund and grow our business. There can be no assurance that additional capital will be available to us on acceptable terms, or at all, which could adversely impact our business, results of operations, liquidity, capital resources and financial condition. If we are not able to secure additional funding when needed, we may have to delay, reduce the scope of, or eliminate one or more of our clinical trials or research and development programs. To the extent that we raise additional funds by issuing equity securities, our stockholders may experience additional significant dilution, and debt financing, if available, may involve restrictive covenants. To the extent that we raise additional funds through collaboration and licensing arrangements, it may be necessary to relinquish some rights to our technologies or our products and product candidates or grant licenses on terms that may not be favorable to us. We may seek to access the public or private capital markets whenever conditions are favorable, even if we do not have an immediate need for additional capital at that time.

Our research and development activities may not result in commercially viable products.

Many of our product candidates are in the early stages of development and are prone to the risks of failure inherent in drug, diagnostic, and medical device product development. These risks further include the possibility that such products would:

- be found to be ineffective, unreliable, or otherwise inadequate or otherwise fail to receive regulatory approval;
- be difficult or impossible to manufacture on a commercial scale;
- be uneconomical to market or otherwise not be effectively marketed;
- fail to be successfully commercialized if adequate reimbursement from government health administration authorities, private health insurers, and other organizations for the costs of these products is unavailable;
- be impossible to commercialize because they infringe on the proprietary rights of others or compete with products marketed by others that are superior; or
- fail to be commercialized prior to the successful marketing of similar products by competitors.

The results of pre-clinical trials and previous clinical trials for our products may not be predictive of future results, and our current and planned clinical trials may not satisfy the requirements of the FDA or other non-U.S. regulatory authorities.

Positive results from pre-clinical studies and early clinical trial experience should not be relied upon as evidence that later-stage or large-scale clinical trials will succeed. Likewise, there can be no assurance that the results of studies conducted by collaborators or other third parties will be viewed favorably or are indicative of our own future study results. We may be required to demonstrate with substantial evidence through well-controlled clinical trials that our product candidates are either (i) with respect to drugs or Class III devices, safe and effective for use in a diverse population of their intended uses or (ii) with respect to Class I or Class II devices, are substantially equivalent in terms of safety and effectiveness to devices that are already marketed under section 510(k) of the Food, Drug and Cosmetic Act. Success in early clinical trials does not mean that future clinical trials will be successful because product candidates in later-stage clinical trials may fail to demonstrate sufficient safety and efficacy to the satisfaction of the FDA and other non-U.S. regulatory authorities despite having progressed through initial clinical trials.

Further, our drug candidates may not be approved or cleared even if they achieve their primary endpoints in phase 3 clinical trials or registration trials. In addition our diagnostic test candidates may not be approved or cleared, as the case may be, even though clinical or other data are, in our view, adequate to support an approval or clearance. The FDA or other non-regulatory authorities may disagree with our trial design and our interpretation of data from pre-clinical studies and clinical trials. In addition, any of these regulatory authorities may change requirements for the approval or clearance of a product candidate even after reviewing and providing comment on a protocol for a pivotal clinical trial that has the potential to result in FDA and other non-U.S. regulatory authorities' approval. Any of these regulatory authorities may also approve or clear a product candidate for fewer or more limited indications or uses than we request or may grant approval or clearance contingent on the performance of costly post-marketing clinical trials. The FDA or other non-U.S. regulatory authorities may not approve the labeling claims necessary or desirable for the successful commercialization of our product candidates.

The results of our clinical trials may show that our product candidates may cause undesirable side effects, which could interrupt, delay or halt clinical trials, resulting in the denial of regulatory approval by the FDA and other non-U.S. regulatory authorities.

In light of widely publicized events concerning the safety risk of certain drug products, regulatory authorities, members of Congress, the Government Accounting Office, medical professionals, and the general public have raised concerns about potential drug safety issues. These events have resulted in the withdrawal of drug products, revisions to drug labeling that

further limit use of the drug products, and establishment of risk management programs that may, for instance, restrict distribution of drug products. The increased attention to drug safety issues may result in a more cautious approach by the FDA to clinical trials. Data from clinical trials may receive greater scrutiny with respect to safety, which may make the FDA or other regulatory authorities more likely to terminate clinical trials before completion, or require longer or additional clinical trials that may result in substantial additional expense and a delay or failure in obtaining approval or approval for a more limited indication than originally sought.

The failure to successfully commercialize Rayaldee would have a material adverse effect on our business.

In June 2016, the FDA approved the Company's New Drug Application for *Rayaldee* (calcifediol) extended release capsules for the treatment of secondary hyperparathyroidism (SHPT) in adults with stage 3 or 4 chronic kidney disease (CKD) and serum total 25-hydroxyvitamin D levels less than 30 ng/mL. The commercial launch for *Rayaldee* began in November 2016. *Rayaldee* is our only pharmaceutical product approved for marketing in the U.S. and our ability to generate revenue from product sales and achieve profitability is substantially dependent on our ability to effectively commercialize *Rayaldee* . Our failure to successfully commercialize *Rayaldee* would have a material adverse effect on our business, financial condition, cash flows and results of operations.

Additionally, the market perception and reputation of *Rayaldee* and its safety and efficacy are important to our business and the continued acceptance of our product candidates and products. Any negative publicity about *Rayaldee* , such as the discovery of safety issues, adverse events, or even public rumors about such events, could have a material adverse effect on our business. Levels of market acceptance for *Rayaldee* could be impacted by several factors, some of which are not within our control, including but not limited to the:

- safety, efficacy, convenience and cost-effectiveness of our products compared to products of our competitors;
- scope of approved uses and marketing approval;
- availability of patent or regulatory exclusivity;
- timing of market approvals and market entry;
- ongoing regulatory obligations following approval;
- any restrictions or "black box" warnings required on the labeling of such products:
- availability of alternative products from our competitors;
- acceptance of the price of our products;
- effectiveness of our sales forces and promotional efforts;
- the level of reimbursement of our products;
- acceptance of our products on government and private formularies;
- ability to market our products effectively at the retail level or in the appropriate setting of care; and
- the reputation of our products.

If *Rayaldee* fails to gain, or loses, market acceptance, our revenues would be adversely impacted and we may be required to take material impairment charges, all of which could have a material adverse effect on our business, financial condition, cash flows and results of operations.

We rely on a licensing agreement with Vifor Fresenius Medical Renal Care Pharma Ltd ("VFMCRP") for the international development and marketing of Rayaldee. Failure to maintain this license agreement could prevent us from successfully developing and commercializing Rayaldee worldwide.

In May 2016, EirGen, our wholly-owned subsidiary, partnered with VFMCRP through a Development and License Agreement for the development and marketing of Rayaldee in Europe, Canada, Mexico, Australia, South Korea and certain other international markets. The license to VFMCRP potentially covers all therapeutic and prophylactic uses of the product in human patients, provided that initially the license is for the use of the product for the treatment or prevention of secondary

hyperparathyroidism related to patients with stage 3 or 4 chronic kidney disease and vitamin D insufficiency/deficiency. We received a non-refundable and non-creditable upfront payment of $50 million and are eligible to receive up to an additional $232 million upon the achievement of certain regulatory and sales-based milestones. In addition, we are eligible to receive tiered, double digit royalty payments or a minimum royalty, whichever is greater, upon commencement of sales of the product. The success of the Development and License Agreement with VFMCRP is dependent in part on, among other things, the skills, experience and efforts of VFMCRP's employees responsible for the project, VFMCRP's commitment to the arrangement, and the financial condition of VFMCRP, all of which are beyond our control. In the event that VFMCRP, for any reason, including but not limited to early termination of the agreement, fails to devote sufficient resources to successfully develop and market Rayaldee internationally, our ability to earn milestone payments or receive royalty payments would be adversely affected, which would have a material adverse effect on our financial condition and prospects.

Our exclusive worldwide agreement with Pfizer Inc. is important to our business. If we do not successfully develop hGH- CTP and/or Pfizer Inc. does not successfully commercialize hGH-CTP, our business could be adversely affected.

In December 2014, we entered into a development and commercialization agreement with Pfizer relating to our long-acting hGH- CTP for the treatment of growth hormone deficiency in adults and children. Under the terms of the agreements with Pfizer, we received non-refundable and non-creditable upfront payments of $295 million and are eligible to receive up to an additional $275 million upon the achievement of certain regulatory milestones. In addition, we are eligible to receive initial royalty payments associated with the commercialization of hGH-CTP for Adult GHD. Upon the launch of hGH-CTP for Pediatric GHD, the royalties will transition to a regional, tiered gross profit sharing for both hGH-CTP and Pfizer's Genotropin®. We are also responsible for the development program and are obligated to pay for the development up to an agreed cap, which may be exceeded under certain circumstances. If we are required to exceed the agreed cap, it could have a material adverse impact on the expected benefits to us from the Pfizer transaction and our overall financial condition. In the event that the parties are able to obtain regulatory approvals to market a product covered by the agreement, we will be substantially dependent on Pfizer for the successful commercialization of such product. The success of the collaboration arrangement with Pfizer is dependent in part on, among other things, the skills, experience and efforts of Pfizer's employees responsible for the project, Pfizer's commitment to the arrangement, and the financial condition of Pfizer, all of which are beyond our control. In the event that Pfizer, for any reason, including but not limited to early termination of the agreement, fails to devote sufficient resources to successfully develop and commercialize any product resulting from the collaboration arrangement, our ability to earn milestone payments or receive royalty or profit sharing payments would be adversely affected, which would have a material adverse effect on our financial condition and prospects.

Our business is substantially dependent on the success of clinical trials for hGH-CTP and our ability to achieve regulatory approval for the marketing of this product.

There is no assurance that clinical trials for hGH-CTP will be successful or support marketing approval, or that we will be able to obtain marketing approval for the product, or any other product candidate we are developing. Before they can be marketed, our products in development must be approved by the FDA or similar foreign governmental agencies. The process for obtaining FDA approval is both time-consuming and costly, with no certainty of a successful outcome. Before obtaining regulatory approval for the sale of any drug candidate, we must conduct extensive preclinical tests and clinical trials to demonstrate the safety and efficacy in humans of our product candidates. Although the safety profile for hGH-CTP has been consistent with that observed with those treated with daily growth hormone, further testing or patient use may undermine those determinations or unexpected side effects may arise. A failure of any preclinical study or clinical trial can occur at any stage of testing. The results of preclinical and initial clinical testing of these products may not necessarily indicate the results that will be obtained from later or more extensive testing. It also is possible to suffer significant setbacks in advanced clinical trials, even after obtaining promising results in earlier trials. In December 2016, we announced preliminary topline data from our Phase 3, double blind, placebo controlled study of hGH-CTP in adults with GHD. Although there was no statistically significant difference between hGH-CTP and placebo on the primary endpoint of change in trunk fat mass from baseline to 26 weeks, after unblinding the study, we identified an exceptional value of trunk fat mass reduction in the placebo group that may have affected the primary outcome. We believe the exceptional data point warrants an outlier sensitivity analysis of the primary endpoint and related secondary endpoints. Upon completion of the data sensitivity analysis, we plan to discuss the study results and outlier analysis with the regulatory authorities to determine next steps in obtaining regulatory approval. There can be no assurance that the statistical analysis will be favorable or that the FDA will consider the sensitivity analysis. If phase 3 clinical trials for hGH-CTP are not successful or we are unable to achieve regulatory approval for this product, our business will be significantly adversely impacted, which could have a materially adverse effect on our business, financial condition and results of operations.

Our business is substantially dependent on our ability to develop, launch and generate revenue from our diagnostic products.

Our business is dependent on our ability to successfully commercialize the *4Kscore* test and other diagnostic products, including the *Claros 1.* We are committing significant resources to the development and commercialization of these products, and there is no guarantee that we will be able to successfully commercialize these tests. We have limited experience in developing, manufacturing, selling, marketing and distributing diagnostic tests. If we fail to leverage the national marketing, sales and distribution resources of Bio-Reference to enhance sale of, and reimbursement for, the *4Kscore* test and other diagnostic products including the *Claros 1* , our ability to generate substantial revenue from the sale of these products will be adversely impacted. If we are not able to successfully develop, market or sell diagnostic tests we develop for any reason, including the failure to obtain any required regulatory approvals, obtain reimbursement for, or successfully integrate Bio-Reference, we will not generate any meaningful revenue from the sale of such tests. Even if we are able to develop effective diagnostic tests for sale in the marketplace, a number of factors could impact our ability to sell such tests or generate any significant revenue from the sale of such tests, including without limitation:

- our ability to establish and maintain adequate infrastructure to support the commercial launch and sale of our diagnostic tests, including establishing adequate laboratory space, information technology infrastructure, sample collection and tracking systems, electronic ordering and reporting systems and other infrastructure and hiring adequate laboratory and other personnel;
- the success of the validation studies for our diagnostic tests under development and our ability to publish study results in peer-reviewed journals;
- the availability of alternative and competing tests or products and technological innovations or other advances in medicine that cause our technologies to be less competitive;
- the accuracy rates of such tests, including rates of false-negatives and/or false-positives;
- concerns regarding the safety or effectiveness or clinical utility of our diagnostic tests;
- changes in the regulatory environment affecting health care and health care providers, including changes in laws regulating laboratory testing and/or device manufacturers;
- the extent and success of our sales and marketing efforts and ability to drive adoption of our diagnostic tests;
- coverage and reimbursement levels by government payors and private insurers;
- pricing pressures and changes in third-party payor reimbursement policies; and
- intellectual property rights held by others or others infringing our intellectual property rights.

Our business is substantially dependent on our ability to generate profits and cash flow from our laboratory operations.

We have made a significant investment in our laboratory operations through the acquisition of Bio-Reference. We compete in the clinical laboratory market primarily on the basis of the quality of testing, reporting and information systems, reputation in the medical community, the pricing of services and ability to employ qualified personnel. Our failure to successfully compete on any of these factors could result in the loss of clients and a reduction in our revenues and profits. To offset efforts by payors to reduce the cost and utilization of clinical laboratory services, we will need to obtain and retain new clients and business partners and grow the laboratory operations. A reduction in tests ordered or specimens submitted by existing clients, without offsetting growth in our client base, could impact our ability to successfully grow our business and could have a material adverse impact on our ability to generate profits and cash flow from the laboratory operations.

Discontinuation or recalls of existing testing products, failure to develop, or acquire, licenses for new or improved testing technologies; or our clients using new technologies to perform their own tests could adversely affect our business.

From time to time, manufacturers discontinue or recall reagents, test kits or instruments used by us to perform laboratory testing. Such discontinuations or recalls could adversely affect our costs, testing volume and revenue.

The clinical laboratory industry is subject to changing technology and new product introductions. Our success in maintaining a leadership position in genomic and other advanced testing technologies will depend, in part, on our ability to develop, acquire or license new and improved technologies on favorable terms and to obtain appropriate coverage and reimbursement for these technologies. We may not be able to negotiate acceptable licensing arrangements and it cannot be certain that such arrangements will yield commercially successful diagnostic tests. If we are unable to license these testing methods at competitive rates, our research and development costs may increase as a result. In addition, if we are unable to license new or improved technologies to expand our esoteric testing operations, our testing methods may become outdated when compared with our competition and testing volume and revenue may be materially and adversely affected.

Currently, most clinical laboratory testing is categorized as "high" or "moderate" complexity, and thereby is subject to extensive and costly regulation under CLIA. The cost of compliance with CLIA makes it impractical for most physicians to operate clinical laboratories in their offices, and other laws limit the ability of physicians to have ownership in a laboratory and to refer tests to such a laboratory. Manufacturers of laboratory equipment and test kits could seek to increase their sales by marketing point-of-care laboratory equipment to physicians and by selling test kits approved for home or physician office use to both physicians and patients. Diagnostic tests approved for home use are automatically deemed to be "waived" tests under CLIA and may be performed in physician office laboratories as well as by patients in their homes with minimal regulatory oversight. Other tests meeting certain FDA criteria also may be classified as "waived" for CLIA purposes. The FDA has regulatory responsibility over instruments, test kits, reagents and other devices used by clinical laboratories and has taken responsibility from the Centers for Disease Control for classifying the complexity of tests for CLIA purposes. Increased approval of "waived" test kits could lead to increased testing by physicians in their offices or by patients at home, which could affect our market for laboratory testing services and negatively impact our revenues. If our competitors develop and market products that are more effective, safer or less expensive than our products and product candidates, our net revenues, profitability and commercial opportunities will be negatively impacted.

If our competitors develop and market products or services that are more effective, safer or less expensive than our current and future products or services, our revenues, profitability and commercial opportunities will be negatively impacted.

The pharmaceutical, diagnostic, and laboratory testing industries are highly competitive and require an ongoing, extensive search for technological innovation. The industries are characterized by rapidly advancing technologies, intense competition and a strong emphasis on proprietary products. They also require, among other things, the ability to effectively discover, develop, test and obtain regulatory approvals for products, as well as the ability to effectively commercialize, market and promote approved products.

Numerous companies, including major pharmaceutical companies, specialty pharmaceutical companies and specialized biotechnology companies, are engaged in the development, manufacture and marketing of pharmaceutical products competitive with those that we intend to commercialize ourselves and through our partners. Competitors to our diagnostics business include major diagnostic companies, reference laboratories, molecular diagnostic firms, universities and research institutions. Most of these companies have substantially greater financial and other resources, larger research and development staffs and more extensive marketing and manufacturing organizations than ours. This enables them, among other things, to make greater research and development investments and efficiently utilize their research and development costs, as well as their marketing and promotion costs, over a broader revenue base. This also provides our competitors with a competitive advantage in connection with the highly competitive product acquisition and product in-licensing process, which may include auctions in which the highest bidder wins. Our competitors may also have more experience and expertise in obtaining marketing approvals from the FDA and other regulatory authorities. We cannot predict with accuracy the timing or impact of the introduction of potentially competitive products or their possible effect on our sales. In addition to product development, testing, approval, and promotion, other competitive factors in the pharmaceutical and diagnostics industry include industry consolidation, product quality and price, product technology, reputation, customer service, and access to technical information.

In our clinical laboratory operations, we compete with three types of providers in a highly fragmented and competitive industry: hospital laboratories, physician-office laboratories and other independent clinical laboratories. Our major competitors in the New York metropolitan area are two of the largest national laboratories, Quest Diagnostics and Laboratory Corporation of America. We are much smaller than these national laboratories.

The clinical laboratory business is intensely competitive both in terms of price and service. Pricing of laboratory testing services is often one of the most significant factors used by health care providers and third-party payors in selecting a laboratory. As a result of the clinical laboratory industry undergoing significant consolidation, larger clinical laboratory providers are able to increase cost efficiencies afforded by large-scale automated testing. This consolidation results in greater price competition. We may be unable to increase cost efficiencies sufficiently, if at all, and as a result, our net earnings and cash flows could be negatively impacted by such price competition. Additionally, we may also face changes in fee schedules, competitive bidding for laboratory services or other actions or pressures reducing payment schedules as a result of increased or additional competition.

If our competitors market products that are more effective, safer, easier to use or less expensive than our current products and product candidates, or that reach the market sooner than our products and product candidates, we may not achieve commercial success. In addition, the biopharmaceutical, diagnostic, medical device, and laboratory industries are characterized by rapid technological change. Because our research approach integrates many technologies, it may be difficult for us to stay abreast of the rapid changes in each technology. If we fail to stay at the forefront of technological change, we may be unable to compete effectively. Technological advances or products developed by our competitors may render our technologies, products or product candidates obsolete or less competitive.

Our product development activities could be delayed or stopped.

We do not know whether our current or planned pre-clinical and clinical studies will be completed on schedule, or at all. Furthermore, we cannot guarantee that our planned pre-clinical and clinical studies will begin on time or at all. The commencement of our planned clinical trials could be substantially delayed or prevented by several factors, including:

- a limited number of, and competition for, suitable patients with the particular types of disease required for enrollment in our clinical trials or that otherwise meet the protocol's inclusion criteria and do not meet any of the exclusion criteria;
- a limited number of, and competition for, suitable serum or other samples from patients with particular types of disease required for our validation studies;
- a limited number of, and competition for, suitable sites to conduct our clinical trials;
- delay or failure to obtain FDA or other non-U.S. regulatory authorities' approval or agreement to commence a clinical trial;
- delay or failure to obtain sufficient supplies of the product candidate for our clinical trials;
- requirements to provide the drugs, diagnostic tests, or medical devices required in our clinical trial protocols or clinical trials at no cost or cost, which may require significant expenditures that we are unable or unwilling to make;
- delay or failure to reach agreement on acceptable clinical trial agreement terms or clinical trial protocols with prospective sites or investigators; and
- delay or failure to obtain institutional review board ("IRB") approval to conduct or renew a clinical trial at a prospective site.

The completion of our clinical trials could also be substantially delayed or prevented by several factors, including:

- slower than expected rates of patient recruitment and enrollment;
- failure of patients to complete the clinical trial;
- unforeseen safety issues;
- lack of efficacy evidenced during clinical trials;
- termination of our clinical trials by one or more clinical trial sites;
- inability or unwillingness of patients or medical investigators to follow our clinical trial protocols; and
- inability to monitor patients adequately during or after treatment.

Our clinical trials may be suspended or terminated at any time by the FDA, other regulatory authorities, the IRB for any given site, or us. Additionally, changes in regulatory requirements and guidance may occur and we may need to amend clinical trial protocols to reflect these changes with appropriate regulatory authorities. Amendments may require us to resubmit our clinical trial protocols to IRBs for re-examination, which may impact the costs, timing, or successful completion of a clinical trial. Any failure or significant delay in commencing or completing clinical trials for our product candidates could materially harm our results of operations and financial condition, as well as the commercial prospects for our product candidates.

We currently have a fifty person specialized sales and marketing team for Rayaldee in the U.S. If we are unable to develop or maintain a strong sales, marketing and distribution capability on our own or through collaborations with marketing partners, we will not be successful in commercializing Rayaldee or our other pharmaceutical products or product candidates in the U.S.

Other than our 50 person specialized sales and marketing team dedicated to *Rayaldee* , we currently have no pharmaceutical marketing, sales or distribution capabilities in the U.S. Any failure or inability to maintain adequate sales, marketing, and distribution capabilities would adversely impact the commercialization of *Rayaldee* or our other pharmaceutical products or candidates. If we are not successful in commercializing our existing and future pharmaceutical products and product candidates, either on our own or through collaborations with one or more third parties, our product revenue will suffer and we may incur significant additional losses.

Our approved products or product candidates may have undesirable side effects and cause our products to be taken off the market.

If we or others identify undesirable side effects caused by our products:

- regulatory authorities may require the addition of labeling statements, specific warnings, a contraindication, or field alerts to physicians and pharmacies;
- regulatory authorities may withdraw their approval of the product and require us to take our approved product off the market;
- we may be required to change the way the product is administered, conduct additional clinical trials, or change the labeling of the product;
- we may have limitations on how we promote our products;
- sales of products may decrease significantly;
- we may be subject to litigation or product liability claims; and
- our reputation may suffer.

Any of these events could prevent us from achieving or maintaining market acceptance of the affected product or could substantially increase our commercialization costs and expenses, which in turn could delay or prevent us from generating significant revenues from its sale.

Our inability to meet regulatory quality standards applicable to our manufacturing and quality processes and to address quality control issues in a timely manner could delay the production and sale of our products or result in recalls of products.

Manufacturing or design defects, unanticipated use of our products, or inadequate disclosure of risks relating to the use of our products could lead to injury or other adverse events. These events could lead to recalls or safety alerts relating to our products (either voluntary or required by governmental authorities) and could result, in certain cases, in the removal of a product from the market. Any recall could result in significant costs as well as negative publicity that could reduce demand for our products. Personal injuries relating to the use of our products can also result in product liability claims being brought against us. In some circumstances, such adverse events could also cause delays in new product approvals.

We are committed to providing high quality products to our customers, and we plan to meet this commitment by working diligently to continue implementing updated and improved quality systems and concepts throughout our organization. We cannot assure you that we will not have quality control issues in the future, which may result in warning letters and citations from the FDA. If we receive any warning letters from the FDA in the future, there can be no assurances regarding the length of time or cost it will take us to resolve such quality issues to our satisfaction and to the satisfaction of the FDA. If our remedial actions are not satisfactory to the FDA, we may have to devote additional financial and human resources to our efforts, and the FDA may take further regulatory actions against us including, but not limited to, assessing civil monetary penalties or imposing a consent decree on us, which could result in further regulatory constraints, including the governance of our quality system by a third party. Our inability to resolve these issues or the taking of further regulatory action by the FDA may weaken our competitive position and have a material adverse effect on our business, results of operations and financial condition.

We manufacture pharmaceutical products in Ireland, Mexico, Spain, and Israel. We also prepare necessary test reagents and assemble and package the cassettes for our point-of-care diagnostic system at our facility in Woburn, Massachusetts. Any quality control issues at our facilities may weaken our competitive position and have a material adverse effect on our business results of operations and financial condition.

As a medical device manufacturer, we are required to register with the FDA and are subject to periodic inspection by the FDA for compliance with its Quality System Regulation ("QSR") requirements, which require manufacturers of medical devices to adhere to certain regulations, including testing, quality control and documentation procedures. Compliance with applicable regulatory requirements is subject to continual review and is monitored rigorously through periodic inspections by the FDA. In addition, most international jurisdictions have adopted regulatory approval and periodic renewal requirements for medical devices, and we must comply with these requirements in order to market our products in these jurisdictions. In the European Community, we are required to maintain certain ISO certifications in order to sell our products and must undergo periodic inspections by notified bodies to obtain and maintain these certifications. Further, some emerging markets rely on the FDA's Certificate for Foreign Government ("CFG") in lieu of their own regulatory approval requirements. Our failure, or our manufacturers' failure to meet QSR, ISO, or any other regulatory requirements or industry standards could delay production of our products and lead to fines, difficulties in obtaining regulatory clearances, recalls or other consequences, which could, in turn, have a material adverse effect on our business, results of operations, and our financial condition.

Failure to establish, and perform to, appropriate quality standards to assure that the highest level of quality is observed in the performance of our testing services could adversely affect the results of our operations and adversely impact our reputation.

The provision of clinical testing services, including anatomic pathology services, and related services, and the design, manufacture and marketing of diagnostic products involve certain inherent risks. The services that we provide and the products that we design, manufacture and market are intended to provide information for healthcare providers in providing patient care. Therefore, users of our services and products may have a greater sensitivity to errors than the users of services or products that are intended for other purposes.

Similarly, negligence in performing our services can lead to injury or other adverse events. We may be sued under physician liability or other liability law for acts or omissions by our pathologists, laboratory personnel and hospital employees who are under the supervision of our hospital-based pathologists. We are subject to the attendant risk of substantial damages awards and risk to our reputation.

Even after we receive regulatory approval or clearance to market our product candidates, the market may not be receptive to our products.

Our products may not gain market acceptance among physicians, patients, health care payors and/or the medical community. We believe that the degree of market acceptance will depend on a number of factors, including:

- timing of market introduction of competitive products;
- safety and efficacy of our product compared to other products;
- prevalence and severity of any side effects;
- potential advantages or disadvantages over alternative treatments;
- strength of marketing and distribution support;
- price of our products, both in absolute terms and relative to alternative treatments;
- availability of coverage and reimbursement from government and other third-party payors;
- potential product liability claims;
- limitations or warnings contained in a product's regulatory authority-approved labeling; and
- changes in the standard of care for the targeted indications for any of our products or product candidates, which could reduce the marketing impact of any claims that we could make following applicable regulatory authority approval.

In addition, our efforts to educate the medical community and health care payors on the benefits of our products and product candidates may require significant resources and may never be successful. If our products do not gain market acceptance, it would have a material adverse effect on our business, results of operations, and financial condition.

If our products are not covered and eligible for reimbursement from government and third party payors, we may not be able to generate significant revenue or achieve or sustain profitability.

The coverage and reimbursement status of newly approved or cleared drugs, diagnostic and laboratory tests is uncertain, and failure of our pharmaceutical products, diagnostic tests or laboratory to be adequately covered by insurance and eligible for adequate reimbursement could limit our ability to market any future product candidates we may develop and decrease our ability to generate revenue from any of our existing and future product candidates that may be approved or cleared. The commercial success of our existing and future products in both domestic and international markets will depend in part on the availability of coverage and adequate reimbursement from third-party payors, including government payors, such as the Medicare and Medicaid programs, managed care organizations, and other third-party payors. The government and other third-party payors are increasingly attempting to contain health care costs by limiting both insurance coverage and the level of reimbursement for new drugs and diagnostic tests and, as a result, they may not cover or provide adequate payment for our product candidates. These payors may conclude that our products are less safe, less effective, or less cost-effective than existing or later-introduced products. These payors may also conclude that the overall cost of the procedure using one of our devices exceeds the overall cost of the competing procedure using another type of device, and third-party payors may not approve our products for insurance coverage and adequate reimbursement.

The failure to obtain coverage and adequate or any reimbursement for our products, or health care cost containment initiatives that limit or restrict reimbursement for our products, may reduce any future product revenue. Even though a drug

(not administered by a physician) may be approved by the FDA, this does not mean that a Prescription Drug Plan ("PDP"), a private insurer operating under Medicare Part D, will list that drug on its formulary or will set a reimbursement level. PDPs are not required to make every FDA-approved drug available on their formularies. If our drug products are not listed on sufficient number of PDP formularies or if the PDPs' levels of reimbursement are inadequate, our business, results of operations, and financial condition could be materially adversely affected.

Additionally, our failure to comply with applicable Medicare, Medicaid and other governmental payor rules could result in our inability to participate in a governmental payor program, our returning funds already paid to us, civil monetary penalties, criminal penalties and/or limitations on the operational function of our laboratory. If we were unable to receive reimbursement under a governmental payor program, a substantial portion of our revenues would be lost, which would adversely affect our results of operations and financial condition.

As we evolve from a company primarily involved in development to a company also involved in commercialization of our pharmaceutical and diagnostic products as well as our laboratory testing services, we may encounter difficulties in managing our growth and expanding our operations successfully.

As we advance our product candidates and expand our business, we will need to expand our development, regulatory and commercial infrastructure. As our operations expand, we expect that we will need to manage additional relationships with various third parties, collaborators and suppliers. Maintaining these relationships and managing our future growth will impose significant added responsibilities on members of our management. We must be able to: manage our development efforts and operations effectively; manage our clinical trials effectively; hire, train and integrate additional management, administrative and sales and marketing personnel; improve our managerial, development, operational and finance systems; implement and manage an effective marketing strategy; and expand our facilities, all of which may impose a strain on our administrative and operational infrastructure.

Furthermore, we may acquire additional businesses, products or product candidates that complement or augment our existing business. Integrating any newly acquired business or product could be expensive and time-consuming. We may not be able to integrate any acquired business or product successfully or operate any acquired business profitably. Our future financial performance will depend, in part, on our ability to manage any future growth effectively and our ability to integrate any acquired businesses. We may not be able to accomplish these tasks, and our failure to accomplish any of them could prevent us from successfully growing our company, which would have a material adverse effect on our business, results of operations and financial condition.

Our success is dependent to a significant degree upon the involvement and efforts of our Chairman and Chief Executive Officer, Phillip Frost, M.D.

Our success is dependent to a significant degree upon the efforts of our Chairman and Chief Executive Officer, Phillip Frost, M.D., who is essential to our business. The departure of our CEO for whatever reason or the inability of our CEO to continue to serve in his present capacity could have a material adverse effect upon our business, financial condition, and results of operations. Our CEO has a highly regarded reputation in the pharmaceutical and medical industry and attracts business opportunities and assists both in negotiations with acquisition targets, investment targets, and potential joint venture partners. Our CEO has also provided financing to the Company, both in terms of a credit agreement and equity investments. If we lost his services, our relationships with acquisition and investment targets, joint ventures, and investors may suffer and could cause a material adverse impact on our operations, financial condition, and the value of our Common Stock.

If we fail to attract and retain key management and scientific personnel, we may be unable to successfully operate our business and develop or commercialize our products and product candidates.

We will need to expand and effectively manage our managerial, operational, sales, financial, development, and other resources in order to successfully operate our business and pursue our research, development, and commercialization efforts for our products and product candidates. Our success depends on our continued ability to attract, retain, and motivate highly qualified management and pre-clinical and clinical personnel. The loss of the services or support of any of our senior management, particularly Dr. Phillip Frost, our Chairman of the Board and CEO, could delay or prevent the development and commercialization of our products and product candidates.

If the FDA or other applicable regulatory authorities approve generic products that compete with any of our products or product candidates, the sale of our products or product candidates may be adversely affected.

Once an NDA is approved, the product covered thereby becomes a "listed drug" which, in turn can be relied upon by potential competitors in support of an approval of an abbreviated new drug application, or ANDA, or 505(b)(2) application. U.S. laws and other applicable policies provide incentives to manufacturers to create modified, non-infringing versions of a

drug to facilitate the approval of an ANDA or other application for a generic substitute. These manufacturers might only be required to conduct a relatively inexpensive study to show that their product has the same active ingredient(s), dosage form, strength, route of administration, and conditions of use, or labeling, as our product or product candidate and that the generic product is bioequivalent to ours, meaning it is absorbed in the body at the same rate and to the same extent as our product or product candidate. These generic equivalents, which must meet the same quality standards as branded pharmaceuticals, would be significantly less costly than ours to bring to market and companies that produce generic equivalents are generally able to offer their products at lower prices. Thus, after the introduction of a generic competitor, a significant percentage of sales of any branded product is typically lost to the generic product. Accordingly, competition from generic equivalents to our products or product candidates would materially adversely impact our revenues, profitability and cash flows and substantially limit our ability to obtain a return on the investments that we have made in our products and product candidates.

If we fail to acquire and develop other products or product candidates at all or on commercially reasonable terms, we may be unable to diversify or grow our business.

We intend to continue to rely on acquisitions and in-licensing as a source of our products and product candidates for development and commercialization. The success of this strategy depends upon our ability to identify, select, and acquire pharmaceutical and diagnostic products, drug delivery technologies, and medical device product candidates. Proposing, negotiating, and implementing an economically viable product acquisition or license is a lengthy and complex process. We compete for partnering arrangements and license agreements with pharmaceutical, biotechnology and medical device companies, and academic research institutions. Our competitors may have stronger relationships with third parties with whom we are interested in collaborating and/or may have more established histories of developing and commercializing products.

Most of our competitors also have substantially greater financial and other resources than us. As a result, our competitors may have a competitive advantage in entering into partnering arrangements with such third parties, as such partnering arrangements are often decided in an auction process in which the highest bidder wins. In addition, even if we find promising products and product candidates, and generate interest in a partnering or strategic arrangement to acquire such products or product candidates, we may not be able to acquire rights to additional product candidates or approved products on terms that we find acceptable, or at all.

We expect that any product candidate to which we acquire rights will require additional development efforts prior to commercial sale, including extensive clinical testing and approval or clearance by the FDA and other non-U.S. regulatory authorities. All product candidates are subject to the risks of failure inherent in pharmaceutical, diagnostic test or medical device product development, including the possibility that the product candidate will not be shown to be sufficiently safe and effective for approval by regulatory authorities. Even if the product candidates are approved or cleared for marketing, we cannot be sure that they would be capable of economically feasible production or commercial success. If we fail to acquire or develop other product candidates that are capable of economically feasible production and commercial success, our business, results of operations and financial condition and cash flows may be materially adversely affected.

We rely on third parties to manufacture and supply our pharmaceutical and diagnostic products and product candidates.

If our manufacturing partners are unable to produce our products in the amounts that we require, we may not be able to establish a contract and obtain a sufficient alternative supply from another supplier on a timely basis and in the quantities we require. We expect to continue to depend on third-party contract manufacturers for the foreseeable future.

Our products and product candidates require precise, high quality manufacturing. Any of our contract manufacturers will be subject to ongoing periodic unannounced inspection by the FDA and other non-U.S. regulatory authorities to ensure strict compliance with QSR regulations for devices or cGMPs for drugs, and other applicable government regulations and corresponding standards relating to matters such as testing, quality control, and documentation procedures. If our contract manufacturers fail to achieve and maintain high manufacturing standards in compliance with QSR or cGMPs, we may experience manufacturing errors resulting in patient injury or death, product recalls or withdrawals, delays or interruptions of production or failures in product testing or delivery, delay or prevention of filing or approval of marketing applications for our products, cost overruns, or other problems that could seriously harm our business.

Any performance failure on the part of our contract manufacturers could delay clinical development or regulatory approval or clearance of our product candidates or commercialization of our products and product candidates, depriving us of potential product revenue and resulting in additional losses. In addition, our dependence on a third party for manufacturing may adversely affect our future profit margins. Our ability to replace an existing manufacturer may be difficult because the number of potential manufacturers is limited and the FDA must approve any replacement manufacturer before it can begin manufacturing our products or product candidates. Such approval would result in additional non-clinical testing and compliance inspections. It may be difficult or impossible for us to identify and engage a replacement manufacturer on acceptable terms in a timely manner, or at all.

Independent clinical investigators and contract research organizations that we engage to conduct our clinical trials may not be diligent, careful or timely.

We depend on independent clinical investigators to conduct our clinical trials. Contract research organizations may also assist us in the collection and analysis of data. These investigators and contract research organizations will not be our employees, and we will not be able to control, other than by contract, the amount of resources, including time, that they devote to products that we develop. If independent investigators fail to devote sufficient resources to the development of product candidates or clinical trials, or if their performance is substandard, it will delay the marketing approval or clearance and commercialization of any products that we develop. Further, the FDA requires that we comply with standards, commonly referred to as good clinical practice, for conducting, recording and reporting clinical trials to assure that data and reported results are credible and accurate and that the rights, integrity, and confidentiality of trial subjects are protected. If our independent clinical investigators and contract research organizations fail to comply with good clinical practice, the results of our clinical trials could be called into question and the clinical development of our product candidates could be delayed.

Failure of clinical investigators or contract research organizations to meet their obligations to us or comply with federal regulations and good clinical practice procedures could adversely affect the clinical development of our product candidates and harm our business, results of operations, and financial condition.

If the validity of an informed consent from a subject was to be challenged, it may negatively impact our product development efforts.

We take steps to ensure that all clinical data and genetic and other biological samples are collected from subjects who provide informed consent for the data and samples and we work to ensure that the subjects from whom our data and samples are collected do not retain any proprietary or commercial rights to the data or samples or any discoveries derived from them. However, because we may collect data and samples from countries that are governed by a number of different regulatory regimes, there are many complex legal questions relating to the adequacy of informed consent that we must continually address. The adequacy of any given subject's informed consent may be challenged in the future, and any given informed consent may prove unlawful or otherwise inadequate for our purposes. Any findings against us, or our clinical collaborators, could obligate us to stop using some of our clinical samples, which in turn may hinder our product development efforts. Such a result would also likely involve legal challenges that may consume our management and financial resources.

Failure to timely or accurately bill for our services could have a material adverse effect on our business.

Billing for laboratory testing services is extremely complicated and is subject to extensive and non-uniform rules and administrative requirements. Depending on the billing arrangement and applicable law, we bill various payors, such as patients, insurance companies, Medicare, Medicaid, physicians, hospitals and employer groups. Changes in laws and regulations could increase the complexity and cost of our billing process. Additionally, in the U.S., third-party payors generally require billing codes on claims for reimbursement that describe the services provided. For laboratory services, the American Medical Association establishes most of the billing codes using a data code set called Current Procedural Terminology, or CPT, codes. Each third-party payor generally develops payment amounts and coverage policies for their beneficiaries or members that ties to the CPT code established for the laboratory test and, therefore, coverage and reimbursement may differ by payor even if the same billing code is reported for claims filing purposes. For laboratory tests without a specific billing code, payors often review claims on a claim-by-claim basis and there are increased uncertainties as to coverage and eligibility for reimbursement.

We implemented a new billing system for our laboratory business in the third quarter of 2016. The adoption of the new billing system, which replaced the old billing system, poses several challenges relating to, among other things, training of personnel, communication of new rules and procedures, changes in corporate culture, migration of data, and the potential instability of the new system.

Incorrect or incomplete documentation and billing information could result in non-payment for services rendered or having to pay back amounts incorrectly billed and collected. Further, the failure to timely or correctly bill could lead to various penalties, including: (1) exclusion from participation in CMS and other government programs; (2) asset forfeitures; (3) civil and criminal fines and penalties; and (4) the loss of various licenses, certificates and authorizations necessary to operate our business, any of which could have a material adverse effect on our results of operations or cash flows.

Failure in our information technology systems, including by cybersecurity attacks or other data security incidents, could significantly increase testing turn-around time or billing processes and otherwise disrupt our operations.

Our operations depend, in part, on the continued performance of our information technology systems. Our information technology systems are potentially vulnerable to physical or electronic break-ins, computer viruses and similar disruptions. In

addition, we are in the process of integrating the information technology systems of our recently acquired subsidiaries, and we may experience system failures or interruptions as a result of this process. Sustained system failures or interruption of our systems in one or more of our laboratory operations could disrupt our ability to process laboratory requisitions, perform testing, provide test results in a timely manner and/or bill the appropriate party. Failure of our information technology systems could adversely affect our business, profitability and financial condition.

A successful cybersecurity attack or other data security incident could result in the misappropriation and/or loss of confidential or personal information, create system interruptions, or deploy malicious software that attacks our systems. It is possible that a cybersecurity attack might not be noticed for some period of time. The occurrence of a cybersecurity attack or incident could result in business interruptions from the disruption of our information technology systems, or negative publicity resulting in reputational damage with our customers, shareholders and other stakeholders and/or increased costs to prevent, respond to or mitigate cybersecurity events. In addition, the unauthorized dissemination of sensitive personal information or proprietary or confidential information could expose us or other third-parties to regulatory fines or penalties, litigation and potential liability, or otherwise harm our business.

Healthcare plans have taken steps to control the utilization and reimbursement of healthcare services, including clinical test services.

We also face efforts by non-governmental third-party payors, including healthcare plans, to reduce utilization and reimbursement for clinical testing services.

The healthcare industry has experienced a trend of consolidation among healthcare insurance plans, resulting in fewer but larger insurance plans with significant bargaining power to negotiate fee arrangements with healthcare providers, including clinical testing providers. These healthcare plans, and independent physician associations, may demand that clinical testing providers accept discounted fee structures or assume all or a portion of the financial risk associated with providing testing services to their members through capped payment arrangements. In addition, some healthcare plans have been willing to limit the PPO or POS laboratory network to only a single national laboratory to obtain improved fee-for-service pricing. There are also an increasing number of patients enrolling in consumer driven products and high deductible plans that involve greater patient cost-sharing.

The increased consolidation among healthcare plans also has increased the potential adverse impact of ceasing to be a contracted provider with any such insurer. The 2010 Health Care Reform Legislation includes provisions, such as the creation of healthcare exchanges, which may encourage healthcare insurance plans to increase exclusive contracting.

We expect continuing efforts to reduce reimbursements, to impose more stringent cost controls and to reduce utilization of clinical test services. These efforts, including future changes in third-party payor rules, practices and policies, or ceasing to be a contracted provider to a healthcare plan, may have a material adverse effect on our business.

The success of our business may be dependent on the actions of our collaborative partners.

We have entered into and expect in the future to enter into collaborative arrangements with established multi-national pharmaceutical, diagnostic, and medical device companies, which will finance or otherwise assist in the development, manufacture and marketing of products incorporating our technology. We anticipate deriving some revenues from research and development fees, license fees, milestone payments, and royalties from collaborative partners. Our prospects, therefore, may depend to some extent upon our ability to attract and retain collaborative partners and to develop technologies and products that meet the requirements of prospective collaborative partners. In addition, our collaborative partners may have the right to abandon research projects, guide strategy regarding prosecution of relevant patent applications and terminate applicable agreements, including funding obligations, prior to or upon the expiration of the agreed-upon research terms. There can be no assurance that we will be successful in establishing collaborative arrangements on acceptable terms or at all, that collaborative partners will not terminate funding before completion of projects, that our collaborative arrangements will result in successful product commercialization, or that we will derive any revenues from such arrangements. To the extent that we are unable to develop and maintain collaborative arrangements, we would need substantial additional capital to undertake research, development, and commercialization activities on our own.

If we are unable to obtain and enforce patent protection for our products, our business could be materially harmed.

Our success depends, in part, on our ability to protect proprietary methods and technologies that we develop or license under the patent and other intellectual property laws of the U.S. and other countries, so that we can prevent others from unlawfully using our inventions and proprietary information. However, we may not hold proprietary rights to some patents required for us to commercialize our products and product candidates. Because certain U.S. patent applications are confidential, third parties may have filed patent applications for technology covered by our pending patent applications without

our being aware of those applications, and our patent applications may not have priority over those applications. For this and other reasons, we or our third-party collaborators may be unable to secure desired patent rights, thereby losing desired exclusivity. If licenses are not available to us on acceptable terms, we may not be able to market the affected products or conduct the desired activities, unless we challenge the validity, enforceability, or infringement of the third-party patent or otherwise circumvent the third-party patent.

Our strategy depends on our ability to rapidly identify and seek patent protection for our discoveries. In addition, we will rely on third-party collaborators to file patent applications relating to proprietary technology that we develop jointly during certain collaborations. The process of obtaining patent protection is expensive and time-consuming. If our present or future collaborators fail to file and prosecute all necessary and desirable patent applications at a reasonable cost and in a timely manner, our business will be adversely affected. Unauthorized parties may be able to obtain and use information that we regard as proprietary.

The issuance of a patent does not guarantee that it is valid or enforceable. Any patents we have obtained, or obtain in the future, may be challenged, invalidated, unenforceable, or circumvented. Moreover, the U.S. Patent and Trademark Office ("USPTO") may commence interference proceedings involving our patents or patent applications. In addition, court decisions may introduce uncertainty in the enforceability or scope of patents owned by biotechnology, pharmaceutical, and medical device companies. Any challenge to, finding of unenforceability or invalidation or circumvention of, our patents or patent applications would be costly, would require significant time and attention of our management, and could have a material adverse effect on our business, results of operations and financial condition.

Our pending patent applications may not result in issued patents. The patent position of pharmaceutical, biotechnology, diagnostic, and medical device companies, including ours, is generally uncertain and involves complex legal and factual considerations. The standards that the USPTO and its foreign counterparts use to grant patents are not always applied predictably or uniformly and can change. There is also no uniform, worldwide policy regarding the subject matter and scope of claims granted or allowable in pharmaceutical, biotechnology, diagnostic, or medical device patents. Accordingly, we do not know the degree of future protection for our proprietary rights or the breadth of claims that will be allowed in any patents issued to us or to others. The legal systems of certain countries do not favor the aggressive enforcement of patents, and the laws of foreign countries may not protect our rights to the same extent as the laws of the U.S. Therefore, the enforceability or scope of our owned or licensed patents in the U.S. or in foreign countries cannot be predicted with certainty, and, as a result, any patents that we own or license may not provide sufficient protection against competitors. We may not be able to obtain or maintain patent protection for our pending patent applications, those we may file in the future, or those we may license from third parties.

We cannot assure you that any patents that have issued, that may issue, or that may be licensed to us will be enforceable or valid, or will not expire prior to the commercialization of our products and product candidates, thus allowing others to more effectively compete with us. Therefore, any patents that we own or license may not adequately protect our products and product candidates or our future products, which could have a material adverse effect on our business, results of operations, and financial condition.

If we are unable to protect the confidentiality of our proprietary information and know-how, the value of our technology and products could be adversely affected.

In addition to patent protection, we also rely on other proprietary rights, including protection of trade secrets, know-how, and confidential and proprietary information. To maintain the confidentiality of trade secrets and proprietary information, we will seek to enter into confidentiality agreements with our employees, consultants, and collaborators upon the commencement of their relationships with us. These agreements generally require that all confidential information developed by the individual or made known to the individual by us during the course of the individual's relationship with us be kept confidential and not disclosed to third parties. Our agreements with employees also generally provide that any inventions conceived by the individual in the course of rendering services to us shall be our exclusive property.

However, we may not obtain these agreements in all circumstances, and individuals with whom we have these agreements may not comply with their terms. In the event of unauthorized use or disclosure of our trade secrets or proprietary information, these agreements, even if obtained, may not provide meaningful protection, particularly for our trade secrets or other confidential information. To the extent that our employees, consultants, or contractors use technology or know-how owned by third parties in their work for us, disputes may arise between us and those third parties as to the rights in related inventions.

Adequate remedies may not exist in the event of unauthorized use or disclosure of our confidential information. The disclosure of our trade secrets would impair our competitive position and may materially harm our business, financial condition, and results of operations.

We will rely heavily on licenses from third parties. Failure to comply with the provisions of these licenses could result in the loss of our rights under the license agreements.

Many of the patents and patent applications in our patent portfolio are not owned by us, but are licensed from third parties. Such license agreements give us rights for the commercial exploitation of the patents resulting from the respective patent applications, subject to certain provisions of the license agreements. Failure to comply with these provisions could result in the loss of our rights under these license agreements. Our inability to rely on these patents and patent applications, which are the basis of our technology, would have a material adverse effect on our business, results of operations and financial condition.

We license patent rights to certain of our technology from third-party owners. If such owners do not properly maintain or enforce the patents underlying such licenses, our competitive position and business prospects will be harmed.

We have obtained licenses from, among others, INEOS Healthcare, UT Southwestern, the President and Fellows of Harvard College, The Scripps Research Institute, Arctic Partners, TESARO, and Academia Sinica, among others, that are necessary or useful for our business. In addition, we intend to enter into additional licenses of third-party intellectual property in the future. We cannot guarantee that no third parties will step forward and assert inventorship or ownership in our in-licensed patents. In some cases, we may rely on the assurances of our licensors that all ownership rights have been secured and that all necessary agreements are intact or forthcoming.

Our success will depend in part on our ability or the ability of our licensors to obtain, maintain, and enforce patent protection for our licensed intellectual property and, in particular, those patents to which we have secured exclusive rights in our field. We or our licensors may not successfully prosecute the patent applications which are licensed to us. Even if patents issue in respect of these patent applications, we or our licensors may fail to maintain these patents or may determine not to pursue litigation against other companies that are infringing these patents. Without protection for the intellectual property we have licensed, other companies might be able to offer substantially identical products for sale, which could adversely affect our competitive business position and harm our business, results of operations and financial condition.

Our commercial success depends significantly on our ability to operate without infringing the patents and other proprietary rights of third parties.

Other entities may have or obtain patents or proprietary rights that could limit our ability to develop, manufacture, use, sell, offer for sale or import products, or impair our competitive position. In addition, other entities may have or obtain patents or proprietary rights that cover our current research and preclinical studies. The U.S. case law pertaining to statutory exemptions to patent infringement for those who are using third party patented technology in the process of pursuing FDA regulatory approval changes over time. Lawsuits involving such exemptions are very fact intensive and it is currently unclear under U.S. case law whether preclinical studies would always qualify for such an exemption, and whether such exemptions would apply to research tools. To the extent that our current research and preclinical studies may be covered by the patent rights of others, the risk of suit may continue after such patents expire because the statute of limitations for patent infringement runs for six years. To the extent that a third party develops and patents technology that covers our products, we may be required to obtain licenses to that technology, which licenses may not be available or may not be available on commercially reasonable terms, if at all. If licenses are not available to us on acceptable terms, we will not be able to market the affected products or conduct the desired activities, unless we challenge the validity, enforceability or infringement of the third-party patent, or circumvent the third-party patent, which would be costly and would require significant time and attention of our management. Third parties may have or obtain by license or assignment valid and enforceable patents or proprietary rights that could block us from developing products using our technology. Our failure to obtain a license to any technology that we require may materially harm our business, financial condition, and results of operations.

If we become involved in patent litigation or other proceedings related to a determination of rights, we could incur substantial costs and expenses, substantial liability for damages or be required to stop our product development and commercialization efforts.

Third parties may sue us for infringing their patent rights. Likewise, we may need to resort to litigation to enforce a patent issued or licensed to us or to determine the scope and validity of proprietary rights of others. In addition, a third-party may claim that we have improperly obtained or used its confidential or proprietary information. Furthermore, in connection with our third-party license agreements, we generally have agreed to indemnify the licensor for costs incurred in connection with litigation relating to intellectual property rights. The cost to us of any litigation or other proceeding relating to intellectual property rights, even if resolved in our favor, could be substantial, and the litigation would divert our management's efforts. Some of our competitors may be able to sustain the costs of complex patent litigation more effectively than we can because they have substantially greater resources. Uncertainties resulting from the initiation and continuation of any litigation could

limit our ability to continue our operations. Our involvement in patent litigation and other proceedings could have a material adverse effect on our business, results of operations, and financial condition.

If any parties successfully claim that our creation or use of proprietary technologies infringes upon their intellectual property rights, we might be forced to pay damages, potentially including treble damages, if we are found to have willfully infringed on such parties' patent rights. In addition to any damages we might have to pay, a court could require us to stop the infringing activity or obtain a license. Any license required under any patent may not be made available on commercially acceptable terms, if at all. In addition, such licenses are likely to be non-exclusive and, therefore, our competitors may have access to the same technology licensed to us. If we fail to obtain a required license and are unable to design around a patent, we may be unable to effectively market some of our technology and products, which could limit our ability to generate revenues or achieve profitability and possibly prevent us from generating revenue sufficient to sustain our operations.

We have faced, and may in the future face, intellectual property infringement claims that could be time-consuming and costly to defend, and could result in our loss of significant rights and the assessment of treble damages.

We may from time to time receive notices of claims of infringement and misappropriation or misuse of other parties' proprietary rights. Some of these additional claims may also lead to litigation. We cannot assure you that we will prevail in such actions, or that other actions alleging misappropriation or misuse by us of third-party trade secrets, infringement by us of third-party patents and trademarks or the validity of our patents, will not be asserted or prosecuted against us.

We may also initiate claims to defend our intellectual property or to seek relief on allegations that we use, sell, or offer to sell technology that incorporates third party intellectual property. Intellectual property litigation, regardless of outcome, is expensive and time-consuming, could divert management's attention from our business and have a material negative effect on our business, operating results or financial condition. If there is a successful claim of infringement against us, we may be required to pay substantial damages (including treble damages if we were to be found to have willfully infringed a third party's patent) to the party claiming infringement, develop non-infringing technology, stop selling our tests or using technology that contains the allegedly infringing intellectual property or enter into royalty or license agreements that may not be available on acceptable or commercially practical terms, if at all. Our failure to develop non-infringing technologies or license the proprietary rights on a timely basis could harm our business.

It is possible that a third party or patent office might take the position that one or more patents or patent applications constitute prior art in the field of genomic-based diagnostics. In such a case, we might be required to pay royalties, damages and costs to firms who own the rights to these patents, or we might be restricted from using any of the inventions claimed in those patents.

We may become subject to product liability for our diagnostic tests, clinical trials, pharmaceutical products and medical device products.

Our success depends on the market's confidence that we can provide reliable, high-quality pharmaceuticals, medical devices, and diagnostics tests. Our reputation and the public image of our products or technologies may be impaired if our products fail to perform as expected or our products are perceived as difficult to use. Our products are complex and may develop or contain undetected defects or errors. Furthermore, if product or future product candidate harms people, or is alleged to be harmful, we may be subject to costly and damaging product liability claims brought against us by clinical trial participants, consumers, health care providers, corporate partners or others. We have product liability insurance covering commercial sales of current products and our ongoing clinical trials. Any defects or errors could lead to the filing of product liability claims, which could be costly and time-consuming to defend and result in substantial damages. If we experience a sustained material defect or error, this could result in loss or delay of revenues, delayed market acceptance, damaged reputation, diversion of development resources, legal claims, increased insurance costs or increased service and warranty costs, any of which could materially harm our business. We cannot assure you that our product liability insurance would protect our assets from the financial impact of defending a product liability claim. A product liability claim could have a serious adverse effect on our business, financial condition and results of operations.

Adverse results in material litigation matters or governmental inquiries could have a material adverse effect upon our business and financial condition.

We may from time to time become subject in the ordinary course of business to material legal action related to, among other things, intellectual property disputes, professional liability, contractual and employee-related matters, as well as inquiries from governmental agencies and Medicare or Medicaid carriers requesting comment and information on allegations of billing irregularities and other matters that are brought to their attention through billing audits, third parties or other sources. The health care industry is subject to substantial federal and state government regulation and audit. Legal actions could result in

substantial monetary damages as well as damage to the Company's reputation with customers, which could have a material adverse effect upon our results of operations and financial position.

Significant developments stemming from the recent U.S. federal elections could have a material adverse effect on us.

Under the new Presidential administration and U.S. Congress, we expect that there will be many changes to existing U.S. laws, regulations, and standards, as well as to existing international agreements. These changes in U.S. social, political, regulatory and economic conditions may lead to conditions, both domestically and abroad where we conduct international operations, that will have an adverse effect on our business. Because of this uncertainty regarding existing law, we cannot quantify or predict with any certainty the likely impact of such change on our business model, prospects, financial condition or results of operations. We cannot assure you as to the ultimate content, timing, or effect of changes, nor is it possible at this time to estimate the impact of any such potential legislation.

RISKS RELATED TO REGULATORY COMPLIANCE

Our ability to successfully operate our laboratories and develop and commercialize certain of our diagnostic tests and LDTs will depend on our ability to maintain required regulatory licensures and comply with all the CLIA requirements.

In order to successfully operate our laboratory business and offer certain of our diagnostic tests and LDTs, we must maintain our CLIA certification and comply with all the CLIA requirements. CLIA is designed to ensure the quality and reliability of clinical laboratories by mandating specific standards in the areas of personnel qualifications, administration and participation in proficiency testing, patient test management, quality control, quality assurance and inspections. The sanction for failure to comply with CLIA requirements may be suspension, revocation or limitation of a laboratory's CLIA certificate, which is necessary to conduct business, as well as significant fines and/or criminal penalties. Laboratories must undergo on-site surveys at least every two years, which may be conducted by the Federal CLIA program or by a private CMS approved accrediting agency such as CAP, among others. Our laboratories are also subject to regulation of laboratory operations under state clinical laboratory laws as will be any new CLIA-certified laboratory that we establish or acquire. State clinical laboratory laws may require that laboratories and/or laboratory personnel meet certain qualifications, specify certain quality controls or require maintenance of certain records. Certain states, such as California, Florida, Maryland, New York, Pennsylvania and Rhode Island, require that laboratories obtain licenses to test specimens from patients residing in those states and additional states may require similar licenses in the future. If we are unable to obtain and maintain licenses from states where required, we will not be able to process any samples from patients located in those states. Only Washington and New York States are exempt under CLIA, as these states have established laboratory quality standards at least as stringent as CLIA's. Potential sanctions for violation of these statutes and regulations include significant fines and the suspension or loss of various licenses, certificates and authorizations, which could adversely affect our business and results of operations.

If we fail to comply with CLIA requirements, HHS or state agencies could require us to cease diagnostic testing. Even if it were possible for us to bring our laboratories back into compliance after failure to comply with such requirements, we could incur significant expenses and potentially lose revenues in doing so. Moreover, new interpretations of current regulations or future changes in regulations under CLIA may make it difficult or impossible for us to comply with the CLIA classification, which would significantly harm our business and materially adversely affect our financial condition.

The regulatory approval process is expensive, time consuming and uncertain and may prevent us or our collaboration partners from obtaining approvals for the commercialization of some or all of our product candidates.

The research, testing, manufacturing, labeling, approval, selling, marketing, and distribution of drug products, diagnostic products, or medical devices are subject to extensive regulation by the FDA and other non-U.S. regulatory authorities, which regulations differ from country to country. In general, we are not permitted to market our product candidates in the U.S. until we receive approval of a Biologics License Application (BLA), an approval of a NDA, a clearance letter under the premarket notification process, or 510(k) process, or an approval of a PMA from the FDA. To date, we have only submitted one NDA which was approved in June 2016. We have not received marketing approval or clearance for any of our diagnostic product candidates, other than a CE Mark for our point-of-care PSA test and a CE Mark for our *4Kscore test.* Obtaining approval of a NDA or PMA can be a lengthy, expensive, and uncertain process. With respect to medical devices, while the FDA reviews and clears a premarket notification in as little as three months, there is no guarantee that our products will qualify for this more expeditious regulatory process, which is reserved for Class I and II devices, nor is there any assurance that even if a device is reviewed under the 510(k) process that the FDA will review it expeditiously or determine that the device is substantially equivalent to a lawfully marketed non-PMA device. If the FDA fails to make this finding, then we cannot market the device. In lieu of acting on a premarket notification, the FDA may seek additional information or additional data which would further delay our ability to market the product. Furthermore, we are not permitted to make changes to a device approved through the PMA or 510(k) which affects the safety or efficacy of the device without first submitting a supplement application to the PMA and obtaining FDA approval or cleared premarket notification for that supplement. In some cases, the FDA may require

clinical trials to support a supplement application. In addition, failure to comply with FDA, non-U.S. regulatory authorities, or other applicable U.S. and non-U.S. regulatory requirements may, either before or after product approval or clearance, if any, subject our company to administrative or judicially imposed sanctions, including, but not limited to the following:

- restrictions on the products, manufacturers, or manufacturing process;
- adverse inspectional observations (Form 483), warning letters, or non-warning letters incorporating inspectional observations;
- civil and criminal penalties;
- injunctions;
- suspension or withdrawal of regulatory approvals or clearances;
- product seizures, detentions, or import bans;
- voluntary or mandatory product recalls and publicity requirements;
- total or partial suspension of production;
- imposition of restrictions on operations, including costly new manufacturing requirements; and
- refusal to approve or clear pending NDAs or supplements to approved NDAs, applications or pre-market notifications.

Regulatory approval of an NDA or NDA supplement, PMA, PMA supplement or clearance pursuant to a pre-market notification is not guaranteed, and the approval or clearance process, as the case may be, is expensive and may, especially in the case of an NDA or PMA application, take several years. The FDA also has substantial discretion in the drug and medical device approval and clearance process. Failure can occur at any stage, and we could encounter problems that cause us to abandon clinical trials or to repeat or perform additional pre-clinical studies and clinical trials. The number of pre-clinical studies and clinical trials that will be required for FDA approval or clearance varies depending on the drug or medical device candidate, the disease or condition that the drug or medical device candidate is designed to address, and the regulations applicable to any particular drug or medical device candidate. The FDA can delay, limit or deny approval or clearance of a drug or medical device candidate for many reasons, including:

- a drug candidate may not be deemed safe or effective;
- a medical device candidate may not be deemed to be substantially equivalent to a lawfully marketed non-PMA device, in the case of a premarket notification;
- the FDA may not find the data from pre-clinical studies and clinical trials sufficient;
- the FDA may not approve our or our third-party manufacturer's processes or facilities; or
- the FDA may change its approval or clearance policies or adopt new regulations.

Beyond these risks, there is also a possibility that our licensees or collaborators could decide to discontinue a study at any time for commercial, scientific or other reasons.

Regulation by governmental authorities in the U.S. and other countries may be a significant factor in how we develop, test, produce and market our diagnostic test products. Diagnostic tests like ours may not fall squarely within the regulatory approval process for pharmaceutical or device products as described above, and the regulatory pathway is not as clear. It is possible that the diagnostic products developed by us or our collaborators will be regulated as medical devices by the FDA and comparable agencies of other countries and require either PMA or 510(k) clearance from the FDA prior to marketing. Some companies that have successfully commercialized diagnostic tests for various conditions and disease states have not sought clearance or approval for such tests through the traditional 510(k) or PMA processes, and have instead utilized a process involving LDTs through a CLIA- certified laboratory. CLIA is a federal law that regulates clinical laboratories that perform testing on specimens derived from humans for the purpose of providing information for diagnostic, preventative or treatment purpose. In such instances, the CLIA lab is solely responsible for the development, validation and commercialization of the assay.

Such LDT testing is currently under the purview of CMS and state agencies that provide oversight of the safe and effective use of LDTs. However, the FDA has consistently asserted that it has the regulatory authority to regulate LDTs despite historically exercising enforcement discretion. In furtherance of that position, the FDA issued two draft guidance documents in October 2014: Framework for Regulatory Oversight of Laboratory Developed Tests (the "Framework Guidance"); and (2) FDA Notification and Medical Device Reporting for Laboratory Developed Tests (the "Notification Guidance"). The Framework

Guidance outlines the FDA's plan to adopt over time a risk-based approach to regulating LDTs whereby different classifications of LDTs would be subject to different levels of FDA oversight and enforcement, including, for example, prohibitions on adulteration and misbranding, establishment registration and device listing, premarket notification, banned devices, records and reports, good manufacturing practices, adverse event reporting, premarket review of safety, effectiveness, and clinical validity, and quality system requirements. The Notification Guidance is intended to explain how clinical laboratories should notify the FDA of the LDTs they develop and how to satisfy Medical Device Reporting requirements. On January 13, 2017, the FDA published a synthesis of feedback on the Framework Guidance and Notification Guidance titled, Discussion Paper on Laboratory Developed Tests (the "Discussion Paper"). The Discussion Paper provided notice that the FDA would not issue a final guidance on the oversight of LDTs to allow for further public discussion on appropriate oversight approach, and to give congressional authorizing committees the opportunity to develop a legislative solution. The outcome and ultimate impact of such proposals on the business is difficult to predict at this time. However, the FDA's authority to regulate LDTs continues to be challenged, and the timeline and process for finalizing the draft guidance documents is unknown. We will continue to monitor changes to all domestic and international LDT regulatory policy so as to ensure compliance with the current regulatory scheme.

The terms of approvals and ongoing regulation of our products may limit how we manufacture and market our products and product candidates, which could materially impair our ability to generate anticipated revenues.

We, our approved or cleared products, and the manufacturers of our products are subject to continual review. Our approved or cleared products may only be promoted for its indicated uses. Marketing, labeling, packaging, adverse event reporting, storage, advertising, and promotion for our approved products will be subject to extensive regulatory requirements. We train our marketing and sales force against promoting our products for uses outside of the cleared or approved indications for use, known as "off-label uses." If the FDA determines that our promotional materials or training constitute promotion of unsupported claims or an off-label use, it could request that we modify our training or promotional materials or subject us to regulatory or enforcement actions, including the issuance of an untitled letter, a warning letter, injunction, seizure, civil fine or criminal penalties. It is also possible that other federal, state or foreign enforcement authorities might take action if they consider our business activities to constitute promotion of an off-label use, which could result in significant penalties, including, but not limited to, criminal, civil and/or administrative penalties, damages, fines, disgorgement, exclusion from participation in government healthcare programs, and the curtailment of our operations.

We and the manufacturers of our products are also required to comply with current Good Manufacturing Practices ("cGMP") regulations or the FDA's QSR regulations, which include requirements relating to quality control and quality assurance as well as the corresponding maintenance of records and documentation. Moreover, device manufacturers are required to report adverse events by filing Medical Device Reports with the FDA, which reports are publicly available.

Further, regulatory agencies must approve manufacturing facilities before they can be used to manufacture our products, and these facilities are subject to ongoing regulatory inspection. If we fail to comply with the regulatory requirements of the FDA and other non-U.S. regulatory authorities, or if previously unknown problems with our products, manufacturers, or manufacturing processes are discovered, we could be subject to administrative or judicially imposed sanctions. Furthermore, any limitation on indicated uses for a product or product candidate or our ability to manufacture and promote a product or product candidate could significantly and adversely affect our business, results of operations, and financial condition.

In addition, the FDA and other non-U.S. regulatory authorities may change their policies and additional regulations may be enacted that could prevent or delay marketing approval or clearance of our product candidates. We cannot predict the likelihood, nature or extent of government regulation that may arise from future legislation or administrative action, either in the U.S. or abroad. If we are not able to maintain regulatory compliance, we would likely not be permitted to market our products or product candidates and we may not achieve or sustain profitability, which would materially impair our ability to generate anticipated revenues.

If we fail to comply with complex and rapidly evolving laws and regulations, we could suffer penalties, be required to pay substantial damages or make significant changes to our operations.

We are subject to numerous federal and state regulations, including, but not limited to:

- federal and state laws applicable to billing and claims payment;
- federal and state laboratory anti-mark-up laws;
- federal and state anti-kickback laws;
- physician self-referral law;
- federal and state false claims laws;

- federal self-referral and financial inducement prohibition laws, commonly known as the Stark Law, and the state equivalents;
- federal and state laws governing laboratory licensing and testing, including CLIA;
- federal and state laws governing the development, use and distribution of LDTs;
- HIPAA, along with the revisions to HIPAA as a result of the HITECH Act, and analogous state laws;
- federal, state and foreign regulation of privacy, security, electronic transactions and identity theft;
- federal, state and local laws governing the handling, transportation and disposal of medical and hazardous waste;
- Occupational Safety and Health Administration rules and regulations;
- changes to laws, regulations and rules as a result of the Health Care Reform Law; and
- changes to other federal, state and local laws, regulations and rules, including tax laws.

If we fail to comply with existing or future applicable laws and regulations, we could suffer civil or criminal penalties, including the loss of our licenses to operate our laboratories and our ability to participate in federal and state healthcare programs. Different interpretations and enforcement policies of existing statutes and regulations applicable to our business could subject our current practices to allegations of impropriety or illegality, or could require us to make significant changes to our operations. In addition, we cannot predict the impact of future legislation and regulatory changes on our business or assure that we will be able to obtain or maintain the regulatory approvals required to operate our business.

As a result of political, economic, and regulatory influences, the healthcare delivery industry in the U.S. is under intense scrutiny and subject to fundamental changes. We cannot predict which reform proposals will be adopted, when they may be adopted, or what impact they may have on us. The costs associated with complying with federal and state regulations could be significant and the failure to comply with any such legal requirements could have a material adverse effect on our financial condition, results of operations, and liquidity.

Failure to maintain the security of patient-related information or compliance with security requirements could damage our reputation with customers, cause us to incur substantial additional costs and become subject to litigation.

Pursuant to HIPAA, and certain similar state laws, we must comply with comprehensive privacy and security standards with respect to the use and disclosure of protected health information. If the Company does not comply with existing or new laws and regulations related to protecting privacy and security of personal or health information, it could be subject to monetary fines, civil penalties, or criminal sanctions. Under the HITECH amendments to HIPAA, HIPAA was expanded to require certain data breach notification, to extend certain HIPAA privacy and security standards directly to business associates, to heighten penalties for noncompliance, and enhance enforcement efforts.

In March 2014, CareEvolve, Bio-Reference's wholly-owned connectivity subsidiary, became aware that there had been a HIPAA breach with regard to one of its servers managed at an internet service provider site called XAND, where the server was inadvertently configured so that it was accessible to the Internet for a brief period. Upon becoming aware of the matter, CareEvolve immediately took the server offline and removed all indexed files that could be located on the internet. In the meantime, an Internet data collection "robot" operated by Google, Inc. had briefly acquired data from a server and made it available to Internet searches. To the best of our knowledge, there were no known disclosures of this Patient Health Information ("PHI") to unauthorized parties. Bio-Reference self-reported this incident to the appropriate government agency, the Office of Civil Rights ("OCR") and is awaiting further discussions, investigation and action by OCR. Since March 2014, Bio-Reference has taken meaningful steps to further improve its HIPAA and cybersecurity platform, including hiring a dedicated Chief Information Security Officer, engaging independent and specialized IT consultants to conduct HIPAA and cybersecurity assessments, reviewing data security and internal safeguards, and continuously implementing enhanced security measures to minimize the risk of similar occurrences in the future.

In February 2016, Bio-Reference discovered that some of its phlebotomists had taken pictures of lab test requests with their personal smartphones at several nursing homes in Florida in order to transmit test information to the Bio-Reference laboratory. The records photographed did not contain any passwords, security codes or financial information and BRLI has no evidence that any PHI was improperly used or accessed. After becoming aware of this situation, Bio-Reference immediately undertook an internal investigation, reviewed and modified its data security and internal safeguards, and notified the breach to potentially affected individuals and OCR. Bio-Reference is awaiting further discussions, investigation and action by OCR.

We have and will continue to receive certain personal and financial information about our clients and their patients. In addition, we depend upon the secure transmission of confidential information over public networks. While we take all

reasonable and prudent steps to protect this protected information, a compromise in our security systems that results in client or patient personal information being obtained by unauthorized persons or our failure to comply with security requirements for financial transactions could adversely affect our reputation with our clients and result in litigation against us or the imposition of penalties, all of which may adversely impact our results of operations, financial condition and liquidity.

Failure to comply with environmental, health and safety laws and regulations, including the Federal Occupational Safety and Health Administration Act, the Needlestick Safety and Prevention Act and the Comprehensive Medical Waste Management Act, could result in fines and penalties and loss of licensure, and have a material adverse effect upon our business.

We are subject to licensing and regulation under federal, state and local laws and regulations relating to the protection of the environment and human health and safety, including laws and regulations relating to the handling, transportation and disposal of medical specimens, infectious and hazardous waste and radioactive materials, as well as regulations relating to the safety and health of laboratory employees. The Federal Occupational Safety and Health Administration has established extensive requirements relating to workplace safety for health care employers, including clinical laboratories, whose workers may be exposed to blood-borne pathogens such as HIV and the hepatitis B virus. These requirements, among other things, require work practice controls, protective clothing and equipment, training, medical follow-up, vaccinations and other measures designed to minimize exposure to, and transmission of, blood-borne pathogens. In addition, the Needlestick Safety and Prevention Act requires, among other things, that we include in our safety programs the evaluation and use of engineering controls such as safety needles if found to be effective at reducing the risk of needlestick injuries in the workplace.

Waste management is subject to federal and state regulations governing the transportation and disposal of medical waste including bodily fluids. Federal regulations require licensure of interstate transporters of medical waste. In New Jersey, we are subject to the Comprehensive Medical Waste Management Act ("CMWMA"), which requires us to register as a generator of special medical waste. All of our medical waste is disposed of by a licensed interstate hauler. The hauler provides a manifest of the disposition of the waste products as well as a certificate of incineration, which is retained by us. These records are audited by the State of New Jersey on a yearly basis. We are also subject to the Federal Hazardous materials transportation law, 49 U.S.C. 5101 et seq., and the Hazardous Materials Regulations ("HMR"), 49 CFR parts 171-180. The federal government has classified hazardous medical waste as hazardous materials for the purpose of regulation. These regulations preempt state regulation, which must be "substantively the same," "the non-federal requirement must conform "in every significant respect to the federal requirement. Editorial and other similar de minimis changes are permitted," 49 CFR 107.202(d).

Failure to comply with such federal, state and local laws and regulations could subject us to denial of the right to conduct business, fines, criminal penalties and/or other enforcement actions, any of which could have a material adverse effect on our business. In addition, compliance with future legislation could impose additional requirements us, which may be costly.

Our failure or the failure of third-party payors or physicians to comply with ICD-10-CM Code Set, and our failure to comply with other emerging electronic transaction standards could adversely impact our business.

Compliance with the ICD-10-CM Code Set was required to be in place by October 1, 2015. The Company will continue its assessment of information systems, applications and processes for compliance with these requirements. Clinical laboratories are typically required to submit health care claims with diagnosis codes to third party payors. The diagnosis codes must be obtained from the ordering physician. Our failure or the failure of third party payors or physicians to comply with these requirements could have an adverse impact on reimbursement, days sales and cash collections.

Also, the failure of our IT systems to keep pace with technological advances may significantly reduce our revenues or increase our expenses. Public and private initiatives to create healthcare information technology ("HCIT") standards and to mandate standardized clinical coding systems for the electronic exchange of clinical information, including test orders and test results, could require costly modifications to our existing HCIT systems. If we fail to adopt or delay in implementing HCIT standards, we could lose customers and business opportunities.

Failure to comply with complex federal and state laws and regulations related to submission of claims for clinical laboratory services could result in significant monetary damages and penalties and exclusion from the Medicare and Medicaid programs.

We are subject to extensive federal and state laws and regulations relating to the submission of claims for payment for clinical laboratory services, including those that relate to coverage of our services under Medicare, Medicaid and other governmental health care programs, the amounts that may be billed for our services and to whom claims for services may be submitted. These rules may also affect the Company in light of the practice management products that we market, to the extent that these products are considered to affect the manner in which our customers' submit their own claims for services. Submission of our claims is particularly complex because we provide both anatomic pathology services and clinical laboratory

tests, which generally are paid using different reimbursement principles. The clinical laboratory tests are often paid under a clinical laboratory fee schedule, and the anatomic pathology services are often paid under a physician fee schedule.

Our failure to comply with applicable laws and regulations could result in our inability to receive payment for our services or result in attempts by third-party payors, such as Medicare and Medicaid, to recover payments from us that have already been made. Submission of claims in violation of certain statutory or regulatory requirements can result in penalties, including substantial civil money penalties for each item or service billed to Medicare in violation of the legal requirement, and exclusion from participation in Medicare and Medicaid. Government authorities may also assert that violations of laws and regulations related to submission or causing the submission of claims violate the federal False Claims Act ("FCA") or other laws related to fraud and abuse, including submission of claims for services that were not medically necessary. Violations of the FCA could result in enormous economic liability. The FCA provides that all damages are trebled, and each false claim submitted is subject to a penalty of up to $21,563. For example, we could be subject to FCA liability if it was determined that the services we provided were not medically necessary and not reimbursable, particularly if it were asserted that we contributed to the physician's referrals of unnecessary services to us. It is also possible that the government could attempt to hold us liable under fraud and abuse laws for improper claims submitted by an entity for services that we performed if we were found to have knowingly participated in the arrangement that resulted in submission of the improper claims.

Changes in regulation and policies, including increasing downward pressure on health care reimbursement, may adversely affect reimbursement for diagnostic services and could have a material adverse impact on our business.

Reimbursement levels for health care services are subject to continuous and often unexpected changes in policies, and we face a variety of efforts by government payors to reduce utilization and reimbursement for diagnostic testing services. Changes in governmental reimbursement may result from statutory and regulatory changes, retroactive rate adjustments, administrative rulings, competitive bidding initiatives, and other policy changes.

The U.S. Congress has considered, at least yearly in conjunction with budgetary legislation, changes to one or both of the Medicare fee schedules under which we receive reimbursement, which include the physician fee schedule for anatomical pathology services, and the clinical laboratory fee schedule for our clinical laboratory services. For example, currently there is no copayment or coinsurance required for clinical laboratory services, although there is for our physician services. However, Congress has periodically considered imposing a 20 percent coinsurance on laboratory services. If enacted, this would require us to attempt to collect this amount from patients, although in many cases the costs of collection would exceed the amount actually received. In April 2015, changes to the physician fee schedule were enacted under the Medicare Access and CHIP Reauthorization Act of 2015 ("MACRA").

Our reimbursement for our pathology services is paid primarily under the physician fee schedule of Medicare and Medicaid. Historically, the physician fee schedule was governed by a complex formula, referred to as the Sustainable Growth Rate, or SGR. However, in April 2015, MACRA was passed, which permanently replaces the SGR formula with a value-based payment system. The passage of MACRA also repealed the 21.1% reduction of the physician fee schedule that was scheduled for April 1, 2015. Under MACRA, the physician fee schedule conversion factor increases of 0.5% from July 1, 2015 to December 31, 2015, and 0.5% in each of years 2016-2019, followed by 0.0% updates for 2020-2025. Subsequent years will vary based on participation in alternative payment models. Beginning in 2019, rates will also be adjusted under the new Merit-based Incentive Payment System.

The Center for Medicare and Medicaid Services ("CMS") pays laboratories on the basis of a fee schedule that is reviewed and re-calculated on an annual basis. CMS may change the fee schedule upward or downward on billing codes that we submit for reimbursement on a regular basis. Our revenue and business may be adversely affected if the reimbursement rates associated with such codes are reduced. Even when reimbursement rates are not reduced, policy changes add to our costs by increasing the complexity and volume of administrative requirements. Medicaid reimbursement, which varies by state, is also subject to administrative and billing requirements and budget pressures. Recently, state budget pressures have caused states to consider several policy changes that may impact our financial condition and results of operations, such as delaying payments, reducing reimbursement, restricting coverage eligibility and service coverage, and imposing taxes on our services.

Change in the billing and/or reimbursement procedures by the federal government could affect our ability to be paid as we have in the past for services rendered.

CMS has changed or discussed making changes to certain types of reimbursement which could affect our rate of reimbursement. Certain cases are comprised of both a technical component ("TC") and a professional component ("PC"). In certain specified areas of testing, primarily in the area of anatomic pathology, CMS has determined that some providers have

over-utilized these testing procedures and CMS has introduced changes in reimbursement policies to discourage over-utilization. While we do not currently over-utilize services for self-gain, we are always subject to review by CMS and cannot be certain that CMS won't interpret our practices differently than we do.

Third party payers are increasingly challenging established prices, and new products that are more expensive than existing treatments may have difficulty finding ready acceptance unless there is a clear therapeutic benefit. On April 1, 2014, the Protecting Access to Medicare Act of 2014 ("PAMA") was enacted into law. Under PAMA, Medicare payment for clinical diagnostic laboratory tests will be established by calculating a weighted mean of private payer rates, with new rates to be effective January 1, 2018. Further, applicable laboratories will be required to report payment rates for covered tests starting in 2016 (to establish the payment rates that will be effective January 1, 2018). Failure to report such data may result in a civil money penalty in an amount of up to $10,000 per day. It is anticipated that the market-based payment system will result in lower reimbursement rates for clinical diagnostic laboratory tests. Even though the permitted annual decrease will be capped through 2023, the cap does not apply to new tests or new advanced diagnostic tests. We cannot assure you that any of our products will be considered cost effective, or that reimbursement will be available or sufficient to allow us to sell them competitively and profitably.

The federal government is faced with significant economic decisions in the coming years. Some solutions being offered in the government could substantially change the way laboratory testing is reimbursed by government entities. We cannot be certain what or how any such government changes may affect our business.

Medicare legislation and future legislative or regulatory reform of the health care system may affect our ability to sell our products profitably.

In the U.S., there have been a number of legislative and regulatory initiatives, at both the federal and state government levels, to change the healthcare system in ways that, if approved, could affect our ability to sell our products and provide our laboratory services profitably. As such, we cannot assure you that reimbursement payments under governmental and private third party payor programs will remain at levels comparable to present levels or will be sufficient to cover the costs allocable to patients eligible for reimbursement under these programs. Any changes that lower reimbursement rates under Medicare, Medicaid or private payor programs could negatively affect our business.

Most significantly, on March 23, 2010, President Obama signed into law both the Affordable Care Act and the reconciliation law known as Health Care and Education Affordability Reconciliation Act (the "Reconciliation Act") and, combined we refer to both Acts as the "2010 Health Care Reform Legislation." The constitutionality of the 2010 Health Care Reform Legislation was confirmed on June 28, 2012 by the Supreme Court of the United States. Extending coverage to a large population could substantially change the structure of the health insurance system and the methodology for reimbursing medical services, drugs and devices. These structural changes could entail modifications to the existing system of third-party payors and government programs, such as Medicare and Medicaid, the creation of a government-sponsored healthcare insurance source, or some combination of both, as well as other changes. Additionally, restructuring the coverage of medical care in the U.S. could impact the reimbursement for diagnostic tests. If reimbursement for our diagnostic tests is substantially less than we or our clinical laboratory customers expect, or rebate obligations associated with them are substantially increased, our business could be materially and adversely impacted.

Beyond coverage and reimbursement changes, the 2010 Health Care Reform Legislation subjects manufacturers of medical devices to an excise tax of 2.3% on certain U.S. sales of medical devices in January 2013. However, a two-year moratorium on the tax was issued on December 18, 2015. As such, the excise tax does not apply to sales in 2016 or 2017. The return of the tax in 2018 will likely increase our expense in the future.

Additionally, the 2010 Health Care Reform Legislation includes significant new fraud and abuse measures, including required disclosures under Physician Payments Sunshine Act described above, lower thresholds for violations and increasing potential penalties for such violations. Federal funding available for combating health care fraud and abuse generally has increased. Many of the laws and regulations applicable to our business, particularly those relating to billing and reimbursement of tests and those relating to relationships with physicians, hospitals and patients, contain language that has not been interpreted by courts. We must rely on our interpretation of these laws and regulations based on the advice of our counsel and regulatory or law enforcement authorities may not agree with our interpretation of these laws and regulations and may seek to enforce legal remedies or penalties against us for violations. From time to time we may need to change our operations, particularly pricing or billing practices, in response to changing interpretations of these laws and regulations or regulatory or judicial determinations with respect to these laws and regulations. These occurrences, regardless of their outcome, could damage our reputation and harm important business relationships that we have with healthcare providers, payors and others. Furthermore, if a regulatory or judicial authority finds that we have not complied with applicable laws and regulations, we could be required to refund amounts that were billed and collected in violation of such laws and regulations. In addition, we may voluntarily

refund amounts that were alleged to have been billed and collected in violation of applicable laws and regulations. In either case, we could suffer civil and criminal damages, fines and penalties, exclusion from participation in governmental healthcare programs and the loss of licenses, certificates and authorizations necessary to operate our business, as well as incur liabilities from third-party claims, all of which could harm our operating results and financial condition. Moreover, regardless of the outcome, if we or physicians or other third parties with whom we do business are investigated by a regulatory or law enforcement authority we could incur substantial costs, including legal fees, and our management may be required to divert a substantial amount of time to an investigation.

To enhance compliance with applicable health care laws, and mitigate potential liability in the event of noncompliance, regulatory authorities, such as the United States Health and Human Services Department Office of Inspector General ("OIG"), have recommended the adoption and implementation of a comprehensive health care compliance program that generally contains the elements of an effective compliance and ethics program described in Section 8B2.1 of the United States Sentencing Commission Guidelines Manual, and for many years the OIG has made available a model compliance program targeted to the clinical laboratory industry. In addition, certain states, such as New York, requires that health care providers, such as clinical laboratories, that engage in substantial business under the state Medicaid program have a compliance program that generally adheres to the standards set forth in the Model Compliance Program. Also, under the 2010 Health Care Reform Legislation, the U.S. Department of Health and Human Services, or HHS, requires suppliers, such as the Company, to adopt, as a condition of Medicare participation, compliance programs that meet a core set of requirements. While we have adopted U.S. healthcare compliance and ethics programs that generally incorporate the OIG's recommendations and train our employees in such compliance, having such a program can be no assurance that we will avoid any compliance issues.

Prior to the 2016 U.S. elections (including the new Presidential administration), regulations under the 2010 Health Care Reform Legislation were expected to continue being drafted, released and finalized throughout the next several years. Under the current U.S. Presidential administration and U.S. Congress, it is possible and expected that legislation will be introduced to repeal the 2010 Health Care Reform Legislation in whole or in part. Because of the continued uncertainty about the implementation of the 2010 Health Care Reform Legislation, including the potential for further legal challenges or repeal of that legislation, we cannot quantify or predict with any certainty the likely impact of the 2010 Health Care Reform Legislation or its repeal on our business model, prospects, financial condition or results of operations. We also anticipate that Congress, state legislatures, and third-party payors may continue to review and assess alternative healthcare delivery and payment systems and may in the future propose and adopt legislation or policy changes or implementations effecting additional fundamental changes in the healthcare delivery system. We cannot assure you as to the ultimate content, timing, or effect of changes, nor is it possible at this time to estimate the impact of any such potential legislation.

RISKS RELATED TO INTERNATIONAL OPERATIONS

Failure to obtain regulatory approval outside the U.S. will prevent us from marketing our products and product candidates abroad.

We intend to market certain of our products and product candidates in non-U.S. markets. In order to market our products and product candidates in the European Union and many other non-U.S. jurisdictions, we must obtain separate regulatory approvals. We have had limited interactions with non-U.S. regulatory authorities, the approval procedures vary among countries and can involve additional testing, and the time required to obtain approval may differ from that required to obtain FDA approval or clearance. Approval or clearance by the FDA does not ensure approval by regulatory authorities in other countries, and approval by one or more non-U.S. regulatory authority does not ensure approval by other regulatory authorities in other countries or by the FDA. The non-U.S. regulatory approval process may include all of the risks associated with obtaining FDA approval or clearance. We may not obtain non-U.S. regulatory approvals on a timely basis, if at all. We may not be able to file for non-U.S. regulatory approvals and may not receive necessary approvals to commercialize our products and product candidates in any market, which would have a material adverse effect on our business, results of operations and financial condition.

Non-U.S. governments often impose strict price controls, which may adversely affect our future profitability.

We intend to seek approval to market certain of our products and product candidates in both the U.S. and in non-U.S. jurisdictions. If we obtain approval in one or more non-U.S. jurisdictions, we will be subject to rules and regulations in those jurisdictions relating to our product. In some countries, particularly countries of the European Union, each of which has developed its own rules and regulations, pricing is subject to governmental control. In these countries, pricing negotiations with governmental authorities can take considerable time after the receipt of marketing approval for a drug or medical device candidate. To obtain reimbursement or pricing approval in some countries, we may be required to conduct a clinical trial that compares the cost-effectiveness of our product and product candidates to other available products. If reimbursement of our products and product candidates is unavailable or limited in scope or amount, or if pricing is set at unsatisfactory levels, we

may be unable to generate revenues and achieve or sustain profitability, which would have a material adverse effect on our business, results of operations and financial condition.

Potential political, economic and military instability in the State of Israel, where we have office, laboratory and manufacturing operations, may adversely affect our results of operations.

We maintain office, laboratory and manufacturing facilities in the State of Israel. Political, economic and military conditions in Israel may directly affect our ability to conduct business. Since the State of Israel was established in 1948, a number of armed conflicts have occurred between Israel and its neighbors. Any hostilities involving Israel or the interruption or curtailment of trade between Israel and its present trading partners, or a significant downturn in the economic or financial condition of Israel, could affect adversely our operations. Ongoing and revived hostilities or other Israeli political or economic factors could harm our operations and product development and cause our revenues to decrease.

Due to the international scope of our business activities, our results of operations may be significantly affected by currency fluctuations.

We derive a significant portion of our consolidated net revenues from international sales, subjecting us to risks relating to fluctuations in currency exchange rates. Currency variations can adversely affect margins on sales of our products in countries outside of the U.S. and margins on sales of products that include components obtained from suppliers located outside of the U.S. Through our subsidiaries, we operate in a wide variety of jurisdictions. Certain countries in which we operate or may operate have experienced geopolitical instability, economic problems and other uncertainties from time to time. To the extent that world events or economic conditions negatively affect our future sales to customers in these and other regions of the world, or the collectability of receivables, our future results of operations, liquidity and financial condition may be adversely affected. Although we do not speculate in the foreign exchange market, we may manage exposures arising in the normal course of business related to fluctuations in foreign currency exchange rates by entering into offsetting positions through the use of foreign exchange forward contracts. Certain firmly committed transactions are hedged with foreign exchange forward contracts whereby exchange rates change, gains and losses on the exposed transactions are partially offset by gains and losses related to the hedging contracts. However, our subsidiaries receive their income and pay their expenses primarily in their local currencies. To the extent that transactions of these subsidiaries are settled in their local currencies, a devaluation of those currencies versus the U.S. dollar could reduce the contribution from these subsidiaries to our consolidated results of operations as reported in U.S. dollars. For financial reporting purposes, such depreciation will negatively affect our reported results of operations since earnings denominated in foreign currencies would be converted to U.S. dollars at a decreased value. While we have employed economic cash flow and fair value hedges to minimize the risks associated with these exchange rate fluctuations, the hedging activities may be ineffective or may not offset more than a portion of the adverse financial impact resulting from currency variations. Accordingly, we cannot assure you that fluctuations in the values of the currencies of countries in which we operate will not materially adversely affect our future results of operations.

We may be exposed to liabilities under the Foreign Corrupt Practices Act, and any determination that we violated the Foreign Corrupt Practices Act could have a material adverse effect on our business.

We are subject to the Foreign Corrupt Practice Act ("FCPA") and other laws that prohibit U.S. companies or their agents and employees from providing anything of value to a foreign official or political party for the purposes of influencing any act or decision of these individuals in their official capacity to help obtain or retain business, direct business to any person or corporate entity or obtain any unfair advantage. We have operations and agreements with third parties and we generate sales internationally. Our international activities create the risk of unauthorized and illegal payments or offers of payments by our employees, consultants, sales agents or distributors, even though they may not always be subject to our control. We discourage these practices by our employees and agents. However, our existing safeguards and any future improvements may prove to be less than effective, and our employees, consultants, sales agents or distributors may engage in conduct for which we might be held responsible. Any failure by us to adopt appropriate compliance procedures and ensure that our employees and agents comply with the FCPA and applicable laws and regulations in foreign jurisdictions could result in substantial penalties or restrictions on our ability to conduct business in certain foreign jurisdictions.

Violations of the FCPA may result in severe criminal or civil sanctions, and we may be subject to other liabilities, which could negatively affect our business, operating results and financial condition. In addition, the U.S. government may seek to hold our Company liable for successor liability FCPA violations committed by companies in which we invest or that we acquire.

We are subject to risks associated with doing business globally.

Our operations, both within and outside the U.S., are subject to risks inherent in conducting business globally and under the laws, regulations and customs of various jurisdictions and geographies. These risks differ in some respects from those

associated with our U.S. business and our exposure to such risks may increase if our international business continues to grow. These risks include fluctuations in currency exchange rates, changes in exchange controls, loss of business in government tenders that are held annually in many cases, nationalization, increasingly complex labor environments, expropriation and other governmental actions, changes in taxation, including legislative changes in U.S. and international taxation of income earned outside of the U.S., importation limitations, export control restrictions, violations of U.S. or local laws, including the FCPA, dependence on a few government entities as customers, pricing restrictions, economic destabilization, political and economic instability, disruption or destruction in a significant geographic region - due to the location of manufacturing facilities, distribution facilities or customers - regardless of cause, including war, terrorism, riot, civil insurrection or social unrest, or natural or man-made disasters, including famine, flood, fire, earthquake, storm or disease.

Our international business is subject to both U.S. and foreign laws and regulations, including, without limitation, regulations relating to import-export controls, technology transfer restrictions, repatriation of earnings, data privacy and protection, investment, exchange rates and controls, the FCPA and other anti-corruption laws, the anti-boycott provisions of the U.S. Export Administration Act, labor and employment, works councils and other labor groups, taxes, environment, security restrictions, intellectual property, changes in taxation, including legislative changes in U.S. and international taxation of income earned outside of the U.S., handling of regulated substances, and other commercial activities. Failure by us, our employees, affiliates, partners or others with whom we work to comply with these laws and regulations could result in administrative, civil or criminal liabilities. New regulations and requirements, or changes to existing ones in the various countries in which we operate can significantly increase our costs and risks of doing business internationally. Failure to comply with the laws and regulations that affect our global operations, could have an adverse effect on our business, financial condition or results of operations.

Changes in regulations, political leadership and environment, or security risks may dramatically affect our ability to conduct or continue to conduct business in international markets. Our international business may also be impacted by changes in foreign national policies and priorities, which may be influenced by changes in the threat environment, geopolitical uncertainties, government budgets, and economic and political factors more generally, any of which could impact funding for programs or delay purchasing decisions or customer payments. We also could be affected by the legal, regulatory and economic impacts of Britain's exit from the European Union, the impact of which is not known at this time. The occurrence and impact of these factors is difficult to predict, but one or more of them could have a material adverse effect on our financial position, results of operations and/or cash flows.

RISKS RELATED TO ACQUISITIONS AND INVESTMENTS

Acquisitions, investments and strategic alliances that we have made or may make in the future may use significant resources, result in disruptions to our business or distractions of our management, may not proceed as planned, and could expose us to unforeseen liabilities. We intend to continue to expand our business through the acquisition of, investments in and strategic alliances with companies, technologies, products and services. Acquisitions, investments and strategic alliances involve a number of special problems and risks, including, but not limited to:

- difficulty integrating acquired technologies, products, services, operations, and personnel with the existing businesses;
- diversion of management's attention in connection with both negotiating the acquisitions and integrating the businesses;
- strain on managerial and operational resources as management tries to oversee larger operations and investments;
- difficulty implementing and maintaining effective internal control over financial reporting at businesses that we acquire or invest in, particularly if they are not located near our existing operations;
- exposure to unforeseen liabilities of acquired companies or companies in which we invest;
- potential costly and time-consuming litigation, including stockholder lawsuits;
- potential issuance of securities to equity holders of the company being acquired with rights that are superior to the rights of holders of our Common Stock, or which may have a dilutive effect on our stockholders;
- the need to incur additional debt or use cash; and
- the requirement to record potentially significant additional future operating costs for the amortization of intangible assets.

As a result of these or other problems and risks, businesses we acquire or invest in may not produce the revenues, earnings, or business synergies that we anticipated, and acquired products, services, or technologies might not perform as we

expected. As a result, we may incur higher costs and realize lower revenues than we had anticipated. We may not be able to successfully address these problems and we cannot assure you that the acquisitions or investments will be successfully identified and completed or that, if completed, the acquired businesses, investments, products, services, or technologies will generate sufficient revenue to offset the associated costs or other negative effects on our business.

Any of these risks can be greater if an acquisition or investment is large relative to our size. Failure to manage effectively our growth through acquisitions could adversely affect our growth prospects, business, results of operations, financial condition and cash flows.

We may fail to realize the anticipated benefits of the mergers with Bio-Reference, Transition Therapeutics, and other acquisitions.

The success of the mergers will depend on, among other things, our ability to combine our business with that of Bio-Reference and Transition in a manner that facilitates growth opportunities and realizes synergies and cost savings. We believe that the mergers will provide an opportunity for revenue growth. However, we must successfully combine our business with that of Bio-Reference and Transition in a manner that permits these benefits to be realized. In addition, we must achieve the anticipated growth and cost savings without adversely affecting current revenues and investments in future growth. If we are not able to successfully achieve these objectives, the anticipated benefits of the mergers may not be realized fully, or at all, or may take longer to realize than expected.

The failure to integrate successfully the business and operations of Bio-Reference in the expected time frame may adversely affect our future results.

Historically, we and Bio-Reference have operated as independent companies. There can be no assurances that our and Bio-Reference's businesses can be integrated successfully. It is possible that the integration process could result in the loss of our or Bio-Reference's key employees, the loss of customers, the disruption of either company's or both companies' ongoing businesses or in unexpected integration issues, higher than expected integration costs and an overall post-completion integration process that takes longer than originally anticipated. Specifically, the following issues, among others, must be addressed in integrating our operations with Bio-Reference's operations in order to realize the anticipated benefits of the merger so we perform as expected:

- combining the companies' operations and corporate functions, as well as obtaining anticipated synergies;
- combining our business with Bio-Reference's business and meeting the capital requirements of the combined company, in a manner that permits us to achieve the cost savings or revenue synergies anticipated to result from the merger, the failure of which would result in the anticipated benefits of the merger not being realized in the time frame currently anticipated or at all;
- integrating the companies' technologies;
- integrating and unifying the offerings and services available to customers;
- identifying and eliminating redundant and underperforming functions and assets;
- harmonizing and/or addressing differences in the companies' operating practices, employee development and compensation programs, internal controls and other policies, procedures and processes;
- maintaining existing agreements with customers, distributors, providers and vendors and avoiding delays in entering into new agreements with prospective customers, distributors, providers and vendors;
- addressing possible differences in business backgrounds, corporate cultures and management philosophies;
- consolidating the companies' administrative and information technology infrastructure;
- coordinating distribution and marketing efforts;
- managing the movement of certain positions to different locations;
- coordinating geographically dispersed organizations; and
- effecting actions that may be required in connection with obtaining regulatory approvals.

In addition, at times the attention of our management and resources may be focused on the integration of the businesses of the two companies and diverted from day-to-day business operations, which may disrupt our ongoing business.

Funding may not be available for us to continue to make acquisitions, investments and strategic alliances in order to grow our business.

We have made and anticipate that we may continue to make acquisitions, investments and strategic alliances with complementary businesses, technologies, products and services to expand our business. Our growth plans rely, in part, on the successful completion of future acquisitions. At any particular time, we may need to raise substantial additional capital or to issue additional equity to finance such acquisitions, investments, and strategic alliances. There is no assurance that we will be able to secure additional funding on acceptable terms, or at all, or obtain the stockholder approvals necessary to issue additional equity to finance such acquisitions, investments, and strategic alliances. If we are unsuccessful in obtaining the financing, our business would be adversely impacted.

We have a large amount of goodwill and other intangible assets as a result of acquisitions and a significant write-down of goodwill and/or other intangible assets would have a material adverse effect on our reported results of operations and net worth.

We have a large amount of goodwill and other intangible assets and we are required to perform an annual, or in certain situations a more frequent, assessment for possible impairment for accounting purposes. At December 31, 2016 , we have goodwill and other intangible assets of $2.1 billion , or approximately 76% of our total assets. If we do not achieve our planned operating results, we may be required to incur a non-cash impairment charge. Any impairment charges in the future will adversely affect our results of operations. A significant write down of goodwill and/or other intangible assets would have a material adverse effect on our reported results of operations and net worth.

RISKS RELATED TO OWNERSHIP OF OUR COMMON STOCK

The market price of our Common Stock may fluctuate significantly.

The market price of our Common Stock may fluctuate significantly in response to numerous factors, some of which are beyond our control, such as:

- the announcement of new products or product enhancements by us or our competitors;
- results of our clinical trials and other development efforts;
- developments concerning intellectual property rights and regulatory approvals;
- variations in our and our competitors' results of operations;
- changes in earnings estimates or recommendations by securities analysts, if our Common Stock is covered by analysts;
- developments in the biotechnology, pharmaceutical, diagnostic, and medical device industry;
- the results of product liability or intellectual property lawsuits;
- future issuances of our Common Stock or other securities, including debt;
- purchases and sales of our Common Stock by our officers, directors or affiliates;
- the addition or departure of key personnel;
- announcements by us or our competitors of acquisitions, investments, or strategic alliances; and
- general market conditions and other factors, including factors unrelated to our operating performance.

Further, the stock market in general, and the market for biotechnology, pharmaceutical, diagnostic, and medical device companies in particular, has experienced extreme price and volume fluctuations in recent years. Continued market fluctuations could result in extreme volatility in the price of our Common Stock, which could cause a decline in the value of our Common Stock.

Directors, executive officers, principal stockholders and affiliated entities own a substantial amount of our capital stock, and they may make decisions that you do not consider to be in the best interests of our stockholders.

As of February 27, 2017, our directors, executive officers, principal stockholders, and affiliated entities beneficially owned, in the aggregate 40.19% of our outstanding voting securities. Frost Gamma Investments Trust ("Gamma Trust"), of which Phillip Frost, M.D., the Company's Chairman and CEO, is the sole trustee, is deemed to beneficially own in the aggregate approximately 32.36% of our Common Stock as of February 27, 2017. As a result, Dr. Frost acting with other members of management, would have the ability to significantly impact the election of our Board of Directors, the adoption or amendment of provisions in the Company's Certificate of Incorporation, the approval of mergers and other significant corporate transactions, and the outcome of issues requiring approval by our stockholders. This concentration of ownership may al

so have the effect of delaying or preventing a change in control of our company that may be favored by other stockholders. This could prevent transactions in which stockholders might otherwise recover a premium for their shares over current market prices.

A significant short position in our stock could have a substantial impact on the trading price of our stock.

Historically, there has been a significant "short" position in our common stock. As of February 15, 2017, investors held a short position of approximately 74,955,031 million shares of our common stock which represented approximately 13.4% of our outstanding common stock. The anticipated downward pressure on our stock price due to actual or anticipated sales of our stock by some institutions or individuals who engage in short sales of our common stock could cause our stock price to decline. Such stock price decrease could encourage further short-sales that could place additional downward pressure on our stock price. This could lead to further increases in the already large short position in our common stock and cause volatility in our stock price.

The volatility of our stock may cause the value of a stockholder's investment to decline rapidly. Additionally, if our stock price declines, it may be more difficult for us to raise capital and may have other adverse effects on our business.

Failure to maintain effective internal controls in accordance with Section 404 of the Sarbanes-Oxley Act, including with respect to companies we acquire, could have a material adverse effect on our business and operating results. In addition, current and potential stockholders could lose confidence in our financial reporting, which could have a material adverse effect on the price of our Common Stock.

Section 404 of the Sarbanes-Oxley Act of 2002 requires annual management assessments of the effectiveness of our internal control over financial reporting and a report by our independent registered public accounting firm on the effectiveness of internal control over financial reporting as of year end. We are required to report, among other things, control deficiencies that constitute material weaknesses or changes in internal control that, or that are reasonably likely to, materially affect internal control over financial reporting. A "material weakness" is a significant deficiency or combination of significant deficiencies that results in more than a remote likelihood that a material misstatement of the annual or interim financial statements will not be prevented or detected.

We have identified and remediated control deficiencies in the past, and we cannot assure you that we will at all times in the future be able to report that our internal controls are effective. In addition, material weaknesses in the design and operation of the internal control over financial reporting of companies that we acquire could have a material adverse effect on our business and operating results. Our acquisition of Bio-Reference and Transition Therapeutics and possible future acquisitions may increase this risk by expanding the scope and nature of operations over which we must develop and maintain internal control over financial reporting. If we cannot provide reliable financial reports or prevent fraud, our results of operation could be harmed. Our failure to maintain the effective internal control over financial reporting could cause the cost related to remediation to increase and could cause our stock price to decline. In addition, we may not be able to accurately report our financial results, may be subject to regulatory sanction, and investors may lose confidence in our financial statements.

Compliance with changing regulations concerning corporate governance and public disclosure may result in additional expenses.

There have been changing laws, regulations, and standards relating to corporate governance and public disclosure, including the Sarbanes-Oxley Act of 2002, the Dodd-Frank Act, regulations promulgated by the Securities and Exchange Commission and rules promulgated by the NYSE and the other national securities exchanges. These new or changed laws, regulations, and standards are subject to varying interpretations in many cases due to their lack of specificity, and, as a result, their application in practice may evolve over time as new guidance is provided by regulatory and governing bodies, which could result in continuing uncertainty regarding compliance matters and higher costs necessitated by ongoing revisions to disclosure and governance practices. As a result, our efforts to comply with evolving laws, regulations, and standards are likely to continue to result in increased general and administrative expenses and a diversion of management time and attention from revenue-generating activities to compliance activities. Our board members, Chief Executive Officer, Chief Financial Officer, and Principal Accounting Officer could face an increased risk of personal liability in connection with the performance of their duties. As a result, we may have difficulty attracting and retaining qualified board members and executive officers, which could harm our business. If our efforts to comply with new or changed laws, regulations, and standards differ from the activities intended by regulatory or governing bodies, we could be subject to liability under applicable laws or our reputation may be harmed, which could materially adversely affect our business, results of operations and financial condition.

The conversion and redemption features of our 2033 Senior Notes are classified as embedded derivatives and may continue to result in volatility in our financial statements, including having a material impact on our results of operations and the derivative liability recorded.

The conversion rights and redemption options of our 2033 Senior Notes are classified as embedded derivatives and as a result, are marked-to-market to reflect their fair value at each reporting period. The fair value of the embedded derivatives is influenced by a variety of factors, including the actual and anticipated behavior of the holders of the 2033 Senior Notes, the expected volatility of our Common Stock price and our Common Stock price as of the fair value measurement date. Some of these factors are outside of our control. As a result, changes in these factors may have a material impact on our results of operations and the derivative liability recorded in our Consolidated Balance Sheets. Consequently, our financial statements may vary periodically, based on factors other than our revenues and expenses.

ITEM 1B. UNRESOLVED STAFF COMMENTS.

None.

ITEM 2. PROPERTIES.

Our principal corporate office is located at 4400 Biscayne Blvd, Miami, Florida. We lease this space from Frost Real Estate Holdings, LLC ("Frost Real Estate"), an entity which is controlled by Dr. Phillip Frost, our Chairman of the Board and Chief Executive Officer. Pursuant to the lease agreement with Frost Real Estate Holdings, we lease approximately 25,000 square feet, which encompasses space for our corporate offices and administrative services. Effective May 28, 2015, we entered into an amendment to our lease agreement with Frost Real-Estate Holdings. The lease, as amended, is for a five-year term. The lease provides for payments of approximately $66 thousand per month in the first year increasing annually to $75 thousand per month in the fifth year, plus applicable sale tax.

The table below summarizes certain information as to our significant physical properties as of December 31, 2016 :

Location	Segment and Purpose	Type of Occupancy
Miami, FL	Diagnostics & Pharmaceutical: Corporate Headquarters	Leased
Elmwood Park, NJ	Diagnostics: Main Laboratory	Leased
Gaithersburg, MD	Diagnostics: Genetics Laboratory	Leased
Kiryat Gat, Israel	Pharmaceutical: Research and Development, CTP	Leased
Woburn, MA	Diagnostics	Leased
Nesher, Israel	Pharmaceuticals: API Manufacturing	Leased
Guadalajara, Mexico	Pharmaceuticals: Pharmaceutical Manufacturing	Owned
Banyoles, Spain	Pharmaceuticals: Pharmaceutical Manufacturing	Owned
Palol de Revardit, Spain	Warehouse	Leased
Barcelona, Spain	Pharmaceuticals: Research and Development	Leased
Waterford, Ireland	Pharmaceuticals: Pharmaceutical Manufacturing	Leased
Santiago, Chile	Pharmaceuticals: Office; Warehouse	Leased

ITEM 3. LEGAL PROCEEDINGS.

None.

ITEM 4. MINE SAFETY DISCLOSURES.

Not applicable.

PART II

ITEM 5. MARKET FOR REGISTRANT'S COMMON EQUITY, RELATED STOCKHOLDER MATTERS AND ISSUER PURCHASES OF EQUITY SECURITIES.

Our Common Stock is traded publicly on the NASDAQ Stock Market ("NASDAQ") and the Tel Aviv Stock Exchange under the symbol "OPK". On June 24, 2016, we moved our stock exchange listing to NASDAQ from the New York Stock Exchange ("NYSE").

The following table sets forth for the periods indicated the high and low sales prices per share of our Common Stock during each of the quarters set forth below as reported on the NASDAQ or NYSE, as applicable:

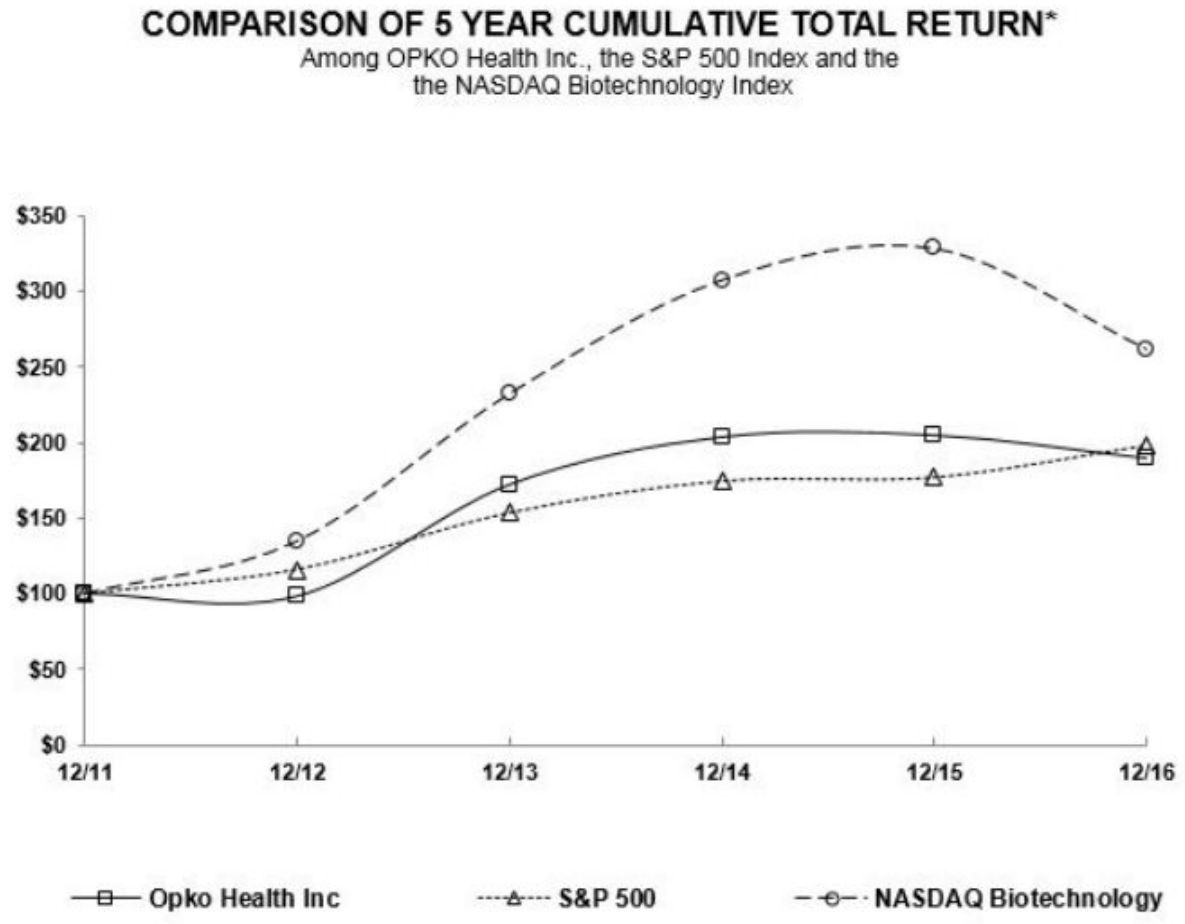
	High	Low
2016		
First Quarter	11.85	7.12
Second Quarter	11.39	8.71
Third Quarter	11.31	8.91
Fourth Quarter	12.15	8.92
2015		
First Quarter	$ 15.23	$ 9.81
Second Quarter	19.20	13.71
Third Quarter	17.51	8.23
Fourth Quarter	11.49	8.20

As of February 20, 2017 , there were approximately 595 holders of record of our Common Stock.

We have not declared or paid any cash dividends on our Common Stock. No cash dividends have been previously paid on our Common Stock and none are anticipated in fiscal 2017.

Stock Performance Graph

The following graph compares the five-year cumulative total return of our Common Stock with the S&P 500 Index and the NASDAQ Biotechnology Index. The graph assumes $100 invested on December 31, 2011 in our Common Stock and in each of the foregoing indices. The stock price performance reflected in the graph below is not necessarily indicative of future price performance.



	12/31/2011	12/31/2012	12/31/2013	12/31/2014	12/31/2015	12/31/2016
OPKO Health, Inc.	$ 100.00	$ 98.16	$ 172.24	$ 203.88	$ 205.10	$ 189.80
S&P 500	100.00	116.00	153.58	174.60	177.01	198.18
NASDAQ Biotechnology	100.00	134.68	232.37	307.67	328.76	262.08

Recent Sales of Unregistered Securities

None.

ITEM 6. SELECTED FINANCIAL DATA.

The following selected historical consolidated statement of operations data for the years ended December 31, 2016, 2015, 2014, 2013 and 2012 and the consolidated balance sheet data as of December 31, 2016, 2015, 2014, 2013 and 2012, below are derived from our audited consolidated financial statements and related notes thereto. This data should be read in conjunction with our "Management's Discussion and Analysis of Financial Condition and Results of Operation" and our consolidated financial statements and the related notes thereto.

	For the years ended December 31,				
(In thousands, except share and per share information)	2016	2015	2014	2013	2012
Statement of operations data:					
Revenues	$ 1,221,661	$ 491,738	$ 91,125	$ 96,530	$ 47,044
Costs and expenses:					
Cost of revenue	611,482	235,239	48,009	48,860	27,878
Operating expenses	683,454	354,980	188,931	127,302	56,435
Total costs and expenses	1,294,936	590,219	236,940	176,162	84,313
Operating loss	(73,275)	(98,481)	(145,815)	(79,632)	(37,269)
Other income and (expense), net	(271)	(39,517)	(25,212)	(24,586)	165
Income tax benefit (provision)	56,115	113,675	(24)	(1,672)	9,626
Net loss	(25,083)	(31,428)	(174,638)	(117,346)	(29,540)
Net loss attributable to common shareholders	$ (25,083)	$ (30,028)	$ (171,666)	$ (114,827)	$ (31,288)
Loss per share, basic and diluted:					
Net loss per share	$ (0.05)	$ (0.06)	$ (0.41)	$ (0.32)	$ (0.11)
Weighted average number of common shares outstanding basic and diluted:	550,846,553	488,065,908	422,014,039	355,095,701	295,750,077
Balance sheet data:					
Total assets	$ 2,766,619	$ 2,799,188	$ 1,267,664	$ 1,391,516	$ 289,830
Long-term liabilities	$ 411,515	$ 567,492	$ 348,812	$ 426,687	$ 34,168
Series D Preferred Stock	$ —	$ —	$ —	$ —	$ 24,386
Total shareholders' equity	$ 2,091,808	$ 1,979,794	$ 835,741	$ 872,979	$ 178,894

ITEM 7. MANAGEMENT'S DISCUSSION AND ANALYSIS OF FINANCIAL CONDITION AND RESULTS OF OPERATIONS.

This Annual Report on Form 10-K contains certain forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995 ("PSLRA"), 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"), about our expectations, beliefs, or intentions regarding our product development efforts, business, financial condition, results of operations, strategies, or prospects. You can identify forward-looking statements by the fact that these statements do not relate strictly to historical or current matters. Rather, forward-looking statements relate to anticipated or expected events, activities, trends, or results as of the date they are made. Because forward-looking statements relate to matters that have not yet occurred, these statements are inherently subject to risks and uncertainties that could cause our actual results to differ materially from any future results expressed or implied by the forward-looking statements. Many factors could cause our actual activities or results to differ materially from the activities and results anticipated in forward-looking statements. These factors include those contained in "Item 1A — Risk Factors" of this Annual Report on Form 10-K. We do not undertake any obligation to update forward-looking statements. We intend that all forward-looking statements be subject to the safe harbor provisions of PSLRA. These forward-looking statements are only predictions and reflect our views as of the date they are made with respect to future events and financial performance.

OVERVIEW

We are a diversified healthcare company that seeks to establish industry-leading positions in large and rapidly growing medical markets. Our diagnostics business includes Bio-Reference Laboratories ("Bio-Reference"), the nation's third-largest clinical laboratory with a core genetic testing business and a 400-person sales and marketing team to drive growth and leverage new products, including the *4Kscore* prostate cancer test and the *Claros 1* in-office immunoassay platform (in development). Our pharmaceutical business features *Rayaldee* , an FDA-approved treatment for secondary hyperparathyroidism ("SHPT") in adults with stage 3 or 4 chronic kidney disease ("CKD") and vitamin D insufficiency (launched in November 2016), and VARUBI™ for chemotherapy-induced nausea and vomiting (oral formulation launched by partner TESARO in November 2015 and pending approval for IV formulation), TT401, a once or twice weekly oxyntomodulin for type 2 diabetes and obesity which is a clinically advanced drug candidate among the new class of GLP-1 glucagon receptor dual agonists (Phase 2b) , and TT701, an androgen receptor modulator for androgen deficiency indications. Our pharmaceutical business also features hGH-CTP, a once-weekly human growth hormone injection (in Phase 3 and partnered with Pfizer), a once-daily Factor VIIa drug for hemophilia (Phase 2a), and long-acting oxyntomodulin ("OXM") for diabetes and obesity (Phase 1).

We operate established pharmaceutical platforms in Spain, Ireland, Chile and Mexico, which are generating revenue and from which we expect to generate positive cash flow and facilitate future market entry for our products currently in development. EirGen, our specialty pharmaceutical manufacturing and development site in Ireland, is focused on the development and commercial supply of high potency, high barrier to entry pharmaceutical products. In addition, we operate a specialty active pharmaceutical ingredients ("APIs") manufacturer in Israel, which we expect will facilitate the development of our pipeline of molecules and compounds for our proprietary products.

RECENT DEVELOPMENTS

In November 2016, we launched commercial sales for *Rayaldee* in the U.S. market. The FDA approved *Rayaldee* extended release capsules in June 2016 for the treatment of secondary hyperparathyroidism (SHPT) in adults with stage 3 or 4 chronic kidney disease (CKD) and serum total 25-hydroxyvitamin D levels less than 30 ng/mL. We have a highly specialized sales and marketing team dedicated to the launch and commercialization of *Rayaldee* , and we expect to increase the sales and marketing team in the second half of 2017.

RESULTS OF OPERATIONS

For The Years Ended December 31, 2016 and December 31, 2015

Revenues . Revenues for the year ended December 31, 2016 increased $729.9 million compared to the prior year. Revenues for the years ended December 31, 2016 and 2015 were as follows:

Revenues

(In thousands)	For the year ended December 31, 2016	2015	Change
Revenue from services	$ 1,012,129	$ 329,739	$ 682,390
Revenue from products	83,467	80,146	3,321
Revenue from transfer of intellectual property and other	126,065	81,853	44,212
Total revenues	$ 1,221,661	$ 491,738	$ 729,923

The increase in Revenue from services is attributable to the acquisition of Bio-Reference in August 2015. The increase in Revenue from products principally reflects an increase in revenue from EirGen, which we acquired in May 2015, and an increase in revenue from OPKO Chile. Revenue from transfer of intellectual property for the year ended December 31, 2016 principally reflects $50.0 million of revenue from the initial payment in the VFMCRP Agreement and $70.6 million of revenue from the transfer of intellectual property related to the Pfizer Transaction. Revenue from transfer of intellectual property for the year ended December 31, 2015 principally reflects $65.5 million of revenue from the transfer of intellectual property related to the Pfizer Transaction and $15.0 million of revenue from a milestone payment from our licensee, TESARO, in the fourth quarter of 2015. We are recognizing the non-refundable $295.0 million upfront payments received in the Pfizer Transaction on a straight-line basis over the expected performance period. The performance period is expected to continue through 2019, when we anticipate completing the various research and development services that are specified in the Pfizer Transaction.

Costs of revenue . Costs of revenue for the year ended December 31, 2016 increased $376.2 million compared to the prior year. Our acquisition of Bio-Reference in August 2015 accounted for $375.9 million of the increase in cost of service revenue. The increase in cost of product revenue is attributable to an increase in cost of revenue from EirGen and OPKO Chile, which was partially offset by the deconsolidation of SciVac Therapeutics Inc. ("STI") in July 2015. Cost of revenue for the years ended December 31, 2016 and 2015 were as follows:

Cost of Revenue

(In thousands)	For the year ended December 31, 2016	2015	Change
Cost of service revenue	$ 564,103	$ 193,305	$ 370,798
Cost of product revenue	47,379	41,934	5,445
Total cost of revenue	$ 611,482	$ 235,239	$ 376,243

Selling, general and administrative expenses . Selling, general and administrative expenses for the years ended December 31, 2016 and 2015 were $490.9 million and $196.6 million , respectively. The increase in selling, general and administrative expenses for the year ended December 31, 2016 was primarily due to the acquisition of Bio-Reference in August 2015, which accounted for $382.4 million of selling, general and administrative expenses in the 2016 period compared to $118.1 million for the comparable period of 2015. In addition, the year ended December 31, 2016 included costs related to the launch of *Rayaldee* . Included in selling, general and administrative expenses for the year ended December 31, 2016 are $17.9 million of severance costs for certain Bio-Reference executives.

Selling, general and administrative expenses during the years ended December 31, 2016 and 2015 , include equity-based compensation expense of $33.4 million and $17.4 million , respectively. The increase in equity-based compensation expense is due to additional options grants made in 2016 and $8.9 million of expense related to the acceleration of stock option vesting for certain Bio-Reference executives.

Research and development expenses . Research and development expenses for the years ended December 31, 2016 and 2015 were $111.2 million and $99.5 million , respectively. Research and development costs include external and internal expenses, partially offset by third-party grants and funding arising from collaboration agreements. External expenses include clinical and non-clinical activities performed by contract research organizations, lab services, purchases of drug and diagnostic product materials and manufacturing development costs. We track external research and development expenses by individual program for phase 3 clinical trials for drug approval and PMA's (pre-market approval) for diagnostics tests, if any. Internal expenses include employee-related expenses including salaries, benefits and stock-based compensation expense. Other internal research and development expenses are incurred to support overall research and development activities and include expenses related to general overhead and facilities.

The following table summarizes the components of our research and development expenses:

	For the years ended December 31,	
	2016	2015
External expenses:		
Phase 3 clinical trials	$ 12,161	$ 12,178
Manufacturing expense for biological products	35,985	31,202
Earlier-stage programs	6,297	6,900
Research and development employee-related expenses	28,676	27,363
Other internal research and development expenses	30,752	24,161
Third-party grants and funding from collaboration agreements	(2,666)	(2,316)
Total research and development expenses	$ 111,205	$ 99,488

The increase in research and development expenses during the year ended December 31, 2016 , is due to an increase in research and development expenses related to hGH-CTP, a long acting human growth hormone which was outlicensed to Pfizer in 2015, and to an increase in research and development expenses for Factor VIIa-CTP. Research and development expenses for the year ended December 31, 2016 also include $8.8 million from the acquisitions of Bio-Reference and EirGen in August 2015 and May 2015, respectively, compared to $4.1 million for the comparable period of 2015. This was partially offset by decreased expenses incurred by OPKO Renal related to the development of *Rayaldee* . In addition, during the years ended December 31, 2016 and 2015 , we recorded, as an offset to research and development expenses, $2.7 million and $2.3 million , respectively, related to research and development grants received from our collaboration and funding agreements. Research and development expenses for the year ended December 31, 2016 and 2015 include equity-based compensation expenses of $7.5 million and $7.9 million , respectively. We expect our research and development expenses to increase as we continue to expand our research and development of potential future products.

Contingent consideration . Contingent consideration expense for the years ended December 31, 2016 and 2015 , were $17.0 million and $5.1 million , respectively. The increase in contingent consideration is attributable to OPKO Renal resulting from an increase in the fair value of our contingent obligations due to changes in assumptions regarding the timing of successful achievement of future milestones driven by the FDA approval of *Rayaldee* in June 2016. The contingent consideration liabilities at December 31, 2016 relate to potential amounts payable to former stockholders of CURNA, OPKO Diagnostics, OPKO Health Europe and OPKO Renal pursuant to our acquisition agreements in January 2011, October 2011, August 2012 and March 2013, respectively.

Amortization of intangible assets . Amortization of intangible assets was $64.4 million and $28.0 million , respectively, for the years ended December 31, 2016 and 2015 . Amortization expense reflects the amortization of acquired intangible assets with defined useful lives. Amortization of intangible assets for the year ended December 31, 2016 also includes $8.0 million of amortization expense related to intangible assets for *Rayaldee.* Upon the FDA's approval of *Rayaldee* in June 2016, we reclassified $187.6 million of IPR&D related to *Rayaldee* from In-process research and development to Intangible assets, net in our Consolidated Balance Sheet and began to amortize that asset. Amortization of intangible assets for the year ended December 31, 2016 includes $43.2 million and $2.5 million from Bio-Reference and EirGen which we acquired in August 2015 and May 2015, respectively, compared to $14.6 million and $1.7 million, respectively, for the comparable period of 2015. Our IPR&D assets will not be amortized until the underlying development programs are completed. Upon obtaining regulatory approval by the U.S. FDA, the IPR&D assets will be accounted for as a finite-lived intangible asset and amortized on a straight-line basis over its estimated useful life.

Grant repayment. During the year ended December 31, 2015 , we made a payment of $25.9 million to the Office of the Chief Scientist of the Israeli Ministry of Economy ("OCS") in connection with repayment obligations resulting from grants previously made by the OCS to OPKO Biologics to support development of hGH-CTP and the outlicense of the technology outside of Israel. We did not have any such activity for the year ended December 31, 2016 .

Interest income. Interest income for the years ended December 31, 2016 and 2015 , was not significant as our cash investment strategy emphasizes the security of the principal invested and fulfillment of liquidity needs.

Interest expense. Interest expense for the years ended December 31, 2016 and 2015 , was $7.4 million and $8.4 million , respectively. Interest expense is principally related to interest incurred on the 2033 Senior Notes including amortization of related deferred financing costs and to the interest incurred on Bio-Reference's outstanding debt under its credit facility. The decrease in interest expense for the year ended December 31, 2016 is due to a decrease in the average principal amount of the 2033 Senior Notes outstanding in 2016 compared to 2015. Interest expense for the year ended December 31, 2015 also reflects

a non-cash write-off of deferred financing costs of $1.0 million as interest expense related to the exchange of $55.4 million principal of 2033 Senior Notes in 2015. This was partially offset by interest incurred on Bio-Reference's outstanding debt under its credit facility for the year ended December 31, 2016 .

Fair value changes of derivative instruments, net. Fair value changes of derivative instruments, net for the years ended December 31, 2016 and 2015 , were $2.8 million of income and $39.1 million of expense, respectively. Fair value changes of derivative instruments, net related to non-cash income (expense) reflects the changes in the fair value of the embedded derivatives in the 2033 Senior Notes of $7.0 million and $(36.6) million for the years ended December 31, 2016 and 2015 , respectively. Fair value changes of derivative instruments, net for the year ended December 31, 2016 also reflects $4.2 million of expense related to the change in the fair value of warrants and options to purchase additional shares of Neovasc, Cocrystal Pharma, Inc., ARNO Therapeutics, Inc. and MabVax Therapeutics Holdings, Inc.

Other income and (expense), net. Other income and (expense), net for the years ended December 31, 2016 and 2015 , were $3.9 million and $7.7 million of income, respectively. Other income (expense), net for the year ended December 31, 2016 primarily consists of a $2.5 million gain recognized in connection with the merger of STI and VBI Vaccines Inc., a $5.0 million gain recognized in connection with the settlement of a legal matter and foreign currency transaction gains recognized during the period, which was partially offset by a $4.8 million other-than-temporary impairment charge to write our investments in Xenetic, ARNO and RXi down to their respective fair values. Other income (expense), net for the year ended December 31, 2015 primarily consists of a $15.9 million gain recognized on the deconsolidation of STI in 2015 which was partially offset by a $7.3 million other-than-temporary impairment charge to write our investment in RXi Pharmaceuticals Corporation down to its fair value.

Income tax benefit (provision) . Our income tax benefit for the years ended December 31, 2016 and 2015 was $56.1 million , and $113.7 million , respectively. The change in income taxes is primarily due to a $93.4 million release of OPKO's valuation allowance in 2015 on our U.S. deferred tax assets as a result of the merger with Bio-Reference and to changes in the geographic mix of revenues and expenses. In addition, income taxes in 2016 benefited from a favorable corporate tax rate reduction in Israel.

Loss from investments in investees . We have made investments in other early stage companies that we perceive to have valuable proprietary technology and significant potential to create value for us as a shareholder or member. We account for these investments under the equity method of accounting, resulting in the recording of our proportionate share of their losses until our share of their loss exceeds our investment. Until the investees' technologies are commercialized, if ever, we anticipate they will continue to report a net loss. Loss from investments in investees was $7.7 million and $7.1 million for the years ended December 31, 2016 and 2015 , respectively.

For The Years Ended December 31, 2015 and December 31, 2014

Revenues . Revenues for the year ended December 31, 2015 increased $400.6 million compared to the prior year. Our acquisition of Bio-Reference in August 2015 accounted for $321.9 million of the year-over-year revenue growth. Revenues for the years ended December 31, 2015 and 2014 were as follows:

Revenues

(In thousands)	For the year ended December 31, 2015	2014	Change
Revenue from services	$ 329,739	$ 8,666	$ 321,073
Revenue from products	80,146	76,983	3,163
Revenue from transfer of intellectual property and other	81,853	5,476	76,377
Total revenues	$ 491,738	$ 91,125	$ 400,613

The increase in Revenue from services was attributable to the acquisition of Bio-Reference in August 2015. The increase in Revenue from products principally reflected $12.1 million of revenue from EirGen, which we acquired in May 2015, which was partially offset by the unfavorable impact of foreign exchange rates of approximately $8.7 million, and decreased revenue from STI, a VIE we deconsolidated in July 2015. The increase in Revenue from transfer of intellectual property principally reflected $65.5 million of revenue from the transfer of intellectual property related to the Pfizer Transaction and $15.0 million of revenue from a milestone payment from our licensee TESARO in the fourth quarter of 2015 compared to $5.0 million of revenue from a milestone payment from our licensee TESARO in 2014.

Costs of revenue . Costs of revenue for the year ended December 31, 2015 increased $187.2 million compared to the prior year. Our acquisition of Bio-Reference in August 2015 accounted for $183.3 million of the year-over-year cost of revenue growth. Cost of revenue for the years ended December 31, 2015 and 2014 were as follows:

Cost of Revenue

(In thousands)	For the year ended December 31, 2015	2014	Change
Cost of service revenue	$ 193,305	$ 9,372	$ 183,933
Cost of product revenue	41,934	38,637	3,297
Total cost of revenue	$ 235,239	$ 48,009	$ 187,230

The increase in cost of service revenue was attributable to the acquisition of Bio-Reference in August 2015. The increase in cost of product revenue principally reflected cost of revenue of $6.8 million from EirGen, which we acquired in May 2015, which was partially offset by the impact of foreign exchange rates of approximately $5.2 million and the deconsolidation of STI in July 2015.

Selling, general and administrative expenses . Selling, general and administrative expenses for the years ended December 31, 2015 and 2014 were $196.6 million and $57.9 million, respectively. The increase in selling, general and administrative expenses for the year ended December 31, 2015 was primarily due to the acquisitions of Bio-Reference and EirGen in 2015, which recognized $118.1 million and $1.8 million of selling, general and administrative expenses in 2015, respectively, increased personnel expenses as we expand our sales, marketing and administrative staff and add infrastructure, and an increase in professional fees attributable to our acquisitions of Bio-Reference and EirGen. Selling, general and administrative expenses during the years ended December 31, 2015 and 2014, included bad debt expense of $24.6 million and $0.7 million, respectively, and equity-based compensation expense of $17.4 million and $9.7 million, respectively. The increase in bad debt expense was due to the acquisition of Bio-Reference. The increase in equity-based compensation expense was due to additional options grants made in 2015 and fluctuations in the price of our common stock.

Research and development expenses . Research and development expenses for the years ended December 31, 2015 and 2014 were $99.5 million and $83.6 million, respectively. Research and development costs included external and internal expenses, partially offset by third-party grants and funding arising from collaboration agreements. External expenses included clinical and non-clinical activities performed by contract research organizations, lab services, purchases of drug and diagnostic product materials and manufacturing development costs. We tracked external research and development expenses by individual program for phase 3 clinical trials for drug approval and PMA’s (pre-market approval) for diagnostics tests, if any. Internal expenses include employee-related expenses including salaries, benefits and stock-based compensation expense. Other internal research and development expenses were incurred to support overall research and development activities and included expenses related to general overhead and facilities.

The following table summarizes the components of our research and development expenses:

	For the years ended December 31,	
	2015	2014
External expenses:		
Phase 3 clinical trials	$ 12,178	$ 14,512
Manufacturing expense for biological products	31,202	18,692
Earlier-stage programs	6,900	9,093
Research and development employee-related expenses	27,363	21,642
Other internal research and development expenses	24,161	21,982
Third-party grants and funding from collaboration agreements	(2,316)	(2,350)
Total research and development expenses	$ 99,488	$ 83,571

The increase in research and development expenses during the year ended December 31, 2015, was primarily due to a $16.7 million increase in research and development expenses related to hGH-CTP, a long acting human growth hormone which was outlicensed to Pfizer in 2015, including manufacturing expense for biological products, and the recognition of $2.3 million of expense for our NDA submission to the FDA for oral *Rayaldee* in May 2015. Research and development expenses for the year ended December 31, 2015 also included $4.1 million from the acquisitions of Bio-Reference and EirGen in August 2015 and May 2015, respectively. This was partially offset by decreased expenses incurred by OPKO Renal related to phase 3 clinical trials for *Rayaldee* , which were completed in 2014. In addition, during the year ended December 31, 2015 and 2014, we recorded, as an offset to research and development expenses, $2.3 million and $2.4 million, respectively, related to research and development grants received from our collaboration and funding agreements. Research and development expenses for the year ended December 31, 2015 and 2014 included equity-based compensation expense of $7.9 million and $5.0 million, respectively.

In-Process Research and Development. In May 2014, we acquired Inspiro in a stock for stock transaction. We recorded the transaction as an asset acquisition and recorded the assets and liabilities at fair value, and as a result, we recorded $10.1 million of acquired in-process research and development expense. In addition, pursuant to our agreement with Merck & Co. (“Merck”), we were required to make a $2.0 million payment upon the achievement of a milestone for VARUBI™ which was achieved in the fourth quarter of 2014. The agreement was accounted for as an asset acquisition and the entire $2.0 million milestone payment was allocated to in-process research and development expense. No In-process research and development expense was incurred during the year ended December 31, 2015.

Contingent consideration . Contingent consideration expenses for the years ended December 31, 2015 and 2014, were $5.1 million and $24.4 million, respectively. The decrease in contingent consideration expense was attributable to OPKO Renal resulting from an increase in the fair value of our contingent obligations to OPKO Renal in 2014 due to changes in assumptions regarding probabilities of successful achievement of future milestones driven by the two successful phase 3 trials of *Rayaldee* in 2014. The contingent consideration liabilities at December 31, 2015 related to potential amounts payable to former stockholders of CURNA, OPKO Diagnostics, OPKO Health Europe and OPKO Renal pursuant to our acquisition agreements in January 2011, October 2011, August 2012 and March 2013, respectively.

Amortization of intangible assets . Amortization of intangible assets was $28.0 million and $10.9 million, respectively, for the years ended December 31, 2015 and 2014. Amortization expense reflected the amortization of acquired intangible assets with defined useful lives. Amortization of intangible assets for the year ended December 31, 2015 included $14.6 million and $1.7 million from Bio-Reference and EirGen which we acquired in August 2015 and May 2015, respectively. Our IPR&D assets will not be amortized until the underlying development programs are completed. Upon obtaining regulatory approval by the U.S. FDA, the IPR&D assets will then be accounted for as a finite-lived intangible asset and amortized on a straight-line basis over its estimated useful life.

Grant repayment. During the year ended December 31, 2015, we made a payment of $25.9 million to the Office of the Chief Scientist of the Israeli Ministry of Economy (“OCS”) in connection with repayment obligations resulting from grants previously made by the OCS to OPKO Biologics to support development of hGH-CTP and the outlicense of the technology outside of Israel.

Interest income. Interest income for the years ended December 31, 2015 and 2014, was not significant as our cash investment strategy emphasizes the security of the principal invested and fulfillment of liquidity needs.

Interest expense. Interest expense for the years ended December 31, 2015 and 2014, was $8.4 million and $12.3 million, respectively. Interest expense was principally related to interest incurred on the 2033 Senior Notes and the amortization of related deferred financing costs. The decrease in interest expense for the year ended December 31, 2015 compared to 2014 was due to a decrease in the principal amount of 2033 Senior Notes outstanding from $87.6 million at December 31, 2014 to $32.2 million as of December 31, 2015. This was partially offset by interest expense of $1.9 million from Bio-Reference due to outstanding debt under their credit facility. Interest expense for the years ended December 31, 2015 and 2014 also reflected non-cash write-offs of deferred financing costs of $1.0 million and $1.5 million as interest expense related to exchange or conversion of $55.4 million and $70.4 million principal of 2033 Senior Notes during the years ended December 31, 2015 and 2014, respectively.

Fair value changes of derivative instruments, net. Fair value changes of derivative instruments, net for the years ended December 31, 2015 and 2014, were $39.1 million and $10.6 million of expense, respectively. Fair value changes of derivative instruments, net principally related to non-cash expense related to the changes in the fair value of the embedded derivatives in the 2033 Senior Notes of $36.6 million and $12.2 million for the years ended December 31, 2015 and 2014, respectively.

Other income and (expense), net. Other income and (expense), net for the years ended December 31, 2015 and 2014, were $7.7 million of income and $3.1 million of expense, respectively. The increase in other income and (expense), net for the year ended December 31, 2015 compared to 2014 was primarily due to a $15.9 million gain recognized on the deconsolidation of STI in the third quarter of 2015. This was partially offset by a $7.3 million other-than-temporary impairment charge to write our investment in RXi Pharmaceuticals Corporation down to its fair value of $0.9 million as of December 31, 2015 compared to a $1.4 million other-than-temporary impairment charge to our investment in ARNO Therapeutics in 2014.

Income tax benefit (provision) . Our income tax benefit was due to a $93.4 million release of OPKO's valuation allowance on our U.S. deferred tax assets as a result of the merger with Bio-Reference. This was partially offset by expense recognized on taxable income from the Pfizer Transaction during the year ended December 31, 2015. In addition, our income tax benefit (provision) reflected the projected income tax payable in the U.S., Ireland, Israel, Chile, Spain, Mexico, and Luxembourg.

Loss from investments in investees . We have made investments in other early stage companies that we perceive to have valuable proprietary technology and significant potential to create value for us as a shareholder or member. We accounted for these investments under the equity method of accounting, resulting in the recording of our proportionate share of their losses until our share of their loss exceeds our investment. Until the investees' technologies are commercialized, if ever, we anticipated they would continue to report a net loss. Loss from investments in investees was $7.1 million and $3.6 million for the years ended December 31, 2015 and 2014, respectively. In the third quarter of 2015, we deconsolidated STI, and account for our retained interest in STI as an equity method investment.

LIQUIDITY AND CAPITAL RESOURCES

At December 31, 2016 , we had cash and cash equivalents of approximately $168.7 million . Cash provided by operations during 2016 principally reflects a $50.0 million upfront payment received from the VFMCRP Agreement, our operations at Bio-Reference, and a $39.4 million payment received from the Internal Revenue Service for a change in accounting method, partially offset by expenses related to general and administrative activities related to our corporate operations, research and development activities and our launch activities related to *Rayaldee* . Cash used in investing activities primarily reflects capital expenditures of $18.5 million , investments of $14.4 million and acquisitions of intangible assets of $5.0 million , partially offset by cash acquired in the acquisition of Transition Therapeutics of $15.9 million . Cash used in financing activities primarily reflects net repayments on lines of credit of $43.8 million , partially offset by $8.6 million received from Common Stock option and Common Stock warrant exercises. We have not generated sustained positive cash flow sufficient to offset our operating and other expenses and our primary source of cash has been from the public and private placement of stock, the issuance of the 2033 Senior Notes and credit facilities available to us.

In November 2016, we launched commercial sales for *Rayaldee* in the U.S. market. The FDA approved *Rayaldee* extended release capsules in June 2016 for the treatment of SHPT in adults with stage 3 or 4 CKD and serum total 25-hydroxyvitamin D levels less than 30 ng/mL. We have a highly specialized sales and marketing team dedicated to the launch and commercialization of *Rayaldee* , and we expect to increase the sales and marketing team in the second half of 2017 as market access improves and prescription trends increase.

In August 2016, we completed the acquisition of Transition Therapeutics, a clinical stage biotechnology company. Holders of Transition Therapeutics common stock received 6,431,899 shares of OPKO Common Stock. The transaction was valued at approximately $58.5 million, based on a closing price per share of our Common Stock of $9.10 as reported by NASDAQ on the closing date.

In May 2016, EirGen, our wholly-owned subsidiary, partnered with VFMCRP through a Development and License Agreement for the development and marketing of *Rayaldee* in Europe, Canada, Mexico, Australia, South Korea and certain other international markets. The license to VFMCRP potentially covers all therapeutic and prophylactic uses of the product in human patients, provided that initially the license is for the use of the product for the treatment or prevention of secondary hyperparathyroidism related to patients with stage 3 or 4 chronic kidney disease and vitamin D insufficiency/deficiency ("Initial Indication"). We received a non-refundable and non-creditable upfront payment of $50 million and are eligible to receive up to an additional $232 million upon the achievement of certain regulatory and sales-based milestones. In addition, we are eligible to receive tiered, double digit royalty payments or a minimum royalty, whichever is greater, upon commencement of sales of the product.

As part of the arrangement, the companies will share responsibility for the conduct of trials specified within an agreed-upon development plan, with each company leading certain activities within the plan. For the initial development plan , the companies have agreed to certain cost sharing arrangements. VFMCRP will be responsible for all other development costs that VFMCRP considers necessary to develop the product for the Initial Indication in the Territory except as otherwise provided in the VFMCRP Agreement. EirGen also granted to VFMCRP an option to acquire an exclusive license to use, import, offer for sale, sell, distribute and commercialize the product in the United States for treatment of SHPT in dialysis patients with stage 5 CKD and vitamin D insufficiency (the "Dialysis Indication") Upon exercise of the Option, VFMCRP will reimburse EirGen for all of the development costs incurred by EirGen with respect to the product for the Dialysis Indication in the United States. VFMCRP would also pay EirGen up to an additional aggregate amount of $555 million upon the achievement of certain milestones and would be obligated to pay double digit royalties on VFMCRP’s sales in the United States for the Dialysis Indication.

In January 2015, we partnered with Pfizer through a worldwide agreement for the development and commercialization of our long-acting hGH-CTP for the treatment of GHD in adults and children, as well as for the treatment of growth failure in children born SGA. Under the terms of the agreements with Pfizer, we received non-refundable and non-creditable upfront payments of $295.0 million in the first quarter of 2015 and are eligible to receive up to an additional $275 million upon the achievement of certain regulatory milestones. Pfizer received the exclusive license to commercialize hGH-CTP worldwide. In addition, we are eligible to receive initial tiered royalty payments associated with the commercialization of hGH-CTP for Adult GHD with percentage rates ranging from the high teens to mid-twenties. Upon the launch of hGH-CTP for Pediatric GHD in certain major markets, the royalties will transition to regional, tiered gross profit sharing for both hGH-CTP and Pfizer’s Genotropin®.

We will lead the clinical activities and will be responsible for funding the development programs for the key indications, which includes Adult and Pediatric GHD and Pediatric SGA. Pfizer will be responsible for all development costs for additional indications as well as all post-marketing studies. In addition, Pfizer will fund the commercialization activities for all

indications and lead the manufacturing activities covered by the global development plan. In December 2016, we announced preliminary topline data from our Phase 3, double blind, placebo controlled study of hGH-CTP in adults with GHD. Although there was no statistically significant difference between hGH-CTP and placebo on the primary endpoint of change in trunk fat mass from baseline to 26 weeks, after unblinding the study, we identified an exceptional value of trunk fat mass reduction in the placebo group that may have affected the primary outcome. We believe the exceptional data point warrants an outlier sensitivity analysis of the primary endpoint and related secondary endpoints. Upon completion of the data sensitivity analysis, we plan to discuss the study results and outlier analysis with the regulatory authorities to determine next steps in obtaining regulatory approval.

In August 2015, we completed the acquisition of Bio-Reference, the third largest full service clinical laboratory in the United States, known for its innovative technological solutions and pioneering leadership in the areas of genomics and genetic sequencing. Holders of Bio-Reference common stock received 76,566,147 shares of OPKO Common Stock for the outstanding shares of Bio-Reference common stock. The transaction was valued at approximately $950.1 million , based on a closing price per share of our Common Stock of $12.38 as reported by the New York Stock Exchange, or $34.05 per share of Bio-Reference common stock. Included in the transaction value is $2.3 million related to the value of replacement stock option awards attributable to pre-merger service.

In May 2015, we entered into a series of purchase agreements to acquire all of the issued and outstanding shares of EirGen, a specialty pharmaceutical company incorporated in Ireland focused on the development and commercial supply of high potency, high barrier to entry pharmaceutical products, for $133.8 million . We acquired the outstanding shares of EirGen for approximately $100.2 million in cash and delivered 2,420,487 shares of our Common Stock valued at approximately $33.6 million based on the closing price per share of our Common Stock as reported by the New York Stock Exchange on the closing date of the acquisition, $13.88 per share.

We plan to construct a research, development and manufacturing center in Waterford, Ireland, for which we expect to incur between $30 million and $40 million for the construction and validation of the facility with expenditures beginning in the fourth quarter of 2016 and expected completion in 2019. Currently, we plan to fund the project from cash on hand or from third party funding sources that may be available to us.

Our licensee, TESARO, received approval by the U.S. FDA in September 2015 for oral VARUBI™, a neurokinin-1 receptor antagonist for the prevention of chemotherapy-induced nausea and vomiting. In November 2015, TESARO announced the commercial launch of VARUBI™ in the United States. We are eligible to receive milestone payments of up to $30.0 million (of which $20.0 million has been received to date) upon achievement of certain regulatory and commercial sale milestones and additional commercial milestone payments of up to $85.0 million if specified levels of annual net sales are achieved. TESARO is also obligated to pay us tiered royalties on annual net sales achieved in the United States and Europe at percentage rates that range from the low double digits to the low twenties, and outside of the United States and Europe at low double-digit percentage rates.

2033 Senior Notes. In January 2013, we issued $175.0 million of the 2033 Senior Notes. The 2033 Senior Notes were sold in a private placement in reliance on exemptions from registration under the Securities Act. At December 31, 2016 , $31.9 million principal amount of 2033 Senior Notes was outstanding.

On January 3, 2017, we announced that our 2033 Senior Notes continue to be convertible by holders of such 2033 Senior Notes through March 31, 2017. We have elected to satisfy the conversion obligation in shares of our Common Stock. This conversion right has been extended because the closing price per share of our Common Stock has exceeded $9.19 , or 130% of the applicable conversion price of $7.07 , for at least 20 of 30 consecutive trading days during the quarter ended on December 31, 2016 . The 2033 Senior Notes will continue to be convertible until March 31, 2017, and may be convertible thereafter, if one or more of the conversion conditions specified in the Indenture is satisfied during future measurement periods. Pursuant to the Indenture, a holder who elects to convert the 2033 Senior Notes will receive 141.4827 shares of our Common Stock plus such number of additional shares as is applicable on the conversion date per $1,000 principal amount of 2033 Senior Notes based on the early conversion provisions in the Indenture.

In connection with our acquisitions of CURNA, OPKO Diagnostics, OPKO Health Europe and OPKO Renal, we agreed to pay future consideration to the sellers upon the achievement of certain events, including up to an additional $19.1 million in shares of our Common Stock to the former stockholders of OPKO Diagnostics upon and subject to the achievement of certain milestones; and up to an additional $125.0 million in either shares of our Common Stock or cash, at our option subject to the achievement of certain milestones, to the former shareholders of OPKO Renal.

During the year ended December 31, 2016 , we also satisfied a $25.0 million contingent payment to the former owners of OPKO Renal through the issuance of 2,611,648 shares of our common stock in 2016.

On November 5, 2015, Bio-Reference and certain of its subsidiaries entered into a credit agreement with JPMorgan Chase Bank, N.A. ("CB"), as lender and administrative agent, as amended (the "Credit Agreement"). The Credit Agreement provides for a $175.0 million secured revolving credit facility and includes a $20.0 million sub-facility for swingline loans and a $20.0 million sub-facility for the issuance of letters of credit. Bio-Reference may increase the credit facility to up to $275.0 million on a secured basis, subject to the satisfaction of specified conditions. The Credit Agreement matures on November 5, 2020 and is guaranteed by all of Bio-Reference's domestic subsidiaries. The Credit Agreement is also secured by substantially all assets of Bio-Reference and its domestic subsidiaries, as well as a non-recourse pledge by us of our equity interest in Bio-Reference. Availability under the Credit Agreement is based on a borrowing base comprised of eligible accounts receivables of Bio-Reference and certain of its subsidiaries, as specified therein. The proceeds of the new credit facility were used to refinance existing indebtedness, to finance working capital needs and for general corporate purposes of Bio-Reference and its subsidiaries.

As of December 31, 2016 , the total availability under our Credit Agreement with CB and our lines of credit with financial institutions in Chile and Spain was $151.9 million , of which $47.3 million was used and outstanding at December 31, 2016 . The weighted average interest rate on these lines of credit is approximately 4.7% . These lines of credit are short-term and are used primarily as a source of working capital. The highest balance at any time during the year ended December 31, 2016 , was $83.5 million . We intend to continue to enter into these lines of credit as needed. There is no assurance that these lines of credit or other funding sources will be available to us on acceptable terms, or at all, in the future.

We expect to continue to incur substantial research and development expenses, including expenses related to the hiring of personnel and additional clinical trials. We expect that selling, general and administrative expenses will also increase as we expand our sales, marketing and administrative staff and add infrastructure.

We believe that the cash and cash equivalents on hand at December 31, 2016 , and the amounts available to be borrowed under our lines of credit are sufficient to meet our anticipated cash requirements for operations and debt service beyond the next 12 months. We based this estimate on assumptions that may prove to be wrong or are subject to change, and we may be required to use our available cash resources sooner than we currently expect. If we acquire additional assets or companies, accelerate our product development programs or initiate additional clinical trials, we will need additional funds. Our future cash requirements will depend on a number of factors, including our relationship with Pfizer, success of the commercial launch of *Rayaldee* , Bio-Reference's financial performance, possible acquisitions, the continued progress of research and development of our product candidates, the timing and outcome of clinical trials and regulatory approvals, the costs involved in preparing, filing, prosecuting, maintaining, defending, and enforcing patent claims and other intellectual property rights, the status of competitive products, the availability of financing, and our success in developing markets for our product candidates. If we are not able to secure additional funding when needed, we may have to delay, reduce the scope of, or eliminate one or more of our clinical trials or research and development programs or possible acquisitions.

The following table provides information as of December 31, 2016 , with respect to the amounts and timing of our known contractual obligation payments due by period.

Contractual obligations (In thousands)	2017	2018	2019	2020	2021	Thereafter	Total
Open purchase orders	$ 86,262	$ 2,955	$ 1,032	$ 9	$ —	$ —	$ 90,258
Operating leases	16,751	12,396	9,967	4,761	2,964	6,173	53,012
Capital leases	3,006	2,633	2,137	1,409	485	571	10,241
2033 Senior Notes	—	—	31,850	—	—	—	31,850
Deferred payments	5,000	5,000	5,000	—	—	—	15,000
Mortgages and other debts payable	3,310	406	362	356	356	981	5,771
Lines of credit	8,512	—	—	38,809	—	—	47,321
Severance payments	6,327	—	—	—	—	—	6,327
Interest commitments	1,082	1,011	205	34	53	—	2,385
Total	$ 130,250	$ 24,401	$ 50,553	$ 45,378	$ 3,858	$ 7,725	$ 262,165

The preceding table does not include information where the amounts of the obligations are not currently determinable, including the following:

- Contractual obligations in connection with clinical trials, which span over two years, and that depend on patient enrollment. The total amount of expenditures is dependent on the actual number of patients enrolled and as such, the contracts do not specify the maximum amount we may owe.

- Product license agreements effective during the lesser of 15 years or patent expiration whereby payments and amounts are determined by applying a royalty rate on uncapped future sales.

- Contingent consideration that includes payments upon achievement of certain milestones including meeting development milestones such as the completion of successful clinical trials, NDA approvals by the FDA and revenue milestones upon the achievement of certain revenue targets all of which are anticipated to be paid within the next seven years and are payable in either shares of our Common Stock or cash, at our option, and that may aggregate up to $159.4 million .

CRITICAL ACCOUNTING POLICIES AND ESTIMATES

Accounting estimates. The preparation of financial statements in conformity with accounting principles generally accepted in the United States requires management to make estimates and assumptions that affect the reported amounts of assets and liabilities and disclosure of contingent assets and liabilities at the date of the financial statements and the reported amounts of revenues and expenses during the reporting period. Actual results could differ significantly from these estimates.

Goodwill and intangible assets. Goodwill and other intangible assets, including IPR&D, acquired in business combinations, licensing and other transactions at December 31, 2016 and 2015 was $2.1 billion and $2.2 billion , respectively, representing approximately 76% and 78% of total assets, respectively.

Assets acquired and liabilities assumed in business combinations, licensing and other transactions are generally recognized at the date of acquisition at their respective fair values. Any excess of the purchase price over the estimated fair values of the net assets acquired is recognized as goodwill. We determined the fair value of intangible assets, including IPR&D, using the "income method." This method starts with a forecast of net cash flows, risk adjusted for estimated probabilities of technical and regulatory success (for IPR&D) and adjusted to present value using an appropriate discount rate that reflects the risk associated with the cash flow streams. All assets are valued from a market participant view which might be different than our specific views. The valuation process is very complex and requires significant input and judgment using internal and external sources. Although a valuation is required to be finalized within a one-year period, it must consider all and only those facts and evidence which existed at the acquisition date. The most complex and judgmental matters applicable to the valuation process are summarized below:

- Unit of account – Most intangible assets are valued as single global assets rather than multiple assets for each jurisdiction or indication after considering the development stage, expected levels of incremental costs to obtain additional approvals, risks associated with further development, amount and timing of benefits expected to be derived in the future, expected patent lives in various jurisdictions and the intention to promote the asset as a global brand.

- Estimated useful life – The asset life expected to contribute meaningful cash flows is determined after considering all pertinent matters associated with the asset, including expected regulatory approval dates (if unapproved), exclusivity periods and other legal, regulatory or contractual provisions as well as the effects of any obsolescence, demand, competition, and other economic factors, including barriers to entry.

- Probability of Technical and Regulatory Success ("PTRS") Rate – PTRS rates are determined based upon industry averages considering the respective program's development stage and disease indication and adjusted for specific information or data known at the acquisition date. Subsequent clinical results or other internal or external data obtained could alter the PTRS rate and materially impact the estimated fair value of the intangible asset in subsequent periods leading to impairment charges.

- Projections – Future revenues are estimated after considering many factors such as initial market opportunity, pricing, sales trajectories to peak sales levels, competitive environment and product evolution. Future costs and expenses are estimated after considering historical market trends, market participant synergies and the timing and level of additional development costs to obtain the initial or additional regulatory approvals, maintain or further enhance the product. We generally assume initial positive cash flows to commence shortly after the receipt of expected regulatory approvals which typically may not occur for a number of years. Actual cash flows attributed to the project are likely to be different than those assumed since projections are subjected to multiple factors including trial results and regulatory matters which could materially change the ultimate commercial success of the asset as well as significantly alter the costs to develop the respective asset into commercially viable products.

- Tax rates – The expected future income is tax effected using a market participant tax rate. In determining the tax rate, we consider the jurisdiction in which the intellectual property is held and location of research and manufacturing infrastructure. We also consider that any repatriation of earnings would likely have U.S. tax consequences.

- Discount rate – Discount rates are selected after considering the risks inherent in the future cash flows; the assessment of the asset's life cycle and the competitive trends impacting the asset, including consideration of any technical, legal, regulatory, or economic barriers to entry, as well as expected changes in standards of practice for indications addressed by the asset.

Goodwill was $704.6 million and $743.3 million , respectively, at December 31, 2016 and 2015 . Goodwill is tested at least annually for impairment or when events or changes in circumstances indicate that the carrying amount of such assets may not be recoverable, by assessing qualitative factors or performing a quantitative analysis in determining whether it is more likely than not that its fair value exceeds the carrying value. Examples of qualitative factors include our share price, our

financial performance compared to budgets, long-term financial plans, macroeconomic, industry and market conditions as well as the substantial excess of fair value over the carrying value of net assets from the annual impairment test previously performed. No goodwill impairment was recorded for the year ended December 31, 2016 as a result of our testing. We recorded $87 thousand of goodwill impairment during the year ended December 31, 2015 as a result of our testing.

The estimated fair value of a reporting unit is highly sensitive to changes in projections and assumptions; therefore, in some instances changes in these assumptions could potentially lead to impairment. We perform sensitivity analyses around our assumptions in order to assess the reasonableness of the assumptions and the results of our testing. Ultimately, future potential changes in these assumptions may impact the estimated fair value of a reporting unit and cause the fair value of the reporting unit to be below its carrying value. We believe that our estimates are consistent with assumptions that marketplace participants would use in their estimates of fair value. However, if actual results are not consistent with our estimates and assumptions, we may be exposed to an impairment charge that could be material.

Intangible assets, net were $1.4 billion and $1.4 billion , including IPR&D of $644.7 million and $792.3 million , respectively, at December 31, 2016 and 2015 . Intangible assets are tested for impairment whenever events or changes in circumstances indicate that the carrying amount of such assets may not be recoverable, although IPR&D is required to be tested at least annually until the project is completed or abandoned. Upon obtaining regulatory approval, the IPR&D asset is then accounted for as a finite-lived intangible asset and amortized on a straight-line basis over its estimated useful life. If the project is abandoned, the IPR&D asset is charged to expense.

Intangible assets are highly vulnerable to impairment charges, particularly newly acquired assets for recently launched products and IPR&D. These assets are initially measured at fair value and therefore any reduction in expectations used in the valuations could potentially lead to impairment. Some of the more common potential risks leading to impairment include competition, earlier than expected loss of exclusivity, pricing pressures, adverse regulatory changes or clinical trial results, delay or failure to obtain regulatory approval and additional development costs, inability to achieve expected synergies, higher operating costs, changes in tax laws and other macro-economic changes. The complexity in estimating the fair value of intangible assets in connection with an impairment test is similar to the initial valuation.

Considering the high risk nature of research and development and the industry’s success rate of bringing developmental compounds to market, IPR&D impairment charges are likely to occur in future periods. IPR&D is closely monitored and assessed each period for impairment.

We amortize intangible assets with definite lives on a straight-line basis over their estimated useful lives, ranging from 3 to 20 years. We use the straight-line method of amortization as there is no reliably determinable pattern in which the economic benefits of our intangible assets are consumed or otherwise used up. Amortization expense was $64.4 million and $28.0 million for the years ended December 31, 2016 and 2015 , respectively.

Revenue recognition. Revenue for laboratory services is recognized at the time test results are reported, which approximates when services are provided. Services are provided to patients covered by various third-party payer programs including various managed care organizations, as well as the Medicare and Medicaid programs. Billings for services under third-party payer programs are included in revenue net of allowances for contractual discounts and allowances for differences between the amounts billed and estimated program payment amounts. Adjustments to the estimated payment amounts based on final settlement with the programs are recorded upon settlement as an adjustment to revenue. For the years ended December 31, 2016 and 2015, approximately 16% and 9% , respectively, of our revenues from services were derived directly from the Medicare and Medicaid programs. The increase in revenues from laboratory services, including revenue from Medicare and Medicaid programs, is due to the acquisition of Bio-Reference in August 2015.

We recognize revenue from product sales when persuasive evidence of an arrangement exists, delivery has occurred, collectability is reasonably assured, and the price to the buyer is fixed or determinable, which is generally when goods are shipped and title and risk of loss transfer to our customers. Our estimates for sales returns and allowances are based upon the historical patterns of product returns and allowances taken, matched against the sales from which they originated, and our evaluation of specific factors that may increase or decrease the risk of product returns. Product revenues are recorded net of estimated rebates, chargebacks, discounts, co-pay assistance and other deductions (collectively, "Sales Deductions") as well as estimated product returns. Allowances are recorded as a reduction of revenue at the time product revenues are recognized.

We launched *Rayaldee* in the U.S. through our dedicated renal sales force in November 2016. *Rayaldee* is distributed in the U.S. principally through the retail pharmacy channel, which initiates with the largest wholesalers in the U.S. (collectively, " *Rayaldee* Customers"). In addition to distribution agreements with *Rayaldee* Customers, we have entered into arrangements with many health care providers and payers that provide for government-mandated and/or privately-negotiated rebates, chargebacks and discounts with respect to the purchase of *Rayaldee* .

We lack the experiential data which would allow us to estimate Sales Deductions and returns. Therefore, as of December 31, 2016 , we have determined that we do not yet meet the criteria for the recognition of revenue for shipments of *Rayaldee* at the time of shipment to *Rayaldee* Customers as allowances for Sales Deductions and returns are not known or cannot be reasonably estimated. We will not recognize revenue upon shipment until such time as we can reasonably estimate and record provisions for Sales Deductions and returns utilizing historical information and market research projections.

During the year ended December 31, 2016 , we did not recognize any product revenues related to *Rayaldee* sales. Payments received from *Rayaldee* Customers in advance of recognition of revenue are recorded as deferred revenue included in Accrued expenses in our Consolidated Balance Sheet. The related deferred revenue balance as of December 31, 2016 was $1.6 million . The corresponding costs of product revenues for which we have not recognized product revenue have similarly not yet been reflected in our Consolidated Statement of Operations.

Revenue from transfer of intellectual property includes revenue related to the sale, license or transfer of intellectual property such as upfront license payments, license fees, milestone and royalty payments received through our license, and collaboration and commercialization agreements. We analyze our multiple-element arrangements to determine whether the elements can be separated and accounted for individually as separate units of accounting.

Non-refundable license fees for the out-license of our technology are recognized depending on the provisions of each agreement. We recognize non-refundable upfront license payments as revenue upon receipt if the license has standalone value and qualifies for treatment as a separate unit of accounting under multiple-element arrangement guidance. License fees with ongoing involvement or performance obligations that do not have standalone value are recorded as deferred revenue, included in Accrued expenses or Other long-term liabilities, when received and generally are recognized ratably over the period of such performance obligations only after both the license period has commenced and we have delivered the technology.

The assessment of our obligations and related performance periods requires significant management judgment. If an agreement contains research and development obligations, the relevant time period for the research and development phase is based on management estimates and could vary depending on the outcome of clinical trials and the regulatory approval process. Such changes could materially impact the revenue recognized, and as a result, management reviews the estimates related to the relevant time period of research and development on a periodic basis.

Revenue from milestone payments related to arrangements under which we have continuing performance obligations are recognized as Revenue from transfer of intellectual property upon achievement of the milestone only if all of the following conditions are met: the milestone payments are non-refundable; there was substantive uncertainty at the date of entering into the arrangement that the milestone would be achieved; the milestone payment is commensurate with either our performance to achieve the milestone or the enhancement of the value of the delivered item by us; the milestone relates solely to past performance; and the amount of the milestone payment is reasonable in relation to the effort expended or the risk associated with the achievement of the milestone. If any of these conditions are not met, the milestone payments are not considered to be substantive and are, therefore, deferred and recognized as Revenue from transfer of intellectual property over the term of the arrangement as we complete our performance obligations.

Concentration of credit risk and allowance for doubtful accounts . Financial instruments that potentially subject us to concentrations of credit risk consist primarily of accounts receivable. Substantially all of our accounts receivable are with either companies in the health care industry or patients. However, credit risk is limited due to the number of our clients as well as their dispersion across many different geographic regions.

While we have receivables due from federal and state governmental agencies, we do not believe that such receivables represent a credit risk since the related health care programs are funded by federal and state governments, and payment is primarily dependent upon submitting appropriate documentation. Accounts receivable balances (net of contractual adjustments) from Medicare and Medicaid were $50.5 million and $26.1 million at December 31, 2016 and 2015 , respectively.

The portion of our accounts receivable due from individual patients comprises the largest portion of credit risk. At December 31, 2016 and 2015 , receivables due from patients represent approximately 7.3% and 7.5% , respectively, of our consolidated accounts receivable (prior to allowance for doubtful accounts).

We assess the collectability of accounts receivable balances by considering factors such as historical collection experience, customer credit worthiness, the age of accounts receivable balances, regulatory changes and current economic conditions and trends that may affect a customer’s ability to pay. Actual results could differ from those estimates. Our reported net income (loss) is directly affected by our estimate of the collectability of accounts receivable. The allowance for doubtful accounts was $36.3 million and $25.2 million at December 31, 2016 and 2015 , respectively.

Income taxes. Income taxes are accounted for under the asset-and-liability method. Deferred tax assets and liabilities are

recognized for the future tax consequences attributable to differences between the financial statement carrying amounts of existing assets and liabilities and the respective tax bases and for operating loss and tax credit carryforwards. Deferred tax assets and liabilities are measured using enacted tax rates expected to apply to taxable income in the years in which those temporary differences are expected to be recovered or settled. The effect on deferred tax assets and liabilities of a change in tax rates is recognized in operations in the period that includes the enactment date. We periodically evaluate the realizability of our net deferred tax assets. Our tax accruals are analyzed periodically and adjustments are made as events occur to warrant such adjustment.

Equity-based compensation. We measure the cost of employee services received in exchange for an award of equity instruments based on the grant-date fair value of the award. That cost is recognized in the Consolidated Statement of Operations over the period during which an employee is required to provide service in exchange for the award. We record excess tax benefits, realized from the exercise of stock options as a financing cash inflow and as a reduction of taxes paid in cash flow from operations. Equity-based compensation arrangements to non-employees are recorded at their fair value on the measurement date. The measurement of equity-based compensation to non-employees is subject to periodic adjustment as the underlying equity instruments vest. We estimate the grant-date fair value of our stock option grants using a valuation model known as the Black-Scholes-Merton formula or the "Black-Scholes Model." The Black-Scholes Model requires the use of several variables to estimate the grant-date fair value of stock options including expected term, expected volatility, expected dividends and risk-free interest rate. We perform analyses to calculate and select the appropriate variable assumptions used in the Black-Scholes Model and to estimate forfeitures of equity-based awards. We are required to adjust our forfeiture estimates on at least an annual basis based on the number of share-based awards that ultimately vest. The selection of assumptions and estimated forfeiture rates is subject to significant judgment and future changes to our assumptions and estimates which may have a material impact on our Consolidated Financial Statements.

Inventories. Inventories are valued at the lower of cost or market (net realizable value). Cost is determined by the first-in, first-out method. We consider such factors as the amount of inventory on hand, estimated time required to sell such inventories, remaining shelf-life, and current market conditions to determine whether inventories are stated at the lower of cost or market. Inventories at our diagnostics segment consist primarily of purchased laboratory supplies, which is used in our testing laboratories.

Pre-launch inventories. We may accumulate commercial quantities of certain product candidates prior to the date we anticipate that such products will receive final U.S. FDA approval. The accumulation of such pre-launch inventories involves the risk that such products may not be approved for marketing by the FDA on a timely basis, or ever. This risk notwithstanding, we may accumulate pre-launch inventories of certain products when such action is appropriate in relation to the commercial value of the product launch opportunity. In accordance with our policy, this pre-launch inventory is expensed.

Contingent consideration. Each period we revalue the contingent consideration obligations associated with certain prior acquisitions to their fair value and record increases in the fair value as contingent consideration expense and decreases in the fair value as a reduction in contingent consideration expense. Changes in contingent consideration result from changes in the assumptions regarding probabilities of successful achievement of related milestones, the estimated timing in which the milestones are achieved and the discount rate used to estimate the fair value of the liability. Contingent consideration may change significantly as our development programs progress, revenue estimates evolve and additional data is obtained, impacting our assumptions. The assumptions used in estimating fair value require significant judgment. The use of different assumptions and judgments could result in a materially different estimate of fair value which may have a material impact on our results from operations and financial position.

RECENT ACCOUNTING PRONOUNCEMENTS

Recent accounting pronouncements . In May 2014, the FASB issued Accounting Standards Update ("ASU") No. 2014-09, "Revenue from Contracts with Customers." ASU 2014-09 clarifies the principles for recognizing revenue and develops a common revenue standard for GAAP and International Financial Reporting Standards that removes inconsistencies and weaknesses in revenue requirements, provides a more robust framework for addressing revenue issues, improves comparability of revenue recognition practices across entities, industries, jurisdictions, and capital markets, provides more useful information to users of financial statements through improved disclosure requirements and simplifies the preparation of financial statements by reducing the number of requirements to which an entity must refer. ASU 2014-09 is effective for fiscal years, and interim periods within those years, beginning after December 15, 2017. Companies can choose to apply the ASU using either the full retrospective approach or a modified retrospective approach. We are currently evaluating both methods of adoption and the impact that the adoption of this ASU will have on our Consolidated Financial Statements.

In June 2014, the FASB issued ASU No. 2014-12, "Accounting for Share-Based Payments When the Terms of an Award Provide That a Performance Target Could Be Achieved after the Requisite Service Period (a consensus of the FASB Emerging Issues Task Force)." ASU 2014-12 requires that a performance target that affects vesting and that could be achieved after the requisite service period be treated as a performance condition. ASU 2014-12 was effective for the Company beginning after January 1, 2016. Our adoption of ASU 2014-12 in the first quarter of 2016 using the prospective application did not have a material impact on our Consolidated Financial Statements.

In August 2014, the FASB issued ASU No. 2014-15, "Disclosure of Uncertainties about an Entity's Ability to Continue as a Going Concern," to provide guidance on management's responsibility in evaluating whether there is substantial doubt about a company's ability to continue as a going concern and to provide related footnote disclosures. ASU 2014-15 is effective for annual periods ending after December 15, 2016 with early adoption permitted. Our adoption of ASU 2014-15 in the fourth quarter of 2016 did not have an impact on our Consolidated Financial Statements.

In February 2015, the FASB issued ASU No. 2015-02, "Consolidation (Topic 810): Amendments to the Consolidation Analysis," which amends current consolidation guidance including changes to both the variable and voting interest models used by companies to evaluate whether an entity should be consolidated. The requirements from ASU 2015-02 were effective for the Company beginning January 1, 2016. Our adoption of ASU 2015-02 in the first quarter of 2016 did not have a material impact on our Consolidated Financial Statements.

In April 2015, the FASB issued ASU No. 2015-03, "Interest - Imputation of Interest (Subtopic 835-30): Simplifying the Presentation of Debt Issuance Costs," which requires that debt issuance costs related to a recognized debt liability be presented in the balance sheet as a direct deduction from the carrying amount of that debt liability, consistent with debt discounts. ASU 2015-03 was effective for the Company beginning January 1, 2016. Our adoption of ASU 2015-03 in the first quarter of 2016 did not have a material impact on our Consolidated Financial Statements.

In July 2015, the FASB issued ASU No. 2015-11, "Inventory (Topic 330): Simplifying the Measurement of Inventory," which changes the measurement principle for entities that do not measure inventory using the last-in, first-out ("LIFO") or retail inventory method from the lower of cost or market to lower of cost and net realizable value. ASU 2015-11 is effective for fiscal years beginning after December 15, 2016, including interim periods within those fiscal years, with early adoption permitted. We are currently evaluating the impact of this new guidance on our Consolidated Financial Statements.

In September 2015, the FASB issued ASU No. 2015-16, "Business Combinations (Topic 805): Simplifying the Accounting for Measurement-Period Adjustments," which replaces the requirement that an acquirer in a business combination account for measurement period adjustments retrospectively with a requirement that an acquirer recognize adjustments to the provisional amounts that are identified during the measurement period in the reporting period in which the adjustment amounts are determined. ASU 2015-16 requires that the acquirer record, in the same period's financial statements, the effect on earnings of changes in depreciation, amortization, or other income effects, if any, as a result of the change to the provisional amounts, calculated as if the accounting had been completed at the acquisition date. Our early adoption of ASU 2015-16 in 2015 did not have a significant impact on our Consolidated Financial Statements.

In November 2015, the FASB issued ASU No. 2015-17, "Income Taxes (Topic 740): Balance Sheet Classification of Deferred Taxes," which requires deferred tax liabilities and assets to be classified as noncurrent in a classified statement of financial position. We early adopted the provisions of this ASU prospectively in the fourth quarter of 2015, and did not retrospectively adjust the prior periods. The adoption of this ASU simplifies the presentation of deferred income taxes and reduces complexity without decreasing the usefulness of information provided to users of financial statements. The adoption of ASU 2015-17 did not have a significant impact on our Consolidated Financial Statements.

In January 2016, the FASB issued ASU No. 2016-01, “Financial Instruments - Overall (Subtopic 825-10),” which addresses certain aspects of recognition, measurement, presentation, and disclosure of financial instruments. The ASU requires equity investments (except those accounted for under the equity method of accounting or those that result in consolidation of the investee) to be measured at fair value with changes in fair value recognized in net income. ASU 2016-01 will be effective for fiscal years beginning after December 15, 2018, including interim periods within those fiscal years, with early adoption permitted. We are currently evaluating the impact of this new guidance on our Consolidated Financial Statements.

In February 2016, the FASB issued ASU No. 2016-02, “Leases (Topic 842),” which will require organizations that lease assets with lease terms of more than 12 months to recognize assets and liabilities for the rights and obligations created by those leases on their balance sheets. The ASU will also require new qualitative and quantitative disclosures to help investors and other financial statement users better understand the amount, timing, and uncertainty of cash flows arising from leases. ASU 2016-02 will be effective for fiscal years beginning after December 15, 2018, including interim periods within those fiscal years, with early adoption permitted. We are currently evaluating the impact of this new guidance on our Consolidated Financial Statements.

In March 2016, the FASB issued ASU No. 2016-09, “Compensation - Stock Compensation (Topic 718),” which simplifies several aspects of the accounting for share-based payment award transactions, including the income tax consequences, classification of awards as either equity or liabilities, classification on the statement of cash flows and accounting for forfeitures. ASU 2016-09 will be effective for fiscal years beginning after December 15, 2016, including interim periods within those fiscal years, with early adoption permitted. We are currently evaluating the impact of this new guidance on our Consolidated Financial Statements.

In August 2016, the FASB issued ASU No. 2016-15, “Statement of Cash Flows (Topic 230),” which addresses the classification of eight specific cash flow issues with the objective of reducing the existing diversity in practice. ASU 2016-15 will be effective for fiscal years beginning after December 15, 2017, including interim periods within those fiscal years, with early adoption permitted. We are currently evaluating the impact of this new guidance on our Consolidated Financial Statements.

In January 2017, the FASB issued ASU No. 2017-04, “Intangibles - Goodwill and Other (Topic 350),” which simplifies how an entity is required to test for goodwill impairment. ASU 2017-04 will be effective for annual or interim goodwill impairment tests in fiscal years beginning after December 15, 2019, with early adoption permitted after January 1, 2017. We are currently evaluating the impact of this new guidance on our Consolidated Financial Statements.

ITEM 7A. QUANTITATIVE AND QUALITATIVE DISCLOSURES ABOUT MARKET RISK

In the normal course of doing business, we are exposed to the risks associated with foreign currency exchange rates and changes in interest rates.

Foreign Currency Exchange Rate Risk – We operate globally and, as such, we are subject to foreign exchange risk in our commercial operations as a significant portion of our revenues are exposed to changes in foreign currency exchange rates, primarily the Chilean peso, the Mexican peso, the Euro and the New Israeli shekel.

Although we do not speculate in the foreign exchange market, we may from time to time manage exposures that arise in the normal course of business related to fluctuations in foreign currency exchange rates by entering into offsetting positions through the use of foreign exchange forward contracts. Certain firmly committed transactions may be hedged with foreign exchange forward contracts. As exchange rates change, gains and losses on the exposed transactions are partially offset by gains and losses related to the hedging contracts. Both the exposed transactions and the hedging contracts are translated and fair valued, respectively, at current spot rates, with gains and losses included in earnings.

Our derivative activities, which consist of foreign exchange forward contracts, are initiated to economically hedge forecasted cash flows that are exposed to foreign currency risk. The foreign exchange forward contracts generally require us to exchange local currencies for foreign currencies based on pre-established exchange rates at the contracts' maturity dates. As exchange rates change, gains and losses on these contracts are generated based on the change in the exchange rates that are recognized in the Consolidated Statement of Operations and offset the impact of the change in exchange rates on the foreign currency cash flows that are hedged. If the counterparties to the exchange contracts do not fulfill their obligations to deliver the contracted currencies, we could be at risk for currency related fluctuations. Our foreign exchange forward contracts primarily hedge exchange rates on the Chilean peso to the U.S. dollar. If Chilean pesos were to strengthen or weaken in relation to the U.S. dollar, our loss or gain on hedged foreign currency cash-flows would be offset by the derivative contracts, with a net effect of zero.

We do not engage in trading market risk sensitive instruments or purchasing hedging instruments or "other than trading" instruments that are likely to expose us to significant market risk, whether interest rate, foreign currency exchange, commodity price, or equity price risk.

Interest Rate Risk – Our exposure to interest rate risk relates to our cash and investments and to our borrowings. We maintain an investment portfolio of money market funds and marketable securities. The securities in our investment portfolio are not leveraged, and are, due to their very short-term nature, subject to minimal interest rate risk. We currently do not hedge interest rate exposure. Because of the short-term maturities of our investments, we do not believe that a change in market interest rates would have a significant negative impact on the value of our investment portfolio except for reduced income in a low interest rate environment.

At December 31, 2016 , we had cash and cash equivalents of $168.7 million . The weighted average interest rate related to our cash and cash equivalents for the year ended December 31, 2016 was less than 1%. As of December 31, 2016 , the principal outstanding balance under our Credit Agreement with JPMorgan Chase Bank, N.A. and our Chilean and Spanish credit lines was $47.3 million in the aggregate at a weighted average interest rate of approximately 4.7% .

Our $31.9 million aggregate principal amount of our 2033 Senior Notes has a fixed interest rate, and therefore is not subject to fluctuations in market interest rates.

The primary objective of our investment activities is to preserve principal while at the same time maximizing yields without significantly increasing risk. To achieve this objective, we may invest our excess cash in debt instruments of the U.S. Government and its agencies, bank obligations, repurchase agreements and high-quality corporate issuers, and money market funds that invest in such debt instruments, and, by policy, restrict our exposure to any single corporate issuer by imposing concentration limits. To minimize the exposure due to adverse shifts in interest rates, we maintain investments at an average maturity of generally less than three months.

Equity Price Risk – We are subject to equity price risk related to the (i) rights to convert into shares of our Common Stock, including upon a fundamental change; and (ii) a coupon make-whole payment in the event of a conversion by the holders of the 2033 Senior Notes on or after February 1, 2017 but prior to February 1, 2019. These terms are considered to be embedded derivatives. On a quarterly basis, we are required to record these embedded derivatives at fair value with the changes being recorded in our Consolidated Statement of Operations. Accordingly, our results of operations are subject to exposure associated with increases or decreases in the estimated fair value of our embedded derivatives.

ITEM 8. FINANCIAL STATEMENTS AND SUPPLEMENTARY DATA

Report of Independent Registered Certified Public Accounting Firm

The Board of Directors and Shareholders of OPKO Health, Inc. and subsidiaries

We have audited the accompanying consolidated balance sheets of OPKO Health, Inc. and subsidiaries as of December 31, 2016 and 2015 , and the related consolidated statements of operations, comprehensive loss, equity and cash flows for each of the three years in the period ended December 31, 2016 . Our audits also included the financial statement schedule listed in the index at Item 15(a)(1). These financial statements and schedule are the responsibility of the Company's management. Our responsibility is to express an opinion on these financial statements and schedule based on our audits.

We conducted our audits in accordance with the standards of the Public Company Accounting Oversight Board (United States). Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement. An audit includes examining, on a test basis, evidence supporting the amounts and disclosures in the financial statements. An audit also includes assessing the accounting principles used and significant estimates made by management, as well as evaluating the overall financial statement presentation. We believe that our audits provide a reasonable basis for our opinion.

In our opinion, the financial statements referred to above present fairly, in all material respects, the consolidated financial position of OPKO Health, Inc. and subsidiaries at December 31, 2016 and 2015 , and the consolidated results of their operations and their cash flows for each of the three years in the period ended December 31, 2016 , in conformity with U.S. generally accepted accounting principles. Also, in our opinion, the related financial statement schedule, when considered in relation to the basic financial statements taken as a whole, presents fairly in all material respects the information set forth therein.

We also have audited, in accordance with the standards of the Public Company Accounting Oversight Board (United States), OPKO Health, Inc. and subsidiaries' internal control over financial reporting as of December 31, 2016 , based on criteria established in Internal Control-Integrated Framework issued by the Committee of Sponsoring Organizations of the Treadway Commission (2013 framework) and our report dated March 1, 2017 expressed an unqualified opinion thereon.

/s/ Ernst & Young LLP

Miami, Florida
March 1, 2017

Report of Independent Registered Certified Public Accounting Firm

The Board of Directors and Shareholders of OPKO Health, Inc. and subsidiaries

We have audited OPKO Health, Inc. and subsidiaries' internal control over financial reporting as of December 31, 2016 , based on criteria established in Internal Control-Integrated Framework issued by the Committee of Sponsoring Organizations of the Treadway Commission (2013 framework) (the COSO criteria). OPKO Health, Inc. and subsidiaries' management is responsible for maintaining effective internal control over financial reporting, and for its assessment of the effectiveness of internal control over financial reporting included in the accompanying Management's Annual Report on Internal Control Over Financial Reporting. Our responsibility is to express an opinion on the company's internal control over financial reporting based on our audit.

We conducted our audit in accordance with the standards of the Public Company Accounting Oversight Board (United States). Those standards require that we plan and perform the audit to obtain reasonable assurance about whether effective internal control over financial reporting was maintained in all material respects. Our audit included obtaining an understanding of internal control over financial reporting, assessing the risk that a material weakness exists, testing and evaluating the design and operating effectiveness of internal control based on the assessed risk, and performing such other procedures as we considered necessary in the circumstances. We believe that our audit provides a reasonable basis for our opinion.

A company's internal control over financial reporting is a process designed to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles. A company's internal control over financial reporting includes those policies and procedures that (1) pertain to the maintenance of records that, in reasonable detail, accurately and fairly reflect the transactions and dispositions of the assets of the company; (2) provide reasonable assurance that transactions are recorded as necessary to permit preparation of financial statements in accordance with generally accepted accounting principles, and that receipts and expenditures of the company are being made only in accordance with authorizations of management and directors of the company; and (3) provide reasonable assurance regarding prevention or timely detection of unauthorized acquisition, use, or disposition of the company's assets that could have a material effect on the financial statements.

Because of its inherent limitations, internal control over financial reporting may not prevent or detect misstatements. Also, projections of any evaluation of effectiveness to future periods are subject to the risk that controls may become inadequate because of changes in conditions, or that the degree of compliance with the policies or procedures may deteriorate.

As indicated in the accompanying Management's Annual Report on Internal Control Over Financial Reporting, management's assessment of and conclusion on the effectiveness of internal control over financial reporting did not include the internal controls of Transition Therapeutics, Inc., which is included in the December 31, 2016 consolidated financial statements of OPKO Health, Inc. and subsidiaries and constituted 2% of consolidated total assets, as of December 31, 2016 and 0% of consolidated revenues, for the year then ended. Our audit of internal control over financial reporting of OPKO Health, Inc. and subsidiaries also did not include an evaluation of the internal control over financial reporting of Transition Therapeutics, Inc.

In our opinion, OPKO Health, Inc. and subsidiaries maintained, in all material respects, effective internal control over financial reporting as of December 31, 2016 , based on the COSO criteria.

We also have audited, in accordance with the standards of the Public Company Accounting Oversight Board (United States), the consolidated balance sheets of OPKO Health, Inc. and subsidiaries as of December 31, 2016 and 2015 , and the related consolidated statements of operations, comprehensive loss, equity and cash flows for each of the three years in the period ended December 31, 2016 of OPKO Health, Inc. and subsidiaries and our report dated March 1, 2017 expressed an unqualified opinion thereon.

/s/ Ernst & Young LLP

Miami, Florida
March 1, 2017

OPKO Health, Inc. and Subsidiaries
CONSOLIDATED BALANCE SHEETS
(In thousands, except share and per share data)

	December 31,	
	2016	2015
ASSETS		
Current assets:		
Cash and cash equivalents	$ 168,733	$ 193,598
Accounts receivable, net	220,284	193,875
Inventory, net	47,228	39,681
Other current assets and prepaid expenses	47,356	26,904
Total current assets	483,601	454,058
Property, plant and equipment, net	122,831	131,798
Intangible assets, net	763,976	638,152
In-process research and development	644,713	792,275
Goodwill	704,603	743,348
Investments	41,139	34,716
Other assets	5,756	4,841
Total assets	$ 2,766,619	$ 2,799,188
LIABILITIES AND EQUITY		
Current liabilities:		
Accounts payable	$ 53,360	$ 72,535
Accrued expenses	197,955	167,899
Current portion of lines of credit and notes payable	11,981	11,468
Total current liabilities	263,296	251,902
2033 Senior Notes and estimated fair value of embedded derivatives, net of discount	43,701	48,986
Deferred tax liabilities, net	165,331	226,036
Other long-term liabilities, principally deferred revenue and line of credit	202,483	292,470
Total long-term liabilities	411,515	567,492
Total liabilities	674,811	819,394
Equity:		
Common Stock - $0.01 par value, 750,000,000 shares authorized; 558,576,051 and 546,188,516 shares issued at December 31, 2016 and 2015, respectively	5,586	5,462
Treasury Stock - 586,760 and 1,120,367 shares at December 31, 2016 and 2015, respectively	(1,911)	(3,645)
Additional paid-in capital	2,845,096	2,705,385
Accumulated other comprehensive loss	(27,009)	(22,537)
Accumulated deficit	(729,954)	(704,871)
Total shareholders' equity	2,091,808	1,979,794
Total liabilities and equity	$ 2,766,619	$ 2,799,188

The accompanying Notes to Consolidated Financial Statements are an integral part of these statements.

OPKO Health, Inc. and Subsidiaries
CONSOLIDATED STATEMENTS OF OPERATIONS
(In thousands, except share and per share data)

	For the years ended December 31,		
	2016	2015	2014
Revenues:			
Revenue from services	$ 1,012,129	$ 329,739	$ 8,666
Revenue from products	83,467	80,146	76,983
Revenue from transfer of intellectual property and other	126,065	81,853	5,476
Total revenues	1,221,661	491,738	91,125
Costs and expenses:			
Cost of service revenue	564,103	193,305	9,372
Cost of product revenue	47,379	41,934	38,637
Selling, general and administrative	490,888	196,576	57,940
Research and development	111,205	99,488	83,571
In-process research and development	—	—	12,055
Contingent consideration	16,954	5,050	24,446
Amortization of intangible assets	64,407	27,977	10,919
Grant repayment	—	25,889	—
Total costs and expenses	1,294,936	590,219	236,940
Operating loss	(73,275)	(98,481)	(145,815)
Other income and (expense), net:			
Interest income	478	255	771
Interest expense	(7,430)	(8,419)	(12,263)
Fair value changes of derivative instruments, net	2,778	(39,083)	(10,632)
Other income (expense), net	3,903	7,730	(3,088)
Other income and (expense), net	(271)	(39,517)	(25,212)
Loss before income taxes and investment losses	(73,546)	(137,998)	(171,027)
Income tax benefit (provision)	56,115	113,675	(24)
Net loss before investment losses	(17,431)	(24,323)	(171,051)
Loss from investments in investees	(7,652)	(7,105)	(3,587)
Net loss	(25,083)	(31,428)	(174,638)
Less: Net loss attributable to noncontrolling interests	—	(1,400)	(2,972)
Net loss attributable to common shareholders	$ (25,083)	$ (30,028)	$ (171,666)
Loss per share, basic and diluted:			
Net loss per share	$ (0.05)	$ (0.06)	$ (0.41)
Weighted average number of common shares outstanding, basic and diluted	550,846,553	488,065,908	422,014,039

The accompanying Notes to Consolidated Financial Statements are an integral part of these statements.

OPKO Health, Inc. and Subsidiaries
CONSOLIDATED STATEMENTS OF COMPREHENSIVE LOSS
(In thousands)

	For the years ended December 31,		
	2016	2015	2014
Net loss	$ (25,083)	$ (31,428)	$ (174,638)
Other comprehensive income (loss), net of tax:			
Change in foreign currency translation and other comprehensive income (loss)	(4,955)	(15,074)	(8,088)
Available for sale investments:			
Change in unrealized gain (loss), net of tax	(3,810)	(2,378)	(8,044)
Less: reclassification adjustments for losses included in net loss, net of tax	4,293	7,307	322
Comprehensive loss	(29,555)	(41,573)	(190,448)
Less: Comprehensive loss attributable to noncontrolling interest	—	(1,400)	(2,972)
Comprehensive loss attributable to common shareholders	$ (29,555)	$ (40,173)	$ (187,476)

The accompanying Notes to Consolidated Financial Statements are an integral part of these statements.

OPKO Health, Inc. and Subsidiaries
CONSOLIDATED STATEMENTS OF EQUITY
(In thousands, except share and per share data)
For the years ended December 31, 2016 , 2015 , 2014 (continued)

	Common Stock		Treasury		Additional Paid-In Capital	Accumulated Other Comprehensive Income (Loss)	Accumulated Deficit	Noncontrolling Interests	Total
	Shares	Dollars	Shares	Dollars					
Balance at December 31, 2013	414,818,195	$ 4,148	(2,264,063)	$ (7,362)	$ 1,379,383	$ 3,418	$ (503,177)	$ (3,431)	$ 872,979
Equity-based compensation expense	—	—	—	—	14,737	—	—	—	14,737
Exercise of Common Stock options and warrants	5,392,841	54	—	—	12,874	—	—	—	12,928
Issuance of Treasury Stock for OPKO Uruguay	—	—	19,140	61	98	—	—	—	159
Issuance of Common Stock upon exchange of 2033 Senior Notes	10,974,431	110	—	—	95,555	—	—	—	95,665
Issuance of Treasury Stock for Inspiro at $8.57	—	—	999,556	3,250	5,316	—	—	—	8,566
Issuance of Common Stock for OPKO Renal earnout	2,236,210	22	—	—	21,133	—	—	—	21,155
Net loss attributable to common shareholders	—	—	—	—	—	—	(171,666)	—	(171,666)
Net loss attributable to noncontrolling interests	—	—	—	—	—	—	—	(2,972)	(2,972)
Other comprehensive loss	—	—	—	—	—	(15,810)	—	—	(15,810)
Balance at December 31, 2014	433,421,677	$ 4,334	(1,245,367)	$ (4,051)	$ 1,529,096	$ (12,392)	$ (674,843)	$ (6,403)	$ 835,741

The accompanying Notes to Consolidated Financial Statements are an integral part of these statements.

OPKO Health, Inc. and Subsidiaries
CONSOLIDATED STATEMENTS OF EQUITY
(In thousands, except share and per share data)
For the years ended December 31, 2016 , 2015 , 2014 (continued)

	Common Stock		Treasury		Additional Paid-In Capital	Accumulated Other Comprehensive Loss	Accumulated Deficit	Noncontrolling Interests	Total
	Shares	Dollars	Shares	Dollars					
Balance at December 31, 2014	433,421,677	$ 4,334	(1,245,367)	$ (4,051)	$1,529,096	$ (12,392)	$ (674,843)	$ (6,403)	$ 835,741
Equity-based compensation expense	—	—	—	—	26,074	—	—	—	26,074
Exercise of Common Stock options and warrants	24,467,806	245	—	—	25,675	—	—	—	25,920
Issuance of Common Stock for EirGen purchase	2,420,487	24	—	—	33,572	—	—	—	33,596
Issuance of Common Stock for BRL purchase	76,566,147	766	—	—	949,244	—	—	—	950,010
Issuance of Common Stock upon exchange of 2033 Senior Notes	8,118,062	81	—	—	120,218	—	—	—	120,299
Issuance of Treasury Stock in connection with OPKO Health Europe's Contingent Consideration	—	—	125,000	406	1,406	—	—	—	1,812
Issuance of Common Stock for OPKO Renal earnout	1,194,337	12	—	—	20,100	—	—	—	20,112
Net loss attributable to common shareholders	—	—	—	—	—	—	(30,028)	—	(30,028)
Deconsolidation of SciVac	—	—	—	—	—	—	—	6,403	6,403
Other comprehensive loss	—	—	—	—	—	(10,145)	—	—	(10,145)
Balance at December 31, 2015	546,188,516	$ 5,462	(1,120,367)	$ (3,645)	$2,705,385	$ (22,537)	$ (704,871)	$ —	$1,979,794

The accompanying Notes to Consolidated Financial Statements are an integral part of these statements.

OPKO Health, Inc. and Subsidiaries
CONSOLIDATED STATEMENTS OF EQUITY
(In thousands, except share and per share data)
For the years ended December 31, 2016 , 2015 , 2014 (continued)

	Common Stock		Treasury		Additional Paid-In Capital	Accumulated Other Comprehensive Loss	Accumulated Deficit	Total
	Shares	Dollars	Shares	Dollars				
Balance at December 31, 2015	546,188,516	$ 5,462	(1,120,367)	$ (3,645)	$2,705,385	$ (22,537)	$ (704,871)	$1,979,794
Equity-based compensation expense	—	—	—	—	42,693	—	—	42,693
Exercise of Common Stock options and warrants	3,292,753	33	—	—	8,575	—	—	8,608
Issuance of Common Stock upon exchange of 2033 Senior Notes	51,235	1	—	—	582	—	—	583
Issuance of Treasury Stock in connection with OPKO Health Europe's Contingent Consideration	—	—	39,145	127	186	—	—	313
Issuance of Treasury Stock for investment in Xenetic	—	—	494,462	1,607	3,249	—	—	4,856
Issuance of Common Stock for OPKO Renal earnout	2,611,648	26	—	—	25,960	—	—	25,986
Issuance of Common Stock for Transition Therapeutics purchase	6,431,899	64	—	—	58,466	—	—	58,530
Net loss attributable to common shareholders	—	—	—	—	—	—	(25,083)	(25,083)
Other comprehensive loss	—	—	—	—	—	(4,472)	—	(4,472)
Balance at December 31, 2016	558,576,051	$ 5,586	(586,760)	$ (1,911)	$2,845,096	$ (27,009)	$ (729,954)	$2,091,808

The accompanying Notes to Consolidated Financial Statements are an integral part of these statements.

OPKO Health, Inc. and Subsidiaries
CONSOLIDATED STATEMENTS OF CASH FLOWS
(In thousands)

	For the years ended December 31,		
	2016	2015	2014
Cash flows from operating activities:			
Net loss	$ (25,083)	$ (31,428)	$ (174,638)
Adjustments to reconcile net loss to net cash used in operating activities:			
Depreciation and amortization	96,576	42,248	14,927
Non-cash interest	2,699	2,612	5,662
Amortization of deferred financing costs	237	1,212	2,007
Losses from investments in investees	7,652	7,105	3,587
Equity-based compensation – employees and non-employees	42,693	26,074	14,779
Revenue from receipt of equity	—	(140)	(240)
Realized loss on equity securities and disposal of fixed assets	2,321	7,091	167
Loss (gain) on conversion of 3.00% convertible senior notes	284	(943)	(2,668)
Change in fair value of derivative instruments	(2,778)	39,083	10,632
In-process research and development	—	—	12,055
Change in fair value of contingent consideration	16,954	5,050	24,446
Gain on deconsolidation of SciVac	—	(15,940)	—
Deferred income tax (benefit) provision	(66,300)	(123,536)	1,017
Changes in assets and liabilities, net of the effects of acquisitions:			
Accounts receivable, net	(25,637)	(4,845)	(3,273)
Inventory, net	(6,607)	(4,953)	(670)
Other current assets and prepaid expenses	17,262	(4,391)	3,182
Other assets	(1,899)	(305)	(3,378)
Accounts payable	(19,819)	(18,122)	(3,852)
Foreign currency measurement	(376)	979	945
Deferred revenue	(74,169)	227,671	—
Accrued expenses and other liabilities	68,036	9,502	4,934
Net cash provided by (used in) operating activities	32,046	164,024	(90,379)
Cash flows from investing activities:			
Investments in investees	(14,424)	(4,375)	(589)
Proceeds from sale of equity securities	—	—	1,331
Acquisition of businesses, net of cash acquired	15,878	(79,000)	(1,683)
Acquisition of intangible assets	(5,000)	(5,000)	—
Purchase of marketable securities	(15,644)	—	—
Maturities of short-term marketable securities	15,634	—	—
Proceeds from the sale of property, plant and equipment	1,401	—	—
Capital expenditures	(18,547)	(10,846)	(4,734)
Net cash used in investing activities	(20,702)	(99,221)	(5,675)
Cash flows from financing activities:			
Proceeds from the exercise of Common Stock options and warrants	8,576	25,921	12,928
Cash from non-controlling interest	—	100	2,696
Contingent consideration payments	—	—	(6,435)
Borrowings on lines of credit	22,407	261,339	26,443
Repayments of lines of credit	(66,178)	(254,355)	(28,369)
Net cash (used in) provided by financing activities	(35,195)	33,005	7,263
Effect of exchange rate changes on cash and cash equivalents	(1,014)	(1,117)	(100)
Net (decrease) increase in cash and cash equivalents	(24,865)	96,691	(88,891)
Cash and cash equivalents at beginning of period	193,598	96,907	185,798
Cash and cash equivalents at end of period	$ 168,733	$ 193,598	$ 96,907
SUPPLEMENTAL INFORMATION:			

Interest paid	$	2,890	$	4,572	$	6,276
Income taxes paid, net	$	(27,122)	$	4,879	$	954
Pharmsynthez common stock received	$	—	$	—	$	6,264
Non-cash financing:						
Shares issued upon the conversion of:						
2033 Senior Notes	$	583	$	120,299	$	95,665
Common Stock options and warrants, surrendered in net exercise	$	350	$	14,369	$	3,494
Issuance of capital stock to acquire or contingent consideration settlement:						
Transition Therapeutics, Inc.	$	58,530	$	—	$	—
Bio-Reference Laboratories, Inc.	$	—	$	950,148	$	—
EirGen Pharma Limited	$	—	$	33,569	$	—
OPKO Renal	$	25,986	$	20,113	$	21,155
OPKO Health Europe	$	313	$	1,813	$	—
OPKO Uruguay Ltda.	$	—	$	—	$	159
Inspiro	$	—	$	—	$	8,566
Issuance of stock for investment in Xenetic	$	4,856	$	—	$	—

The accompanying Notes to Consolidated Financial Statements are an integral part of these statements.

Note 1 Business and Organization

We are a diversified healthcare company that seeks to establish industry-leading positions in large and rapidly growing medical markets. Our diagnostics business includes Bio-Reference Laboratories, Inc. ("Bio-Reference"), the nation's third-largest clinical laboratory with a core genetic testing business and a 400 - person sales and marketing team to drive growth and leverage new products, including the *4Kscore* prostate cancer test and the *Claros* 1 in-office immunoassay platform (in development). Our pharmaceutical business features *Rayaldee* , an FDA-approved treatment for secondary hyperparathyroidism ("SHPT") in adults with stage 3 or 4 chronic kidney disease ("CKD") and vitamin D insufficiency and VARUBI™ for chemotherapy-induced nausea and vomiting (oral formulation launched by partner TESARO in November 2015 and pending approval for IV formulation), TT401, a once or twice weekly oxyntomodulin for type 2 diabetes and obesity which is a clinically advanced drug candidate among the new class of GLP-1 glucagon receptor dual agonists (Phase 2b), and TT701, an androgen receptor modulator for androgen deficiency indications. Our pharmaceutical business also includes OPKO Biologics, which features hGH-CTP, a once-weekly human growth hormone injection (in Phase 3 and partnered with Pfizer), a once-daily Factor VIIa drug for hemophilia (Phase 2a), and long-acting oxyntomodulin ("OXM") for diabetes and obesity (Phase 1). We are incorporated in Delaware and our principal executive offices are located in leased offices in Miami, Florida.

In August 2016, we completed the acquisition of Transition Therapeutics, Inc. ("Transition Therapeutics"), a clinical stage biotechnology company developing TT401, a once or twice weekly oxyntomodulin for type 2 diabetes and obesity, and TT701, an androgen receptor modulator for androgen deficiency indications. Holders of Transition Therapeutics common stock received 6,431,899 shares of OPKO Common Stock. The transaction was valued at approximately $58.5 million , based on a closing price per share of our Common Stock of $9.10 as reported by NASDAQ on the closing date.

In August 2015, we completed the acquisition of Bio-Reference, the third largest full service clinical laboratory in the United States, known for its innovative technological solutions and pioneering leadership in the areas of genomics and genetic sequencing. Holders of Bio-Reference common stock received 76,566,147 shares of OPKO Common Stock for the outstanding shares of Bio-Reference common stock. The transaction was valued at approximately $950.1 million , based on a closing price per share of our Common Stock of $12.38 as reported by the New York Stock Exchange, or $34.05 per share of Bio-Reference common stock. Included in the transaction value is $2.3 million related to the value of replacement stock option awards attributable to pre-merger service.

Through our acquisition of Bio-Reference, we provide laboratory testing services, primarily to customers in the larger metropolitan areas across New York, New Jersey, Maryland, Pennsylvania, Delaware, Washington DC, Florida, California, Texas, Illinois and Massachusetts as well as to customers in a number of other states. We offer a comprehensive test menu of clinical diagnostics for blood, urine, and tissue analysis. This includes hematology, clinical chemistry, immunoassay, infectious diseases, serology, hormones, and toxicology assays, as well as Pap smear, anatomic pathology (biopsies) and other types of tissue analysis. We market our laboratory testing services directly to physicians, geneticists, hospitals, clinics, correctional and other health facilities.

In May 2015, we acquired all of the issued and outstanding shares of EirGen Pharma Limited ("EirGen"), a specialty pharmaceutical company incorporated in Ireland focused on the development and commercial supply of high potency, high barrier to entry pharmaceutical products, for $133.8 million . We acquired the outstanding shares of EirGen for approximately $100.2 million in cash and delivered 2,420,487 shares of our Common Stock valued at approximately $33.6 million based on the closing price per share of our Common Stock as reported by the New York Stock Exchange on the closing date of the acquisition, $13.88 per share.

We operate established pharmaceutical platforms in Ireland, Chile, Spain, and Mexico, which are generating revenue and which we expect to facilitate future market entry for our products currently in development. In addition, we have a development and commercial supply pharmaceutical company and a global supply chain operation and holding company in Ireland. We own a specialty active pharmaceutical ingredients ("APIs") manufacturer in Israel, which we expect will facilitate the development of our pipeline of molecules and compounds for our molecular diagnostic and therapeutic products.

Our research and development activities are primarily performed at leased facilities in Miramar, FL, Woburn, MA, Waterford, Ireland, Kiryat Gat, Israel, and Barcelona, Spain.

Note 2 Summary of Significant Accounting Policies

Basis of presentation. The accompanying Consolidated Financial Statements have been prepared in accordance with accounting principles generally accepted in the U.S. and with the instructions to Form 10-K and of Regulation S-X.

Principles of consolidation. The accompanying Consolidated Financial Statements include the accounts of OPKO Health, Inc. and of our wholly-owned subsidiaries. All intercompany accounts and transactions are eliminated in consolidation.

Use of estimates. The preparation of financial statements in conformity with accounting principles generally accepted in the United States requires management to make estimates and assumptions that affect the reported amounts of assets and liabilities and disclosure of contingent assets and liabilities at the date of the financial statements and the reported amounts of revenues and expenses during the reporting period. Actual results could differ significantly from these estimates.

Cash and cash equivalents. Cash and cash equivalents include short-term, interest-bearing instruments with original maturities of 90 days or less at the date of purchase. We also consider all highly liquid investments with original maturities at the date of purchase of 90 days or less as cash equivalents. These investments include money markets, bank deposits, certificates of deposit and U.S. treasury securities.

Inventories. Inventories are valued at the lower of cost or market (net realizable value). Cost is determined by the first-in, first-out method. We consider such factors as the amount of inventory on hand, estimated time required to sell such inventories, remaining shelf-life, and current market conditions to determine whether inventories are stated at the lower of cost or market. Inventories at our diagnostics segment consist primarily of purchased laboratory supplies, which is used in our testing laboratories. The provision for inventory obsolescence for the years ended December 31, 2016 and 2015 was $0.0 million and $0.9 million , respectively.

Pre-launch inventories. We may accumulate commercial quantities of certain product candidates prior to the date we anticipate that such products will receive final U.S. FDA approval. The accumulation of such pre-launch inventories involves the risk that such products may not be approved for marketing by the FDA on a timely basis, or ever. This risk notwithstanding, we may accumulate pre-launch inventories of certain products when such action is appropriate in relation to the commercial value of the product launch opportunity. In accordance with our policy, this pre-launch inventory is expensed.

Goodwill and intangible assets. Goodwill represents the difference between the purchase price and the estimated fair value of the net assets acquired accounted for by the acquisition method of accounting and arose from our acquisitions. Refer to Note 5. Goodwill, in-process research and development ("IPR&D") and other intangible assets acquired in business combinations, licensing and other transactions at December 31, 2016 and 2015 , were $2.1 billion and $2.2 billion , respectively.

Assets acquired and liabilities assumed in business combinations, licensing and other transactions are generally recognized at the date of acquisition at their respective fair values. We determined the fair value of intangible assets, including IPR&D, using the "income method."

Goodwill is tested at least annually for impairment, or when events or changes in circumstances indicate that the carrying amount of such assets may not be recoverable, by assessing qualitative factors or performing a quantitative analysis in determining whether it is more likely than not that its fair value exceeds the carrying value.

Intangible assets are tested for impairment whenever events or changes in circumstances indicate that the carrying amount of such assets may not be recoverable, although IPR&D is required to be tested at least annually until the project is completed or abandoned. Upon obtaining regulatory approval, the IPR&D asset is then accounted for as a finite-lived intangible asset and amortized on a straight-line basis over its estimated useful life. If the project is abandoned, the IPR&D asset is charged to expense.

We reclassified $187.6 million of IPR&D related to *Rayaldee* from In-process research and development to Intangible assets, net in our Consolidated Balance Sheet upon the FDA's approval of *Rayaldee* in June 2016. The assets will be amortized on a straight-line basis over their estimated useful life of approximately 12 years.

We amortize intangible assets with definite lives on a straight-line basis over their estimated useful lives, ranging from 3 to 20 years. We use the straight-line method of amortization as there is no reliably determinable pattern in which the economic benefits of our intangible assets are consumed or otherwise used up. Amortization expense was $64.4 million , $28.0 million and $10.9 million for the years ended December 31, 2016 , 2015 and 2014, respectively. Amortization expense from operations for our intangible assets is expected to be $69.2 million, $66.5 million, $64.2 million, $57.8 million and $51.8 million for the years ended December 2017 , 2018 , 2019 , 2020 and 2021 , respectively.

Fair value measurements . The carrying amounts of our cash and cash equivalents, accounts receivable, accounts payable and short-term debt approximate their fair value due to the short-term maturities of these instruments. Investments that are considered available for sale as of December 31, 2016 and 2015 are carried at fair value. Our debt under the credit agreement with JPMorgan Chase Bank, N.A. approximates fair value due to the variable rate of interest.

In evaluating the fair value information, considerable judgment is required to interpret the market data used to develop the estimates. The use of different market assumptions and/or different valuation techniques may have a material effect on the estimated fair value amounts. Accordingly, the estimates of fair value presented herein may not be indicative of the amounts that could be realized in a current market exchange. Refer to Note 17.

Contingent consideration . Each period we revalue the contingent consideration obligations associated with certain prior acquisitions to their fair value and record increases in the fair value as contingent consideration expense and decreases in the fair value as a reduction in contingent consideration expense. Changes in contingent consideration result from changes in the assumptions regarding probabilities of successful achievement of related milestones, the estimated timing in which the milestones are achieved and the discount rate used to estimate the fair value of the liability. Contingent consideration may change significantly as our development programs progress, revenue estimates evolve and additional data is obtained, impacting our assumptions. The assumptions used in estimating fair value require significant judgment. The use of different assumptions and judgments could result in a materially different estimate of fair value which may have a material impact on our results from operations and financial position.

Derivative financial instruments. We record derivative financial instruments on our Consolidated Balance Sheet at their fair value and recognize the changes in the fair value in our Consolidated Statement of Operations when they occur, the only exception being derivatives that qualify as hedges. For the derivative instrument to qualify as a hedge, we are required to meet strict hedge effectiveness and contemporaneous documentation requirements at the initiation of the hedge and assess the hedge effectiveness on an ongoing basis over the life of the hedge. At December 31, 2016 and 2015 , our foreign currency forward contracts held to economically hedge inventory purchases did not meet the documentation requirements to be designated as hedges. Accordingly, we recognize all changes in the fair values of our derivatives instruments, net, in our Consolidated Statement of Operations. Refer to Note 18.

Property, plant and equipment. Property, plant and equipment are recorded at cost. Depreciation is provided using the straight-line method over the estimated useful lives of the assets and includes amortization expense for assets capitalized under capital leases. The estimated useful lives by asset class are as follows: software - 3 years , machinery, medical and other equipment - 5 - 8 years , furniture and fixtures - 5 - 10 years , leasehold improvements - the lesser of their useful life or the lease term, buildings and improvements - 10 - 40 years , automobiles and aircraft - 3 - 15 years . Expenditures for repairs and maintenance are charged to expense as incurred. Depreciation expense was $33.3 million , $14.2 million and $4.0 million for the years ended December 31, 2016 , 2015 and 2014, respectively. Assets held under capital leases are included within Property, plant and equipment, net in our Consolidated Balance Sheet and are amortized over the shorter of their useful lives or the expected term of their related leases.

Impairment of long-lived assets. Long-lived assets, such as property and equipment, are reviewed for impairment whenever events or changes in circumstances indicate that the carrying amount of an asset may not be recoverable. Recoverability of assets to be held and used is measured by a comparison of the carrying amount of an asset to estimated undiscounted future cash flows expected to be generated by the asset. If the carrying amount of an asset exceeds its estimated future cash flows, then an impairment charge is recognized for the amount by which the carrying amount of the asset exceeds the fair value of the asset.

Income taxes. Income taxes are accounted for under the asset-and-liability method. Deferred tax assets and liabilities are recognized for the future tax consequences attributable to differences between the financial statement carrying amounts of existing assets and liabilities and the respective tax bases and for operating loss and tax credit carryforwards. Deferred tax assets and liabilities are measured using enacted tax rates expected to apply to taxable income in the years in which those temporary differences are expected to be recovered or settled. The effect on deferred tax assets and liabilities of a change in tax rates is recognized in operations in the period that includes the enactment date.

We operate in various countries and tax jurisdictions globally. For the year ended December 31, 2016 , the tax rate differed from the U.S. federal statutory rate of 35% primarily due to the relative mix in earnings and losses in the U.S. versus foreign tax jurisdictions, the impact of certain discrete tax events and operating results in tax jurisdictions which do not result in a tax benefit.

Income tax benefit for the year ended December 31, 2015 was primarily due to a $93.4 million release of a valuation allowance on our U.S. deferred tax assets due to a change in the assessment of recoverability following the merger with Bio-Reference in August 2015.

We periodically evaluate the realizability of our net deferred tax assets. Our tax accruals are analyzed periodically and adjustments are made as events occur to warrant such adjustment. On January 5, 2016, the Israeli Parliament officially published the *Law for the Amendment of the Israeli Tax Ordinance* (Amendment 216), that reduces the standard corporate income tax rate from 26.5% to 25% . The amendment was entered into force on January 1, 2016 and the 25% corporate tax rate will apply to income that was generated from that day onwards. On December 29, 2016, the Israeli parliament further reduced the standard corporate income tax rate to 24% , effective January 1, 2017 and 23% effective January 1, 2018. The new rates have been used in determining Income tax benefit in 2016.

Included in Other long-term liabilities is an accrual of $2.5 million related to uncertain tax positions involving income recognition. We recognize that local tax law is inherently complex and the local taxing authorities may not agree with certain tax positions taken. Consequently, it is reasonably possible that the ultimate resolution of tax matters in any jurisdiction may be significantly more or less than estimated. We evaluated the estimated tax exposure for a range of current likely outcomes to be from $0 to approximately $50.0 million and recorded our accrual to reflect our best expectation of ultimate resolution.

Revenue recognition . Revenue for laboratory services is recognized at the time test results are reported, which approximates when services are provided. Services are provided to patients covered by various third-party payer programs including various managed care organizations, as well as the Medicare and Medicaid programs. Billings for services under third-party payer programs are included in revenue net of allowances for contractual discounts and allowances for differences between the amounts billed and estimated program payment amounts. Adjustments to the estimated payment amounts based on final settlement with the programs are recorded upon settlement as an adjustment to revenue. For the years ended December 31, 2016 and 2015 , approximately 16% and 9% , respectively, of our revenues from services were derived directly from the Medicare and Medicaid programs. The increase in revenues from laboratory services, including revenue from Medicare and Medicaid programs, is due to the acquisition of Bio-Reference in August 2015.

We recognize revenue from product sales when persuasive evidence of an arrangement exists, delivery has occurred, collectability is reasonably assured, and the price to the buyer is fixed or determinable, which is generally when goods are shipped and title and risk of loss transfer to our customers. Our estimates for sales returns and allowances are based upon the historical patterns of product returns and allowances taken, matched against the sales from which they originated, and our evaluation of specific factors that may increase or decrease the risk of product returns. Product revenues are recorded net of estimated rebates, chargebacks, discounts, co-pay assistance and other deductions (collectively, "Sales Deductions") as well as estimated product returns. Allowances are recorded as a reduction of revenue at the time product revenues are recognized.

We launched *Rayaldee* in the U.S. through our dedicated renal sales force in November 2016. *Rayaldee* is distributed in the U.S. principally through the retail pharmacy channel, which initiates with the largest wholesalers in the U.S. (collectively, " *Rayaldee* Customers"). In addition to distribution agreements with *Rayaldee* Customers, we have entered into arrangements with many health care providers and payers that provide for government-mandated and/or privately-negotiated rebates, chargebacks and discounts with respect to the purchase of *Rayaldee* .

We lack the experiential data which would allow us to estimate Sales Deductions and returns. Therefore, as of December 31, 2016 , we have determined that we do not yet meet the criteria for the recognition of revenue for shipments of *Rayaldee* at the time of shipment to *Rayaldee* Customers as allowances for Sales Deductions and returns are not known or cannot be reasonably estimated. We will not recognize revenue upon shipment until such time as we can reasonably estimate and record provisions for Sales Deductions and returns utilizing historical information and market research projections.

During the year ended December 31, 2016 , we did not recognize any product revenues related to *Rayaldee* sales. Payments received from *Rayaldee* Customers in advance of recognition of revenue are recorded as deferred revenue included in Accrued expenses in our Consolidated Balance Sheet. The related deferred revenue balance as of December 31, 2016 was $1.6 million . The corresponding costs of product revenues for which we have not recognized product revenue have similarly not yet been reflected in our Consolidated Statement of Operations.

Revenue from transfer of intellectual property includes revenue related to the sale, license or transfer of intellectual property such as upfront license payments, license fees, milestone and royalty payments received through our license, and collaboration and commercialization agreements. We analyze our multiple-element arrangements to determine whether the elements can be separated and accounted for individually as separate units of accounting.

Non-refundable license fees for the out-license of our technology are recognized depending on the provisions of each agreement. We recognize non-refundable upfront license payments as revenue upon receipt if the license has standalone value and qualifies for treatment as a separate unit of accounting under multiple-element arrangement guidance. License fees with ongoing involvement or performance obligations that do not have standalone value are recorded as deferred revenue, included in Accrued expenses or Other long-term liabilities, when received and generally are recognized ratably over the period of such performance obligations only after both the license period has commenced and we have delivered the technology.

The assessment of our obligations and related performance periods requires significant management judgment. If an agreement contains research and development obligations, the relevant time period for the research and development phase is based on management estimates and could vary depending on the outcome of clinical trials and the regulatory approval process. Such changes could materially impact the revenue recognized, and as a result, management reviews the estimates related to the relevant time period of research and development on a periodic basis. For the years ended December 31, 2016 , 2015 and 2014 we recorded $126.1 million , $81.9 million and $5.5 million of revenue from the transfer of intellectual property, respectively. For the year ended December 31, 2016 , revenue from the transfer of intellectual property included $50.0 million related to the VFMCRP Agreement and $70.6 million related to the Pfizer Transaction. Refer to Note 14. For the year ended December 31, 2015 , revenue from the transfer of intellectual property included $15.0 million related to a milestone payment that TESARO, Inc. ("TESARO") paid us under our license agreement with them and $65.5 million related to the Pfizer Transaction. For the year ended December 31, 2014, $5.0 million related to a milestone payment that TESARO paid us under our license agreement with them.

Revenue from milestone payments related to arrangements under which we have continuing performance obligations are recognized as Revenue from transfer of intellectual property upon achievement of the milestone only if all of the following conditions are met: the milestone payments are non-refundable; there was substantive uncertainty at the date of entering into the arrangement that the milestone would be achieved; the milestone payment is commensurate with either our performance to achieve the milestone or the enhancement of the value of the delivered item by us; the milestone relates solely to past performance; and the amount of the milestone payment is reasonable in relation to the effort expended or the risk associated with the achievement of the milestone. If any of these conditions are not met, the milestone payments are not considered to be substantive and are, therefore, deferred and recognized as Revenue from transfer of intellectual property over the term of the arrangement as we complete our performance obligations.

Total deferred revenue included in Accrued expenses and Other long-term liabilities was $162.4 million and $232.9 million at December 31, 2016 and 2015 , respectively. The deferred revenue balance at December 31, 2016 and 2015 relates primarily to the Pfizer Transaction. Refer to Note 14.

Concentration of credit risk and allowance for doubtful accounts . Financial instruments that potentially subject us to concentrations of credit risk consist primarily of accounts receivable. Substantially all of our accounts receivable are with either companies in the health care industry or patients. However, credit risk is limited due to the number of our clients as well as their dispersion across many different geographic regions.

While we have receivables due from federal and state governmental agencies, we do not believe that such receivables represent a credit risk since the related health care programs are funded by federal and state governments, and payment is primarily dependent upon submitting appropriate documentation. Accounts receivable balances (net of contractual adjustments) from Medicare and Medicaid were $50.5 million and $26.1 million at December 31, 2016 and 2015 , respectively.

The portion of our accounts receivable due from individual patients comprises the largest portion of credit risk. At December 31, 2016 and 2015 , receivables due from patients represent approximately 7.3% and 7.5% , respectively, of our consolidated accounts receivable (prior to allowance for doubtful accounts).

We assess the collectability of accounts receivable balances by considering factors such as historical collection experience, customer credit worthiness, the age of accounts receivable balances, regulatory changes and current economic conditions and trends that may affect a customer's ability to pay. Actual results could differ from those estimates. Our reported net income (loss) is directly affected by our estimate of the collectability of accounts receivable. The allowance for doubtful accounts was $36.3 million and $25.2 million at December 31, 2016 and 2015 , respectively. The provision for bad debts for the years ended December 31, 2016 and 2015 was $83.5 million and $24.5 million , respectively.

Equity-based compensation. We measure the cost of employee services received in exchange for an award of equity instruments based on the grant-date fair value of the award. That cost is recognized in the Consolidated Statement of Operations over the period during which an employee is required to provide service in exchange for the award. We record excess tax benefits, realized from the exercise of stock options as a financing cash inflow and as a reduction of taxes paid in cash flow from operations. Equity-based compensation arrangements to non-employees are recorded at their fair value on the measurement date. The measurement of equity-based compensation to non-employees is subject to periodic adjustment as the underlying equity instruments vest. During the years ended December 31, 2016 , 2015 and 2014, we recorded $42.7 million , $26.1 million and $14.8 million , respectively, of equity-based compensation expense.

Research and development expenses . Research and development expenses include external and internal expenses, partially offset by third-party grants and fundings arising from collaboration agreements. External expenses include clinical and non-clinical activities performed by contract research organizations, lab services, purchases of drug and diagnostic product materials and manufacturing development costs. Research and development employee-related expenses include salaries,

benefits and equity-based compensation expense. Other internal research and development expenses are incurred to support overall research and development activities and include expenses related to general overhead and facilities. We expense these costs in the period in which they are incurred. We estimate our liabilities for research and development expenses in order to match the recognition of expenses to the period in which the actual services are received. As such, accrued liabilities related to third party research and development activities are recognized based upon our estimate of services received and degree of completion of the services in accordance with the specific third party contract.

We record expense for in-process research and development projects acquired as asset acquisitions which have not reached technological feasibility and which have no alternative future use. For in-process research and development projects acquired in business combinations, the in-process research and development project is capitalized and evaluated for impairment until the development process has been completed. Once the development process has been completed the asset will be amortized over its remaining useful life.

Segment reporting. Our chief operating decision-maker ("CODM") is Phillip Frost, M.D., our Chairman and Chief Executive Officer. Our CODM reviews our operating results and operating plans and makes resource allocation decisions on a Company-wide or aggregate basis. We manage our operations in two reportable segments, pharmaceutical and diagnostics. The pharmaceutical segment consists of our pharmaceutical operations we acquired in Chile, Mexico, Ireland, Israel and Spain and our pharmaceutical research and development. The diagnostics segment primarily consists of clinical laboratory operations we acquired through the acquisition of Bio-Reference and point-of-care operations. There are no significant inter-segment sales. We evaluate the performance of each segment based on operating profit or loss. There is no inter-segment allocation of interest expense and income taxes. Refer to Note 16.

Shipping and handling costs. We do not charge customers for shipping and handling costs. Shipping and handling costs are classified as Cost of revenues in the Consolidated Statement of Operations.

Foreign currency translation . The financial statements of certain of our foreign operations are measured using the local currency as the functional currency. The local currency assets and liabilities are generally translated at the rate of exchange to the United States ("U.S.") dollar on the balance sheet date and the local currency revenues and expenses are translated at average rates of exchange to the U.S. dollar during the reporting periods. Foreign currency transaction gains (losses) have been reflected as a component of Other income (expense), net within the Consolidated Statement of Operations and foreign currency translation gains (losses) have been included as a component of the Consolidated Statement of Comprehensive Loss. During the years ended December 31, 2016 , 2015 and 2014, we recorded $0.8 million , $(2.4) million and $(4.8) million , respectively of transaction gains (losses).

Variable interest entities. The consolidation of variable interest entities ("VIE") is required when an enterprise has a controlling financial interest. A controlling financial interest in a VIE will have both of the following characteristics: (a) the power to direct the activities of a VIE that most significantly impact the VIE's economic performance and (b) the obligation to absorb losses of the VIE that could potentially be significant to the VIE. In July 2015, we deconsolidated SciVac Therapeutics Inc. ("STI"), and account for our retained interest in STI as an equity method investment. Refer to Note 4.

Investments. We have made strategic investments in development stage and emerging companies. We record these investments as equity method investments or investments available for sale based on our percentage of ownership and whether we have significant influence over the operations of the investees. Investments for which it is not practical to estimate fair value and which we do not have significant influence are accounted for as cost method investments. For investments classified under the equity method of accounting, we record our proportionate share of their losses in Losses from investments in investees in our Consolidated Statement of Operations. Refer to Note 4. For investments classified as available for sale, we record changes in their fair value as unrealized gain or loss in Other comprehensive income (loss) based on their closing price per share at the end of each reporting period. Refer to Note 4.

Recent accounting pronouncements . In May 2014, the FASB issued Accounting Standards Update ("ASU") No. 2014-09, "Revenue from Contracts with Customers." ASU 2014-09, as amended, clarifies the principles for recognizing revenue and develops a common revenue standard for GAAP and International Financial Reporting Standards that removes inconsistencies and weaknesses in revenue requirements, provides a more robust framework for addressing revenue issues, improves comparability of revenue recognition practices across entities, industries, jurisdictions, and capital markets, provides more useful information to users of financial statements through improved disclosure requirements and simplifies the preparation of financial statements by reducing the number of requirements to which an entity must refer. ASU 2014-09 is effective for fiscal years, and interim periods within those years, beginning after December 15, 2017. Companies can choose to apply the ASU using either the full retrospective approach or a modified retrospective approach. We continue to evaluate both methods of adoption and the impact that the adoption of this ASU will have on our Consolidated Financial Statements.

In June 2014, the FASB issued ASU No. 2014-12, "Accounting for Share-Based Payments When the Terms of an Award

Provide That a Performance Target Could Be Achieved after the Requisite Service Period (a consensus of the FASB Emerging Issues Task Force)." ASU 2014-12 requires that a performance target that affects vesting and that could be achieved after the requisite service period be treated as a performance condition. ASU 2014-12 was effective for the Company beginning after January 1, 2016. Our adoption of ASU 2014-12 in the first quarter of 2016 using the prospective application did not have a material impact on our Consolidated Financial Statements.

In August 2014, the FASB issued ASU No. 2014-15, "Disclosure of Uncertainties about an Entity's Ability to Continue as a Going Concern," to provide guidance on management's responsibility in evaluating whether there is substantial doubt about a company's ability to continue as a going concern and to provide related footnote disclosures. ASU 2014-15 is effective for annual periods ending after December 15, 2016 with early adoption permitted. Our adoption of ASU 2014-15 in 2016 did not have an impact on our Consolidated Financial Statements.

In February 2015, the FASB issued ASU No. 2015-02, "Consolidation (Topic 810): Amendments to the Consolidation Analysis," which amends current consolidation guidance including changes to both the variable and voting interest models used by companies to evaluate whether an entity should be consolidated. The requirements from ASU 2015-02 were effective for the Company beginning January 1, 2016. Our adoption of ASU 2015-02 in the first quarter of 2016 did not have a material impact on our Consolidated Financial Statements.

In April 2015, the FASB issued ASU No. 2015-03, "Interest - Imputation of Interest (Subtopic 835-30): Simplifying the Presentation of Debt Issuance Costs," which requires that debt issuance costs related to a recognized debt liability be presented in the balance sheet as a direct deduction from the carrying amount of that debt liability, consistent with debt discounts. ASU 2015-03, as amended, was effective for the Company beginning January 1, 2016. Our adoption of ASU 2015-03 in the first quarter of 2016 did not have a material impact on our Consolidated Financial Statements.

In July 2015, the FASB issued ASU No. 2015-11, "Inventory (Topic 330): Simplifying the Measurement of Inventory," which changes the measurement principle for entities that do not measure inventory using the last-in, first-out ("LIFO") or retail inventory method from the lower of cost or market to lower of cost and net realizable value. ASU 2015-11 is effective for fiscal years beginning after December 15, 2016, including interim periods within those fiscal years, with early adoption permitted. We do not expect the adoption of this new guidance to have a material impact on our Consolidated Financial Statements.

In September 2015, the FASB issued ASU No. 2015-16, "Business Combinations (Topic 805): Simplifying the Accounting for Measurement-Period Adjustments," which replaces the requirement that an acquirer in a business combination account for measurement period adjustments retrospectively with a requirement that an acquirer recognize adjustments to the provisional amounts that are identified during the measurement period in the reporting period in which the adjustment amounts are determined. ASU 2015-16 requires that the acquirer record, in the same period's financial statements, the effect on earnings of changes in depreciation, amortization, or other income effects, if any, as a result of the change to the provisional amounts, calculated as if the accounting had been completed at the acquisition date. Our early adoption of ASU 2015-16 in 2015 did not have a significant impact on our Consolidated Financial Statements.

In November 2015, the FASB issued ASU No. 2015-17, "Income Taxes (Topic 740): Balance Sheet Classification of Deferred Taxes," which requires deferred tax liabilities and assets to be classified as noncurrent in a classified statement of financial position. We early adopted the provisions of this ASU prospectively in the fourth quarter of 2015, and did not retrospectively adjust the prior periods. The adoption of this ASU simplifies the presentation of deferred income taxes and reduces complexity without decreasing the usefulness of information provided to users of financial statements. The adoption of ASU 2015-17 did not have a significant impact on our Consolidated Financial Statements.

In January 2016, the FASB issued ASU No. 2016-01, "Financial Instruments - Overall (Subtopic 825-10)," which addresses certain aspects of recognition, measurement, presentation, and disclosure of financial instruments. The ASU requires equity investments (except those accounted for under the equity method of accounting or those that result in consolidation of the investee) to be measured at fair value with changes in fair value recognized in net income. ASU 2016-01 will be effective for fiscal years beginning after December 15, 2018, including interim periods within those fiscal years, with early adoption permitted. We are currently evaluating the impact of this new guidance on our Consolidated Financial Statements.

In February 2016, the FASB issued ASU No. 2016-02, "Leases (Topic 842)," which will require organizations that lease assets with lease terms of more than 12 months to recognize assets and liabilities for the rights and obligations created by those leases on their balance sheets. The ASU will also require new qualitative and quantitative disclosures to help investors and other financial statement users better understand the amount, timing, and uncertainty of cash flows arising from leases. ASU 2016-02 will be effective for fiscal years beginning after December 15, 2018, including interim periods within those fiscal years, with early adoption permitted. We are currently evaluating the impact of this new guidance on our Consolidated Financial Statements.

In March 2016, the FASB issued ASU No. 2016-09, “Compensation - Stock Compensation (Topic 718),” which simplifies several aspects of the accounting for share-based payment award transactions, including the income tax consequences, classification of awards as either equity or liabilities, classification on the statement of cash flows and accounting for forfeitures. ASU 2016-09 will be effective for fiscal years beginning after December 15, 2016, including interim periods within those fiscal years, with early adoption permitted. We are currently evaluating the impact of this new guidance on our Consolidated Financial Statements.

In August 2016, the FASB issued ASU No. 2016-15, “Statement of Cash Flows (Topic 230),” which addresses the classification of eight specific cash flow issues with the objective of reducing the existing diversity in practice. ASU 2016-15 will be effective for fiscal years beginning after December 15, 2017, including interim periods within those fiscal years, with early adoption permitted. We are currently evaluating the impact of this new guidance on our Consolidated Financial Statements.

In January 2017, the FASB issued ASU No. 2017-04, “Intangibles - Goodwill and Other (Topic 350),” which simplifies how an entity is required to test for goodwill impairment. ASU 2017-04 will be effective for annual or interim goodwill impairment tests in fiscal years beginning after December 15, 2019, with early adoption permitted after January 1, 2017. We are currently evaluating the impact of this new guidance on our Consolidated Financial Statements.

Note 3 Loss Per Share

Basic loss per share is computed by dividing our net loss by the weighted average number of shares outstanding during the period. For diluted earnings per share, the dilutive impact of stock options, warrants and conversion options of the 2033 Senior Notes is determined by applying the “treasury stock” method. In the periods in which their effect would be antidilutive, no effect has been given to outstanding options, warrants or the potentially dilutive shares issuable pursuant to the 2033 Senior Notes (defined in Note 6) in the dilutive computation.

A total of 9,494,999 , 14,269,717 and 28,456,149 potential shares of Common Stock have been excluded from the calculation of diluted net loss per share for the years ended December 31, 2016 , 2015 and 2014, respectively, because their inclusion would be antidilutive.

During the year ended December 31, 2016 , 3,420,697 Common Stock options and Common Stock warrants to purchase shares of our Common Stock were exercised, resulting in the issuance of 3,292,753 shares of Common Stock. Of the 3,420,697 Common Stock options and Common Stock warrants exercised, 127,944 shares of Common Stock were surrendered in lieu of a cash payment via the net exercise feature of the agreements.

During the year ended December 31, 2015 , 25,686,153 Common Stock options and Common Stock warrants to purchase shares of our Common Stock were exercised, resulting in the issuance of 24,466,106 shares of Common Stock. Of the 25,686,153 Common Stock options and Common Stock warrants exercised, 1,220,047 shares of Common Stock were surrendered in lieu of a cash payment via the net exercise feature of the agreements.

During the year ended December 31, 2014, 5,787,983 Common Stock options and Common Stock warrants to purchase shares of our Common Stock were exercised, resulting in the issuance of 5,392,741 shares of Common Stock. Of the 5,787,983 Common Stock options and Common Stock warrants exercised, 426 shares of Common Stock were surrendered in lieu of a cash payment via the net exercise feature of the agreements.

Note 4 Acquisitions, Investments and Licenses

Transition Therapeutics acquisition

In August 2016, we completed the acquisition of Transition Therapeutics, a clinical stage biotechnology company. Holders of Transition Therapeutics common stock received 6,431,899 shares of OPKO Common Stock. The transaction was valued at approximately $58.5 million , based on a closing price per share of our Common Stock of $9.10 as reported by NASDAQ on the closing date.

The following table summarizes the preliminary purchase price allocation and the estimated fair value of the net assets acquired and liabilities assumed at the date of acquisition. The purchase price allocation for Transition Therapeutics is preliminary pending completion of the fair value analysis of acquired assets and liabilities:

(In thousands)	Transition Therapeutics
Current assets	
Cash and cash equivalents	$ 15,878
IPR&D assets	41,000
Goodwill	3,453
Other assets	634
Accounts payable and other liabilities	(1,035)
Deferred tax liability	(1,400)
Total purchase price	$ 58,530

Goodwill from the acquisition of Transition Therapeutics principally relates to intangible assets that do not qualify for separate recognition (for instance, Transition Therapeutics' assembled workforce) and the deferred tax liability generated as a result of the transaction. Goodwill is not tax deductible for income tax purposes and was assigned to the pharmaceutical reporting segment.

Revenue and Net income (loss) in the Consolidated Statement of Operations for the year ended December 31, 2016 includes revenue and net loss of Transition Therapeutics from the date of acquisition to December 31, 2016 of $0.0 million and $(2.6) million , respectively.

Our IPR&D assets will not be amortized until the underlying development programs are completed. Upon obtaining regulatory approval, the IPR&D assets are then accounted for as finite-lived intangible assets and amortized on a straight-line basis over its estimated useful life.

Pro forma disclosure for Transition Therapeutics acquisition (unaudited)

The following table includes the pro forma results for the years ended December 31, 2016 and 2015 and combines the results of operations of OPKO and Transition Therapeutics as though the acquisition of Transition Therapeutics had occurred on January 1, 2015.

	For the year ended December 31,	
(In thousands)	2016	2015
Revenues	$1,221,661	$491,738
Net loss	(31,807)	(50,660)
Net loss attributable to common shareholders	(31,807)	(49,260)

The unaudited pro forma financial information is presented for information purposes only. The unaudited pro forma financial information may not necessarily reflect our future results of operations or what the results of operations would have been had we owned and operated Transition Therapeutics as of the beginning of the period presented.

Bio-Reference acquisition

In August 2015, we completed the acquisition of Bio-Reference, the third largest full service clinical laboratory in the United States, known for its innovative technological solutions and pioneering leadership in the areas of genomics and genetic sequencing. Holders of Bio-Reference common stock received 76,566,147 shares of OPKO Common Stock for the outstanding shares of Bio-Reference common stock. The transaction was valued at approximately $950.1 million , based on a closing price per share of our Common Stock of $12.38 as reported by the New York Stock Exchange, or $34.05 per share of Bio-Reference common stock. Included in the transaction value is $2.3 million related to the value of replacement stock option awards attributable to pre-merger service.

The following table summarizes the purchase price allocation and the fair value of the net assets acquired and liabilities assumed in the acquisition of Bio-Reference at the date of acquisition finalized during the year ended December 31, 2016:

(In thousands)		Bio-Reference
Purchase price:		
Value of OPKO Common Stock issued to Bio-Reference shareholders	$	947,889
Value of replacement stock options awards to holders of Bio-Reference stock options		2,259
Total purchase price	$	950,148
Preliminary value of assets acquired and liabilities assumed:		
Current assets		
Cash and cash equivalents	$	15,800
Accounts receivable		168,164
Inventory		19,674
Other current assets, principally deferred tax assets		105,765
Total current assets		309,403
Property, plant and equipment		112,457
Intangible assets:		
Trade name		47,100
Customer relationships		389,800
Technology		100,600
Other intangible assets		7,750
Total intangible assets		545,250
Goodwill		401,821
Investments		5,326
Other assets		13,265
Total assets		1,387,522
Accounts payable and accrued expenses		(108,217)
Income taxes payable		(2,921)
Lines of credit and notes payable		(65,701)
Capital lease obligations		(18,293)
Deferred tax liability (non-current)		(235,904)
Other long-term liabilities		(6,338)
Total purchase price	$	950,148

During the year ended December 31, 2016 , we finalized our purchase price allocation during the measurement period and obtained new fair value information related to certain assets acquired and liabilities assumed of Bio-Reference. As a result, for the year ended December 31, 2016 we adjusted the purchase price allocation by increasing Other current assets by $44.6 million , decreasing customer relationships by $5.4 million , increasing Other intangible assets by $7.8 million , decreasing Goodwill by $39.3 million , decreasing Accrued expenses by $0.5 million , increasing Income taxes payable by $2.5 million , decreasing Deferred tax liability (non-current) by $0.6 million and increasing Other long-term liabilities by $6.3 million . As a result of these adjustments, Amortization of intangible assets in our Consolidated Statement of Operations for the year ended December 31, 2016 increased $3.1 million .

The purchase price allocation adjustments are largely due to an approval we received from the Internal Revenue Service during 2016 on an application for a change in accounting method. As a result of the change, we recognized an additional $51.7 million of income tax benefits, of which $39.4 million was recognized as taxes recoverable in Other current assets and $12.3 million was recognized as a reduction of our Deferred tax liability (non-current). In addition, Goodwill was reduced by $51.7 million . OPKO received payment for the $39.4 million taxes recoverable balance during the year ended December 31, 2016 .

Goodwill from the acquisition of Bio-Reference principally relates to intangible assets that do not qualify for separate recognition (for instance, Bio-Reference's assembled workforce), our expectation to develop and market new products, and the deferred tax liability generated as a result of the transaction. Goodwill is not tax deductible for income tax purposes and was assigned to the diagnostics reporting segment.

Revenue and Net income (loss) in the Consolidated Statement of Operations for the year ended December 31, 2015 includes revenue and net income of Bio-Reference from the date of acquisition to December 31, 2015 of $321.9 million and $3.2 million , respectively.

The weighted average amortization periods for intangible assets recognized in the Bio-Reference acquisition are 5 years for trade name, 19.3 years for customer relationships, 10.2 years for technology and 13.0 years in total.

EirGen Pharma Limited acquisition

In May 2015, we acquired all of the issued and outstanding shares of EirGen, a specialty pharmaceutical company incorporated in Ireland focused on the development and commercial supply of high potency, high barrier to entry pharmaceutical products, for $133.8 million . We acquired the outstanding shares of EirGen for approximately $100.2 million in cash and delivered 2,420,487 shares of our Common Stock valued at approximately $33.6 million based on the closing price per share of our Common Stock as reported by the New York Stock Exchange on the closing date of the acquisition, $13.88 per share.

The following table summarizes the final purchase price allocation and the fair value of the net assets acquired and liabilities assumed in the acquisition of EirGen at the date of acquisition:

(In thousands)		EirGen
Current assets [1]	$	11,795
Intangible assets:		
IPR&D assets		560
Customer relationships		34,155
Currently marketed products		3,919
Total intangible assets		38,634
Goodwill		83,373
Property, plant and equipment		8,117
Other assets		1,232
Accounts payable and other liabilities		(6,254)
Deferred tax liability		(3,131)
Total purchase price	$	133,766

(1) Current assets include cash, accounts receivable, inventory and other assets of $5.5 million , $2.7 million , $2.2 million and $1.4 million , respectively, related to the EirGen acquisition. The fair value of the accounts receivable equals the gross contractual amount at the date of acquisition.

Goodwill from the acquisition of EirGen principally relates to intangible assets that do not qualify for separate recognition (for instance, EirGen's assembled workforce), our expectation to develop and market new products, and the deferred tax liability generated as a result of this being a partial stock transaction. Goodwill is not tax deductible for income tax purposes and was assigned to the pharmaceutical reporting segment.

Revenue and Net income (loss) in the Consolidated Statement of Operations for the year ended December 31, 2015 includes revenue and net income of EirGen from the date of acquisition to December 31, 2015 of $13.5 million and $1.4 million , respectively.

Our IPR&D assets will not be amortized until the underlying development programs are completed. Upon obtaining regulatory approval, the IPR&D assets are then accounted for as finite-lived intangible assets and amortized on a straight-line basis over its estimated useful life. The weighted average amortization periods for amortizing intangible assets recognized in the EirGen acquisition are 15.8 years for customer relationships, 10.0 years for currently marketed product and 15.0 years in total.

Investments

The following table reflects the accounting method, carrying value and underlying equity in net assets of our unconsolidated investments as of December 31, 2016 :

(in thousands)

Investment type	Investment Carrying Value	Underlying Equity in Net Assets
Equity method investments	$ 31,471	$ 30,195
Variable interest entity, equity method	516	—
Available for sale investments	4,528	
Cost method investment	607	
Warrants and options	4,017	
Total carrying value of investments	$ 41,139	

Equity method investments

Our equity method investments consist of investments in Pharmsynthez (ownership 17%), Cocrystal Pharma, Inc. (“COCP”) (8%), Sevion Therapeutics, Inc. (“Sevion”) (3%), Non-Invasive Monitoring Systems, Inc. ("NIMS") (1%), Neovasc Inc. (4%), VBI (15%), InCellDx, Inc. (27%), and BioCardia, Inc. ("BioCardia") (5%). The total assets, liabilities, and net losses of our equity method investees as of and for the year ended December 31, 2016 were $430.9 million , $205.1 million , and $208.1 million , respectively. We have determined that we and/or our related parties can significantly influence the success of our equity method investments through our board representation and/or voting power. Accordingly, we account for our investment in these entities under the equity method and record our proportionate share of their losses in Loss from investments in investees in our Consolidated Statement of Operations. The aggregate value of our equity method investments based on the quoted market price of their common stock and the number of shares held by us as of December 31, 2016 is $80.1 million .

Available for sale investments

Our available for sale investments consist of investments in RXi Pharmaceuticals Corporation (“RXi”) (ownership 5%), ChromaDex Corporation (2%), MabVax Therapeutics Holdings, Inc. (“MabVax”) (4%), ARNO Therapeutics, Inc. (“ARNO”) (5%) and Xenetic BioSciences, Inc. ("Xenetic") (4%). We have determined that our ownership, along with that of our related parties, does not provide us with significant influence over the operations of our available for sale investments. Accordingly, we account for our investment in these entities as available for sale, and we record changes in these investments as an unrealized gain or loss in Other comprehensive income (loss) each reporting period.

Based on our evaluation of the value of our investments in RXi, including RXi’s decreasing stock price during the year ended December 31, 2016 , we determined that the decline in fair value of our RXi common shares was other-than-temporary and recorded an impairment charge of $0.4 million in Other income (expense), net in our Consolidated Statement of Operations for the year ended December 31, 2016 to write our investment in RXi common shares down to its fair value of $0.3 million as of December 31, 2016 . Based on our evaluation of the value of our investments in Xenetic, including Xenetic’s decreasing stock price during the year ended December 31, 2016 , we determined that the decline in fair value of our Xenetic common shares was other-than-temporary and recorded an impairment charge of $3.5 million in Other income (expense), net in our Consolidated Statement of Operations for the year ended December 31, 2016 to write our investment in Xenetic common shares down to its fair value of $1.3 million as of December 31, 2016 . Based on our evaluation of the value of our investments in ARNO, including ARNO's decreasing stock price during the year ended December 31, 2016 , we determined that the decline in fair value of our ARNO common shares was other-than-temporary and recorded an impairment charge of $0.8 million in Other income (expense), net in our Consolidated Statement of Operations for the year ended December 31, 2016 to write our investment in ARNO common shares down to zero as of December 31, 2016.

Based on our evaluation of the value of our investments in RXi, including RXi’s decreasing stock price during the year ended December 31, 2015 , we determined that the decline in fair value of our RXi common shares was other-than-temporary and recorded an impairment charge of $7.3 million in Other income (expense), net in our Consolidated Statement of Operations for the year ended December 31, 2015 to write our investment in RXi common shares down to its fair value of $0.9 million as of December 31, 2015 . Based on our evaluation of the value of our investment in ARNO, including ARNO’s decreasing stock price during the year ended December 31, 2014, we determined that the decline in fair value of our ARNO common shares was other-than-temporary and recorded an impairment charge of $1.4 million in Other income (expense), net in our Consolidated Statement of Operations for the year ended December 31, 2014 to write our investment in ARNO common shares down to its fair value of $0.6 million as of December 31, 2014. Refer to Note 17 for further discussion of the fair value of our available for sale investments.

Sales of investments

Gains (losses) included in earnings from sales of our investments for the years ended December 31, 2016 , 2015 and 2014 were $0.0 million , $0.0 million and $1.3 million , respectively, and were recorded in Other income (expense), net in our Consolidated Statement of Operations. The cost of securities sold is based on the specific identification method. Refer to *Investment in SciVac* below.

Warrants and options

In addition to our equity method investments and available for sale investments, we hold options to purchase 1.0 million additional shares of Neovasc, which are fully vested as of December 31, 2016 , options to purchase 5.0 million additional shares of BioCardia, none of which are vested as of December 31, 2016 , and 1.0 million , 2.3 million , 0.3 million , 0.7 million , 0.7 million , 0.5 million and 0.2 million of warrants to purchase additional shares of COCP, ARNO, Sevion, MabVax, InCellDx, Inc., Xenetic and RXi, respectively. We recorded the changes in the fair value of the options and warrants in Fair value changes of derivative instruments, net in our Consolidated Statement of Operations. We also recorded the fair value of the options and warrants in Investments, net in our Consolidated Balance Sheet. See further discussion of the Company's options and warrants in Note 17 and Note 18.

Investments in variable interest entities

We have determined that we hold variable interests in Zebra Biologics, Inc. ("Zebra"). We made this determination as a result of our assessment that Zebra does not have sufficient resources to carry out its principal activities without additional financial support.

We own 1,260,000 shares of Zebra Series A-2 Preferred Stock and 900,000 shares of Zebra restricted common stock (ownership 28% at December 31, 2016). Zebra is a privately held biotechnology company focused on the discovery and development of biosuperior antibody therapeutics and complex drugs. Dr. Richard Lerner, M.D., a member of our Board of Directors, is a founder of Zebra and, along with Dr. Frost, serves as a member of Zebra's Board of Directors.

In order to determine the primary beneficiary of Zebra, we evaluated our investment and our related parties' investment, as well as our investment combined with the related party group's investment to identify if we had the power to direct the activities that most significantly impact the economic performance of Zebra. Based on the capital structure, governing documents and overall business operations of Zebra, we determined that, while a VIE, we do not have the power to direct the activities that most significantly impact Zebra's economic performance and no obligation to fund expected losses. We did determine, however, that we can significantly influence the success of Zebra through our board representation and voting power. Therefore, we have the ability to exercise significant influence over Zebra's operations and account for our investment in Zebra under the equity method.

Investment in SciVac

In June 2012, we acquired a 50% stock ownership in SciVac from FDS Pharma LLP ("FDS"). SciVac was a privately-held Israeli company that produced a third-generation hepatitis B-vaccine. From November 2012 through June 2015, we loaned to SciVac a combined $7.9 million for working capital purposes. We determined that we held variable interests in SciVac based on our assessment that SciVac did not have sufficient resources to carry out its principal activities without financial support. We had also determined we were the primary beneficiary of SciVac through our representation on SciVac's board of directors. As a result of this conclusion, we consolidated the results of operations and financial position of SciVac through June 2015 and recorded a reduction of equity for the portion of SciVac we do not own.

On July 9, 2015, SciVac Therapeutics Inc., formerly Levon Resources Ltd. ("STI") completed a reverse takeover transaction (the "Arrangement") pursuant to which STI acquired all of the issued and outstanding securities of SciVac. As a result of this transaction, OPKO's ownership in STI decreased to 24.5% .

Upon completion of the Arrangement, we determined that STI was not a VIE. We also determined that we do not have the power to direct the activities that most significantly impact the economic performance of STI that would require us to consolidate STI. We recorded a $15.9 million gain on the deconsolidation of SciVac in Other income (expense), net in our Consolidated Statement of Operations for the year ended December 31, 2015. The recognized gain was primarily due to the fair value of the retained interest in STI based on Levon's cash contribution of approximately $21.2 million under the Arrangement.

Following the deconsolidation, we account for our investment in STI under the equity method as we have determined that we and/or our related parties can significantly influence STI through our voting power and board representation. STI is

considered a related party as a result of our board representation in STI and executive management's ownership interests in STI.

In May 2016, STI completed a merger transaction pursuant to which a wholly-owned subsidiary of STI merged with and into VBI Vaccines Inc. with VBI Vaccines Inc. surviving the merger as a wholly-owned subsidiary of STI, and STI changed its name to VBI Vaccines Inc. ("VBI") . We recorded a $2.5 million gain in connection with the merger transaction in Other income (expense), net in our Consolidated Statement of Operations for the year ended December 31, 2016. In June 2016, we invested an additional $5.7 million in VBI for 1,362,370 shares of its common stock. As a result of these two transactions, OPKO's ownership in VBI changed to 15% .

We account for our investment in VBI under the equity method as we have determined that we can significantly influence VBI through our board representation.

Other

On January 5, 2016, we completed a stock exchange agreement (the "Exchange Agreement") with Relative Core Cyprus Limited ("Relative Core") pursuant to which Relative Core agreed to transfer and sell to us $5.0 million of Xenetic shares in exchange for $5.0 million shares of our common stock. We issued 494,462 shares of our common stock to Relative Core and received 10,204,082 shares of Xenetic common stock from Relative Core. The number of shares exchanged in the transaction was calculated based on the average closing sale price for our common stock on the NYSE for the ten (10) consecutive trading day period ending on the second day prior to the closing and the average closing sale price for Xenetic's common stock on the OTC "Pink Sheet" for the ten (10) consecutive trading day period ending on the second day prior to the closing. We account for investment in Xenetic as an available for sale investment.

In March 2016, we entered into an agreement with Relative Core pursuant to which we delivered $5.0 million cash to Relative Core in exchange for a $5.0 million promissory note ("Relative Note") which bears interest at 10% and is due in March 2017. The Relative Note is secured by 4,000,000 shares of common stock of Xenetic and 494,462 shares of OPKO common stock. We recorded the Relative Note within Other current assets and prepaid expenses in our Consolidated Balance Sheet.

Note 5 Composition of Certain Financial Statement Captions

(In thousands)	For the years ended December 31, 2016	2015
Accounts receivable, net		
Accounts receivable	$ 256,552	$ 219,043
Less: allowance for doubtful accounts	(36,268)	(25,168)
	$ 220,284	$ 193,875
Inventories, net		
Consumable supplies	$ 23,448	$ 22,265
Finished products	16,143	13,404
Work in-process	3,896	1,215
Raw materials	4,686	3,848
Less: inventory reserve	(945)	(1,051)
	$ 47,228	$ 39,681
Other current assets and prepaid expenses		
Other receivables	$ 13,021	$ 11,946
Taxes recoverable	16,187	3,076
Prepaid supplies	6,952	8,773
Prepaid insurance	3,688	2,206
Other	7,508	903
	$ 47,356	$ 26,904
Property, plant and equipment, net:		
Machinery, medical and other equipment	$ 100,100	$ 89,936
Leasehold improvements	30,122	27,949
Furniture and fixtures	11,247	11,403
Automobiles and aircraft	13,342	10,271
Software	10,990	10,497
Building	5,696	5,965
Land	2,264	2,394
Construction in process	5,848	425
Less: accumulated depreciation	(56,778)	(27,042)
	$ 122,831	$ 131,798
Intangible assets, net:		
Customer relationships	$ 443,560	$ 449,972
Technologies	340,397	151,709
Trade names	50,442	50,416
Covenants not to compete	16,348	8,612
Licenses	23,506	23,432
Product registrations	7,641	7,512
Other	5,289	5,600
Less: accumulated amortization	(123,207)	(59,101)
	$ 763,976	$ 638,152
Accrued expenses:		
Deferred revenue	$ 73,434	$ 70,246
Employee benefits	43,792	29,751
Taxes payable	4,430	7,605
Contingent consideration	259	22,164

(In thousands)	For the years ended December 31, 2016	2015
Clinical trials	5,935	2,505
Capital leases short-term	3,025	5,373
Milestone payment	4,865	5,000
Professional fees	4,035	1,506
Other	58,180	23,749
	$ 197,955	$ 167,899
Other long-term liabilities:		
Deferred revenue	$ 89,016	$ 162,634
Line of credit	38,809	72,107
Contingent consideration	44,817	32,258
Capital leases long-term	7,216	9,285
Mortgages and other debts payable	717	2,523
Other	21,908	13,663
	$ 202,483	$ 292,470

The following table summarizes the fair values assigned to our major intangible asset classes upon each acquisition:

(In thousands)	Technologies	In-process research and development	Customer relationships	Product registrations	Covenants not to compete	Trade names	Other	Total identified intangible assets	Goodwill
Bio-Reference	$ 100,600	$ —	$ 389,800	$ —	$ 7,750	$ 47,100	$ —	$ 545,250	$ 401,821
CURNA	—	10,000	—	—	—	—	290	10,290	4,827
EirGen	—	560	34,155	—	—	—	3,919	38,634	83,373
FineTech	2,700	—	14,200	—	1,500	400	—	18,800	11,623
OPKO Biologics	—	590,200	—	—	—	—	—	590,200	139,784
OPKO Chile	—	—	3,945	5,829	—	1,032	—	10,806	5,441
OPKO Diagnostics	44,400	—	—	—	—	—	—	44,400	17,977
OPKO Health Europe	3,017	1,459	436	2,930	187	349	—	8,378	8,062
OPKO Lab	1,370	—	3,860	—	6,900	1,830	70	14,030	29,629
OPKO Renal	—	191,530	—	—	—	—	210	191,740	2,411
Transition Therapeutics	—	41,000	—	—	—	—	—	41,000	3,453
Weighted average amortization period	8-12 years	Indefinite	6-20 years	9 years	5 years	4-5 years	3-10 years		Indefinite

All of the intangible assets and goodwill acquired relate to our acquisitions of principally OPKO Renal, OPKO Biologics, EirGen and Bio-Reference. We do not anticipate capitalizing the cost of product registration renewals, rather we expect to expense these costs, as incurred. Our goodwill is not tax deductible for income tax purposes in any jurisdiction we operate in.

We reclassified $187.6 million of IPR&D related to *Rayaldee* from In-process research and development to Intangible assets, net in our Consolidated Balance Sheet upon the FDA's approval of *Rayaldee* in June 2016. In addition, we made certain purchase price allocation adjustments related to the Bio-Reference acquisition during the year ended December 31, 2016 . Refer to Note 4. Other changes in value of the intangible assets and goodwill during 2016 are primarily due to foreign currency fluctuations between the Chilean and Mexican pesos, the Euro and the Shekel against the U.S. dollar. For the year ended December 31, 2015 , the changes in value of the intangible assets and goodwill are primarily due to the acquisitions of Bio-Reference and EirGen and foreign currency fluctuations between the Chilean and Mexican pesos, the Euro and the Shekel against the U.S. dollar.

The following table reflects the changes in the allowance for doubtful accounts, provision for inventory reserve and tax valuation allowance accounts:

(In thousands)	Beginning balance	Charged to expense	Written-off	Charged to other	Ending balance
2016					
Allowance for doubtful accounts	$ (25,168)	(83,463)	68,840	3,523	$ (36,268)
Inventory reserve	$ (1,051)	(20)	296	(170)	$ (945)
Tax valuation allowance	$ (42,147)	7,726	—	(20,994)	$ (55,415)
2015					
Allowance for doubtful accounts	$ (1,906)	(24,548)	928	358	$ (25,168)
Inventory reserve	$ (639)	(926)	435	79	$ (1,051)
Tax valuation allowance	$ (131,931)	—	—	89,784	$ (42,147)

The following table summarizes the changes in Goodwill during the years ended December 31, 2016 and 2015 .

	2016				2015			
(In thousands)	Balance at January 1st	Purchase accounting adjustments	Foreign exchange	Balance at December 31st	Balance at January 1	Purchase accounting adjustments	Foreign exchange	Balance at December 31
Pharmaceuticals								
CURNA	$ 4,827	$ —	$ —	$ 4,827	$ 4,827	$ —	$ —	$ 4,827
EirGen	81,139	—	(2,781)	78,358	—	83,373	(2,234)	81,139
FineTech	11,698	—	—	11,698	11,698	—	—	11,698
OPKO Biologics	139,784	—	—	139,784	139,784	—	—	139,784
OPKO Chile	4,517	—	268	4,785	5,283	—	(766)	4,517
OPKO Health Europe	7,191	—	(255)	6,936	8,013	—	(822)	7,191
OPKO Mexico	—	—	—	—	100	—	(100)	—
OPKO Renal	2,069	—	—	2,069	2,069	—	—	2,069
SciVac	—	—	—	—	1,553	—	(1,553)	—
Transition Therapeutics	—	3,453	(93)	3,360	—	—	—	—
Diagnostics								
Bio-Reference	441,158	(39,337)	—	401,821	—	441,158	—	441,158
OPKO Diagnostics	17,977	—	—	17,977	17,977	—	—	17,977
OPKO Lab	32,988	—	—	32,988	32,988	—	—	32,988
	$ 743,348	$ (35,884)	$ (2,861)	$ 704,603	$ 224,292	$ 524,531	$ (5,475)	$ 743,348

Note 6 Debt

In January 2013, we entered into note purchase agreements (the “2033 Senior Notes”) with qualified institutional buyers and accredited investors (collectively, the “Purchasers”) in a private placement in reliance on exemptions from registration under the Securities Act of 1933, (the “Securities Act”). The 2033 Senior Notes were issued on January 30, 2013 . The 2033 Senior Notes, which totaled $175.0 million in original principal amount, bear interest at the rate of 3.00% per year, payable semiannually on February 1 and August 1 of each year. The 2033 Senior Notes will mature on February 1, 2033 , unless earlier repurchased, redeemed or converted. Upon a fundamental change as defined in the Indenture, dated as of January 30, 2013, by and between the Company and Wells Fargo Bank N.A., as trustee, governing the 2033 Senior Notes (the "Indenture"), subject to certain exceptions, the holders may require us to repurchase all or any portion of their 2033 Senior Notes for cash at a repurchase price equal to 100% of the principal amount of the 2033 Senior Notes being repurchased, plus any accrued and unpaid interest to but not including the fundamental change repurchase date.

The following table sets forth information related to the 2033 Senior Notes which is included in our Consolidated Balance Sheet as of December 31, 2016 :

(In thousands)	Embedded conversion option	2033 Senior Notes	Discount	Debt Issuance Cost	Total
Balance at December 31, 2015	$ 23,737	$ 32,200	$ (6,525)	$ (426)	$ 48,986
Amortization of debt discount	—	—	1,913	153	2,066
Change in fair value of embedded derivative	(7,001)	—	—	—	(7,001)
Conversion	—	(350)	—	—	(350)
Balance at December 31, 2016	$ 16,736	$ 31,850	$ (4,612)	$ (273)	$ 43,701

The following table sets forth information related to the 2033 Senior Notes which is included in our Consolidated Balance Sheet as of December 31, 2015 :

(In thousands)	Embedded conversion option	2033 Senior Notes	Discount	Debt Issuance Cost	Total
Balance at December 31, 2014	$ 65,947	$ 87,642	$ (22,135)	$ (1,638)	$ 129,816
Amortization of debt discount	—	—	2,613	233	2,846
Change in fair value of embedded derivative	36,587	—	—	—	36,587
Conversion	(78,797)	(55,442)	12,997	979	(120,263)
Balance at December 31, 2015	$ 23,737	$ 32,200	$ (6,525)	$ (426)	$ 48,986

The 2033 Senior Notes will be convertible at any time on or after November 1, 2032, through the second scheduled trading day immediately preceding the maturity date, at the option of the holders. Additionally, holders may convert their 2033 Senior Notes prior to the close of business on the scheduled trading day immediately preceding November 1, 2032, under the following circumstances: (1) conversion based upon satisfaction of the trading price condition relating to the 2033 Senior Notes; (2) conversion based on the Common Stock price; (3) conversion based upon the occurrence of specified corporate events; or (4) if we call the 2033 Senior Notes for redemption. The 2033 Senior Notes will be convertible into cash, shares of our Common Stock, or a combination of cash and shares of Common Stock, at our election unless we have made an irrevocable election of net share settlement. The initial conversion rate for the 2033 Senior Notes will be 141.48 shares of Common Stock per $1,000 principal amount of 2033 Senior Notes (equivalent to an initial conversion price of approximately $7.07 per share of Common Stock), and will be subject to adjustment upon the occurrence of certain events. In addition, we will, in certain circumstances, increase the conversion rate for holders who convert their 2033 Senior Notes in connection with a make-whole fundamental change (as defined in the Indenture) and holders who convert upon the occurrence of certain specific events prior to February 1, 2017 (other than in connection with a make-whole fundamental change). Holders of the 2033 Senior Notes may require us to repurchase the 2033 Senior Notes for 100% of their principal amount, plus accrued and unpaid interest, on February 1, 2019, February 1, 2023 and February 1, 2028, or following the occurrence of a fundamental change as defined in the indenture governing the 2033 Senior Notes.

We may not redeem the 2033 Senior Notes prior to February 1, 2017. On or after February 1, 2017 and before February 1, 2019, we may redeem for cash any or all of the 2033 Senior Notes but only if the last reported sale price of our Common Stock exceeds 130% of the applicable conversion price for at least 20 trading days during the 30 consecutive trading day period ending on the trading day immediately prior to the date on which we deliver the redemption notice. The redemption

price will equal 100% of the principal amount of the 2033 Senior Notes to be redeemed, plus any accrued and unpaid interest to but not including the redemption date. On or after February 1, 2019, we may redeem for cash any or all of the 2033 Senior Notes at a redemption price of 100% of the principal amount of the 2033 Senior Notes to be redeemed, plus any accrued and unpaid interest up to but not including the redemption date.

The terms of the 2033 Senior Notes, include, among others: (i) rights to convert into shares of our Common Stock, including upon a fundamental change; and (ii) a coupon make-whole payment in the event of a conversion by the holders of the 2033 Senior Notes on or after February 1, 2017 but prior to February 1, 2019. We have determined that these specific terms are considered to be embedded derivatives. Embedded derivatives are required to be separated from the host contract, the 2033 Senior Notes, and carried at fair value when: (a) the embedded derivative possesses economic characteristics that are not clearly and closely related to the economic characteristics of the host contract; and (b) a separate, stand-alone instrument with the same terms would qualify as a derivative instrument. We have concluded that the embedded derivatives within the 2033 Senior Notes meet these criteria and, as such, must be valued separate and apart from the 2033 Senior Notes and recorded at fair value each reporting period.

For accounting and financial reporting purposes, we combine these embedded derivatives and value them together as one unit of accounting. At each reporting period, we record these embedded derivatives at fair value which is included as a component of the 2033 Senior Notes on our Consolidated Balance Sheet.

In August 2013, one of the conversion rights in the 2033 Senior Notes was triggered. Holders of the 2033 Senior Notes converted $16.9 million principal amount into 2,396,145 shares of the Company's Common Stock. In June 2014, we entered into an exchange agreement with a holder of the Company's 2033 Senior Notes pursuant to which such holder exchanged $70.4 million in aggregate principal amount of 2033 Senior Notes for 10,974,431 shares of the Company's Common Stock and approximately $0.8 million in cash representing accrued interest through the date of completion of the exchange. During 2015, pursuant to a conversion right or through exchange agreements we entered with certain holders of our 2033 Senior Notes, holders of our 2033 Senior Notes converted or exchanged $55.4 million in aggregate principal amount of 2033 Senior Notes for 8,118,062 shares of the Company's Common Stock.

On April 1, 2015, we initially announced that our 2033 Senior Notes were convertible through June 2015 by holders of such notes. This conversion right was triggered because the closing price per share of our Common Stock exceeded $9.19 , or 130% of the initial conversion price of $7.07 , for at least 20 of 30 consecutive trading days during the applicable measurement period. We have elected to satisfy our conversion obligation under the 2033 Senior Notes in shares of our Common Stock. Our 2033 Senior Notes continued to be convertible by holders of such notes for the remainder of 2015 and 2016 and continue to be convertible for the first quarter of 2017, and may be convertible thereafter, if one or more of the conversion conditions specified in the Indenture is satisfied during future measurement periods. Pursuant to the Indenture, a holder who elects to convert the 2033 Senior Notes will receive 141.4827 shares of our Common Stock plus such number of additional shares as is applicable on the conversion date per $1,000 principal amount of 2033 Senior Notes based on the early conversion provisions in the Indenture. See further discussion in Note 14.

We used a binomial lattice model in order to estimate the fair value of the embedded derivative in the 2033 Senior Notes. A binomial lattice model generates two probable outcomes — one up and another down —arising at each point in time, starting from the date of valuation until the maturity date. A lattice model was initially used to determine if the 2033 Senior Notes would be converted, called or held at each decision point. Within the lattice model, the following assumptions are made: (i) the 2033 Senior Notes will be converted early if the conversion value is greater than the holding value; or (ii) the 2033 Senior Notes will be called if the holding value is greater than both (a) the redemption price (as defined in the Indenture) and (b) the conversion value plus the coupon make-whole payment at the time. If the 2033 Senior Notes are called, then the holders will maximize their value by finding the optimal decision between (1) redeeming at the redemption price and (2) converting the 2033 Senior Notes.

Using this lattice model, we valued the embedded derivatives using the "with-and-without method," where the value of the 2033 Senior Notes including the embedded derivatives is defined as the "with," and the value of the 2033 Senior Notes excluding the embedded derivatives is defined as the "without." This method estimates the value of the embedded derivatives by looking at the difference in the values between the 2033 Senior Notes with the embedded derivatives and the value of the 2033 Senior Notes without the embedded derivatives.

The lattice model requires the following inputs: (i) price of our Common Stock; (ii) Conversion Rate (as defined in the Indenture); (iii) Conversion Price (as defined in the Indenture); (iv) maturity date; (v) risk-free interest rate; (vi) estimated stock volatility; and (vii) estimated credit spread for the Company.

The following table sets forth the inputs to the lattice model used to value the embedded derivative:

	December 31, 2016	December 31, 2015	December 31, 2014
Stock price	$9.30	$10.05	$9.99
Conversion Rate	141.4827	141.4827	141.4827
Conversion Price	$7.07	$7.07	$7.07
Maturity date	February 1, 2033	February 1, 2033	February 1, 2033
Risk-free interest rate	1.22%	1.33%	1.40%
Estimated stock volatility	47%	50%	39%
Estimated credit spread	765 basis points	1,142 basis points	1,081 basis points

The following table sets forth the fair value of the 2033 Senior Notes with and without the embedded derivatives, and the fair value of the embedded derivatives at December 31, 2016 , 2015 and 2014 . At December 31, 2016 , 2015 and 2014 , the principal amount of the 2033 Senior Notes was $31.9 million , $32.2 million and $87.6 million , respectively:

(In thousands)	December 31, 2016	December 31, 2015	December 31, 2014
Fair value of 2033 Senior Notes:			
With the embedded derivatives	$ 45,204	$ 48,384	$ 129,009
Without the embedded derivatives	$ 28,468	$ 24,647	$ 63,062
Estimated fair value of the embedded derivatives	$ 16,736	$ 23,737	$ 65,947

Changes in certain inputs into the lattice model can have a significant impact on changes in the estimated fair value of the embedded derivatives. For example, a decrease in our estimated credit spread results in an increase in the estimated value of the embedded derivatives. Conversely, a decrease in the price of our Common Stock results in a decrease in the estimated fair value of the embedded derivatives. For the year ended December 31, 2016 , we observed a decrease in the market price of our Common Stock which primarily resulted in a $7.0 million decrease in the estimated fair value of our embedded derivatives recorded in Fair value changes of derivative instruments, net in our Consolidated Statement of Operations. For the year ended December 31, 2015 , we observed an increase in the market price of our Common Stock which primarily resulted in a $36.6 million increase in the estimated fair value of our embedded derivatives recorded in Fair value changes of derivative instruments, net in our Consolidated Statement of Operations.

On November 5, 2015, Bio-Reference and certain of its subsidiaries entered into a credit agreement with JPMorgan Chase Bank, N.A. (“CB”), as lender and administrative agent, as amended (the “Credit Agreement”), which replaced Bio-Reference’s prior credit facility. The Credit Agreement provides for a $175.0 million secured revolving credit facility and includes a $20.0 million sub-facility for swingline loans and a $20.0 million sub-facility for the issuance of letters of credit. Bio-Reference may increase the credit facility to up to $275.0 million on a secured basis, subject to the satisfaction of specified conditions. The Credit Agreement matures on November 5, 2020 and is guaranteed by all of Bio-Reference’s domestic subsidiaries. The Credit Agreement is also secured by substantially all assets of Bio-Reference and its domestic subsidiaries, as well as a non-recourse pledge by us of our equity interest in Bio-Reference. Availability under the Credit Agreement is based on a borrowing base comprised of eligible accounts receivables of Bio-Reference and certain of its subsidiaries, as specified therein. Principal under the Credit Agreement is due upon maturity on November 5, 2020.

At Bio-Reference’s option, borrowings under the Credit Agreement (other than swingline loans) will bear interest at (i) the CB floating rate (defined as the higher of (a) the prime rate and (b) the LIBOR rate (adjusted for statutory reserve requirements for Eurocurrency liabilities) for an interest period of one month plus 2.50%) plus an applicable margin of 0.35% for the first 12 months and 0.50% thereafter or (ii) the LIBOR rate (adjusted for statutory reserve requirements for Eurocurrency liabilities) plus an applicable margin of 1.35% for the first 12 months and 1.50% thereafter. Swingline loans will bear interest at the CB floating rate plus the applicable margin. The Credit Agreement also calls for other customary fees and charges, including an unused commitment fee of 0.25% of the lending commitments.

The Credit Agreement contains customary covenants and restrictions, including, without limitation, covenants that require Bio-Reference and its subsidiaries to maintain a minimum fixed charge coverage ratio if availability under the new credit facility falls below a specified amount and to comply with laws and restrictions on the ability of Bio-Reference and its subsidiaries to incur additional indebtedness or to pay dividends and make certain other distributions to the Company, subject to certain exceptions as specified therein. Failure to comply with these covenants would constitute an event of default under the Credit Agreement, notwithstanding the ability of Bio-Reference to meet its debt service obligations. The Credit Agreement also includes various customary remedies for the lenders following an event of default, including the acceleration of repayment

of outstanding amounts under the Credit Agreement and execution upon the collateral securing obligations under the Credit Agreement. Substantially all the assets of Bio-Reference and its subsidiaries are restricted from sale, transfer, lease, disposal or distributions to the Company, subject to certain exceptions. Bio-Reference and its subsidiaries net assets as of December 31, 2016 were approximately $1.0 billion , which includes goodwill of $401.8 million and intangible assets of $488.7 million .

In addition to the Credit Agreement with CB, we have line of credit agreements with ten other financial institutions as of December 31, 2016 and ten other financial institutions as of December 31, 2015 in United States, Chile and Spain. These lines of credit are used primarily as a source of working capital for inventory purchases.

The following table summarizes the amounts outstanding under the Bio-Reference, Chilean and Spanish lines of credit:

(Dollars in thousands)			Balance Outstanding	
Lender	Interest rate on borrowings at December 31, 2016	Credit line capacity	December 31, 2016	December 31, 2015
JP Morgan Chase	3.75%	$ 175,000	$ 38,809	$ 72,107
Itau Bank	5.50%	1,450	419	282
Bank of Chile	6.60%	2,500	1,619	2,313
BICE Bank	5.50%	2,000	1,538	1,502
BBVA Bank	5.50%	2,300	1,063	1,825
Security Bank	N/A	—	—	145
Estado Bank	5.50%	2,400	1,870	2,210
Santander Bank	5.50%	3,000	1,196	1,345
Scotiabank	5.00%	1,300	789	939
Corpbanca	5.00%	500	18	—
Banco Bilbao Vizcaya	2.90%	263	—	—
Total		$ 190,713	$ 47,321	$ 82,668

At December 31, 2016 and 2015 , the weighted average interest rate on our lines of credit was approximately 4.7% and 4.3% , respectively.

At December 31, 2016 and 2015 , we had notes payable and other debt (excluding the 2033 Senior Notes, the Credit Agreement and amounts outstanding under lines of credit) as follows:

(In thousands)	December 31, 2016	December 31, 2015
Current portion of notes payable	$ 3,681	$ 1,054
Other long-term liabilities	2,090	1,963
Total	$ 5,771	$ 3,017

The notes and other debt mature at various dates ranging from 2017 through 2024 bearing variable interest rates from 1.8% up to 6.3% . The weighted average interest rate on the notes and other debt at December 31, 2016 and 2015 , was 3.2% and 4.3% , respectively. The notes are secured by our office space in Barcelona.

Note 7 Shareholders' Equity

Our authorized capital stock consists of 750,000,000 shares of Common Stock, par value $0.01 per share, and 10,000,000 shares of Preferred Stock, par value $0.01 per share.

Common Stock

Subject to the rights of the holders of any shares of Preferred Stock currently outstanding or which may be issued in the future, the holders of the Common Stock are entitled to receive dividends from our funds legally available when, as and if declared by our Board of Directors, and are entitled to share ratably in all of our assets available for distribution to holders of Common Stock upon the liquidation, dissolution or winding-up of our affairs subject to the liquidation preference, if any, of any then outstanding shares of Preferred Stock. Holders of our Common Stock do not have any preemptive, subscription, redemption or conversion rights. Holders of our Common Stock are entitled to one vote per share on all matters which they are entitled to vote upon at meetings of stockholders or upon actions taken by written consent pursuant to Delaware corporate law. The holders of our Common Stock do not have cumulative voting rights, which means that the holders of a plurality of the outstanding shares can elect all of our directors. All of the shares of our Common Stock currently issued and outstanding are fully-paid and nonassessable. No dividends have been paid to holders of our Common Stock since our incorporation, and no cash dividends are anticipated to be declared or paid on our Common Stock in the reasonably foreseeable future.

In addition to our equity-based compensation plans, we have issued warrants to purchase our Common Stock. Refer to Note 9 for additional information on our share-based compensation plans. The table below provides additional information for warrants outstanding as of December 31, 2016 .

Warrants	Number of warrants	Weighted average exercise price	Expiration date
Outstanding at December 31, 2015	2,173,723	$ 0.86	Various from January 2017 through March 2017
Exercised	(1,534,125)	0.86	
Expired	—	—	
Outstanding and Exercisable at December 31, 2016	639,598	$ 0.86	Various from January 2017 through March 2017

Of the 1,534,125 Common Stock warrants exercised, 2,564 shares were surrendered in lieu of a cash payment via the net exercise feature of the warrant agreements.

Preferred Stock

Under our certificate of incorporation, our Board of Directors has the authority, without further action by stockholders, to designate up to 10 million shares of Preferred Stock in one or more series and to fix or alter, from time to time, the designations, powers and rights of each series of Preferred Stock and the qualifications, limitations or restrictions of any series of Preferred Stock, including dividend rights, dividend rate, conversion rights, voting rights, rights and terms of redemption (including sinking fund provisions), redemption price or prices, and the liquidation preference of any wholly issued series of Preferred Stock, any or all of which may be greater than the rights of the Common Stock, and to establish the number of shares constituting any such series.

Of the authorized Preferred Stock, 4,000,000 shares, 500,000 shares and 2,000,000 shares were designated Series A Preferred Stock, Series C Preferred Stock and Series D Preferred Stock, respectively. As of December 31, 2016 and 2015, there were no shares of Series A Preferred Stock, Series C Preferred Stock or Series D Preferred Stock issued or outstanding.

Note 8 Accumulated Other Comprehensive Income (Loss)

For the year ended December 31, 2016 , changes in Accumulated other comprehensive income (loss), net of tax, were as follows:

(In thousands)	Foreign currency translation	Unrealized gain (loss) in Accumulated OCI	Total
Balance at December 31, 2015	$ (21,791)	$ (746)	$ (22,537)
Other comprehensive income (loss) before reclassifications	(4,955)	(3,810)	(8,765)
Amounts reclassified from accumulated other comprehensive income (loss), net of tax	—	4,293	4,293
Net other comprehensive loss	(4,955)	483	(4,472)
Balance at December 31, 2016	$ (26,746)	$ (263)	$ (27,009)

Amounts reclassified from Accumulated other comprehensive income (loss) for the year ended December 31, 2016 includes other-than-temporary impairment charges on our investments in Xenetic, ARNO and RXi as discussed in Note 4. Amounts reclassified for our available for sale investments were based on the specific identification method.

For the year ended December 31, 2015 , changes in Accumulated other comprehensive income, net of tax, were as follows:

(In thousands)	Foreign currency translation	Unrealized gain (loss) in Accumulated OCI	Total
Balance at December 31, 2014	$ (6,717)	$ (5,675)	$ (12,392)
Other comprehensive income (loss) before reclassifications	(15,074)	(2,378)	(17,452)
Amounts reclassified from accumulated other comprehensive income, net of tax	—	7,307	7,307
Net other comprehensive loss	(15,074)	4,929	(10,145)
Balance at December 31, 2015	$ (21,791)	$ (746)	$ (22,537)

Amounts reclassified from Accumulated other comprehensive income (loss) for the year ended December 31, 2015 includes an other-than-temporary impairment charge on our investment in RXi as discussed in Note 4. Amounts reclassified for our available for sale investments were based on the specific identification method.

Note 9 Equity-Based Compensation

We maintain six equity-based incentive compensation plans, the 2016 Equity Incentive Plan, the Acuity Pharmaceuticals, Inc. 2003 Equity Incentive Plan, the 2007 Equity Incentive Plan, the 2000 Stock Option Plan, the Modigene Inc. 2005 Stock Incentive Plan and the Modigene Inc. 2007 Equity Incentive Plan that provide for grants of stock options and restricted stock to our directors, officers, key employees and certain outside consultants. Equity awards granted under our 2016 Equity Incentive Plan are exercisable for a period of up to 10 years from the date of grant. Equity awards granted under our 2007 Equity Incentive Plan are exercisable for a period of either 7 years or 10 years from the date of grant. Equity awards granted under our 2000 Stock Option Plan, 2003 Equity Incentive Plan and the two Modigene Plans are exercisable for a period of up to 10 years from date of grant. Vesting periods range from immediate to 5 years.

We classify the cash flows resulting from the tax benefit that arises when the tax deductions exceed the compensation cost recognized for those equity awards (excess tax benefits) as financing cash inflows. There were no excess tax benefits for the years ended December 31, 2016 , 2015 , and 2014 .

Equity-based compensation arrangements to non-employees are accounted for at their fair value on the measurement date. The measurement of equity-based compensation to non-employees is subject to periodic adjustment over the vesting period of the equity instruments.

Valuation and Expense Information

We recorded equity-based compensation expense of $42.7 million , $26.1 million and $14.8 million for the years ended December 31, 2016 , 2015 , and 2014 , respectively, all of which were reflected as operating expenses. Of the $42.7 million of equity based compensation expense recorded in the year ended December 31, 2016 , $33.4 million was recorded as selling, general and administrative expenses, $7.5 million was recorded as research and development expenses and $1.8 million was recorded as a cost of revenue. Of the $26.1 million of equity based compensation expense recorded in the year ended December 31, 2015 , $17.4 million was recorded as selling, general and administrative expense and $7.9 million was recorded as research and development expenses and $0.8 million was recorded as a cost of revenue. Of the $14.8 million of equity based compensation expense recorded in the year ended December 31, 2014 , $9.7 million was recorded as selling, general and administrative expense and $5.0 million was recorded as research and development expenses.

We estimate forfeitures of stock options and recognize compensation cost only for those awards expected to vest. Forfeiture rates are determined for all employees and non-employee directors based on historical experience and our estimate of future vesting. Estimated forfeiture rates are adjusted from time to time based on actual forfeiture experience.

As of December 31, 2016 , there was $72.6 million of unrecognized compensation cost related to the stock options granted under our equity-based incentive compensation plans. Such cost is expected to be recognized over a weighted-average period of approximately 3.0 years .

Stock Options

We estimate the fair value of each stock option on the date of grant using the Black-Scholes-Merton Model option-pricing formula and amortize the fair value to expense over the stock option's vesting period using the straight-line attribution approach for employees and non-employee directors, and for awards issued to non-employees we recognize compensation expense on a graded basis, with most of the compensation expense being recorded during the initial periods of vesting. We apply the following assumptions in our Black-Scholes-Merton Model option-pricing formula:

	Year Ended December 31, 2016	Year Ended December 31, 2015	Year Ended December 31, 2014
Expected term (in years)	1.0 - 10.0	1.0 - 10.0	1.0 - 10.0
Risk-free interest rate	0.71% - 2.51%	0.26% - 2.42%	0.10% - 2.65%
Expected volatility	38% - 64%	32% - 64%	31% - 72%
Expected dividend yield	0%	0%	0%

Expected Term: For the expected term of options granted to employees and non-employee directors, we used an estimate of the expected option life based on historical experience. The expected term of stock options issued to non-employee consultants is the remaining contractual life of the options issued.

Risk-Free Interest Rate: The risk-free interest rate is based on the rates paid on securities issued by the U.S. Treasury with a term approximating the expected life of the option.

Expected Volatility: The expected volatility for stock options was based on the historical volatility of our Common Stock.

Expected Dividend Yield: We do not intend to pay dividends on Common Stock for the foreseeable future. Accordingly, we used a dividend yield of zero in the assumptions.

We maintain incentive stock plans that provide for the grants of stock options to our directors, officers, employees and non-employee consultants. As of December 31, 2016 , there were 26,866,484 shares of Common Stock reserved for issuance under our 2016 Equity Incentive Plan and our 2007 Equity Incentive Plan. We intend to issue new shares upon the exercise of stock options. Stock options granted under these plans have been granted at an option price equal to the closing market value of the stock on the date of the grant. Stock options granted under these plans to employees typically become exercisable over four years in equal annual installments after the date of grant, and stock options granted to non-employee directors become exercisable in full one-year after the grant date, subject to, in each case, continuous service with us during the applicable vesting period. We assumed stock options to grant Common Stock as part of the mergers with Acuity Pharmaceuticals, Inc., Froptix, Inc., OPKO Biologics and Bio-Reference, which reflected various vesting schedules, including monthly vesting to employees and non-employee consultants.

A summary of option activity under our stock option plans as of December 31, 2016 , and the changes during the year is presented below:

Options	Number of options	Weighted average exercise price	Weighted average remaining contractual term (years)	Aggregate intrinsic value (in thousands)
Outstanding at December 31, 2015	31,286,787	$ 9.55	6.97	$ 63,902
Granted	7,945,500	$ 10.22		
Exercised	(1,836,572)	$ 4.67		
Forfeited	(1,472,314)	$ 11.28		
Expired	(1,282,887)	$ 1.53		
Outstanding at December 31, 2016	34,640,514	$ 10.18	6.79	$ 32,984
Vested and expected to vest at December 31, 2016	31,724,227	$ 10.07	6.64	$ 32,477
Exercisable at December 31, 2016	14,494,573	$ 8.59	4.50	$ 29,385

The total intrinsic value of stock options exercised for the years ended December 31, 2016 , 2015 , and 2014 was $9.9 million , $69.9 million and $14.6 million , respectively.

The weighted average grant date fair value of stock options granted for the years ended December 31, 2016 , 2015 , and 2014 was $4.78 , $5.00 , and $4.64 , respectively. The total fair value of stock options vested during the years ended December 31, 2016 , 2015 , and 2014 was $30.2 million , $13.3 million and $10.9 million , respectively.

Note 10 Income Taxes

We operate and are required to file tax returns in the U.S. and various foreign jurisdictions.

The benefit (provision) for incomes taxes consists of the following:

	For the years ended December 31,		
(In thousands)	2016	2015	2014
Current			
Federal	$ —	$ 430	$ 225
State	(2,931)	(2,157)	247
Foreign	(2,438)	(8,134)	(1,514)
	(5,369)	(9,861)	(1,042)
Deferred			
Federal	25,739	109,286	—
State	10,657	12,327	(167)
Foreign	25,088	1,923	1,185
	61,484	123,536	1,018
Total, net	$ 56,115	$ 113,675	$ (24)

Deferred income tax assets and liabilities as of December 31, 2016 and 2015 are comprised of the following:

(In thousands)	December 31, 2016	December 31, 2015
Deferred income tax assets:		
Federal net operating loss	$ 76,792	$ 71,658
State net operating loss	36,285	14,227
Foreign net operating loss	32,895	33,701
Research and development expense	3,246	5,138
Tax credits	20,894	7,388
Stock options	36,485	24,756
Accruals	8,306	7,086
Equity investments	7,011	4,420
Bad debts	14,283	38,809
Lease liability	3,233	7,022
Foreign credits	10,253	—
Available for sale securities	4,792	—
Other	7,795	7,104
Deferred income tax assets	262,270	221,309
Deferred income tax liabilities:		
Intangible assets	(354,043)	(386,588)
Fixed assets	(13,710)	(17,072)
Other	(2,121)	(1,538)
Deferred income tax liabilities	(369,874)	(405,198)
Net deferred income tax liabilities	(107,604)	(183,889)
Valuation allowance	(55,415)	(42,147)
Net deferred income tax liabilities *	$ (163,019)	$ (226,036)

* The components of December 31, 2016 Net deferred income tax liability is presented on the Consolidated Balance Sheet as follows: $(165,331) within Deferred tax liabilities, net and $2,312 within Other assets.

The changes in deferred income tax assets, liabilities and valuation allowances at December 31, 2016 reflect the acquisition of various legal entities, including the tax attributes. The acquisitions were accounted for under U.S. GAAP as stock acquisitions and business combinations. As of December 31, 2016 , we have federal, state and foreign net operating loss carryforwards of approximately $409.3 million , $406.6 million and $186.6 million , respectively, that expire at various dates through 2036. Included in the foreign net operating losses is $98.6 million related to OPKO Biologics. As of December 31, 2016 , we have research and development tax credit carryforwards of approximately $18.5 million that expire in varying amounts through 2036. As of each reporting date, management considers new evidence, both positive and negative, that could affect its view of the future realization of deferred tax assets.

As a result of certain realization requirements of ASC 718, Compensation - Stock Compensation, the table of deferred tax assets and liabilities shown above does not include certain deferred tax assets as of December 31, 2016 and 2015 , that arose directly from (or the use of which was postponed by) tax deductions related to equity compensation that are greater than the compensation recognized for financial reporting. Equity will be increased by $33.7 million if and when such deferred tax assets are ultimately realized. The Company uses ASC 740 ordering when determining when excess tax benefits have been realized.

Under Section 382 of the Internal Revenue Code of 1986, as amended, certain significant changes in ownership may restrict the future utilization of our income tax loss carryforwards and income tax credit carryforwards in the U.S. The annual limitation is equal to the value of our stock immediately before the ownership change, multiplied by the long-term tax-exempt rate (i.e., the highest of the adjusted federal long-term rates in effect for any month in the three-calendar-month period ending with the calendar month in which the change date occurs). This limitation may be increased under the IRC Section 338 Approach (IRS approved methodology for determining recognized Built-In Gain). As a result, federal net operating losses and tax credits may expire before we are able to fully utilize them.

During 2008, we conducted a study to determine the impact of the various ownership changes that occurred during 2007 and 2008. As a result, we have concluded that the annual utilization of our net operating loss carryforwards (“NOLs”) and tax credits is subject to a limitation pursuant to Internal Revenue Code Section 382. Under the tax law, such NOLs and tax credits are subject to expiration from 15 to 20 years after they were generated. As a result of the annual limitation that may be imposed on such tax attributes and the statutory expiration period, some of these tax attributes may expire prior to our being able to use them. There is no current impact on these financial statements as a result of the annual limitation. This study did not conclude whether OPKO's predecessor, eXegenics, pre-merger NOLs were limited under Section 382. As such, of the $409.3 million of federal net operating loss carryforwards, at least approximately $53.4 million may not be able to be utilized.

Uncertain Income Tax Positions

We file federal income tax returns in the U.S. and various foreign jurisdictions, as well as with various U.S. states and the Ontario and Quebec provinces in Canada. We are subject to routine tax audits in all jurisdictions for which we file tax returns. Tax audits by their very nature are often complex and can require several years to complete. It is reasonably possible that some audits will close within the next twelve months, which we do not believe would result in a material change to our accrued uncertain tax positions.

U.S. Federal: Under the tax statute of limitations applicable to the Internal Revenue Code, we are no longer subject to U.S. federal income tax examinations by the Internal Revenue Service for years before 2013. However, because we are carrying forward income tax attributes, such as net operating losses and tax credits from 2013 and earlier tax years, these attributes can still be audited when utilized on returns filed in the future.

State: Under the statute of limitations applicable to most state income tax laws, we are no longer subject to state income tax examinations by tax authorities for years before 2013 in states in which we have filed income tax returns. Certain states may take the position that we are subject to income tax in such states even though we have not filed income tax returns in such states and, depending on the varying state income tax statutes and administrative practices, the statute of limitations in such states may extend to years before 2013.

Foreign: Under the statute of limitations applicable to our foreign operations, we are generally no longer subject to tax examination for years before 2011 in jurisdictions where we have filed income tax returns.

Unrecognized Tax Benefits

As of December 31, 2016 , 2015 , and 2014 , the total amount of gross unrecognized tax benefits was approximately $27.5 million , $8.6 million , and $5.9 million , respectively. As of December 31, 2016 , the total gross unrecognized tax benefit of $27.5 million consisted of increases of $19.9 million as a result of current year activity, and decreases of $0.3 million as a result of the lapse of statutes of limitations. As of December 31, 2016 , the total amount of unrecognized tax benefits that, if recognized, would affect our effective income tax rate was $6.1 million . We account for any applicable interest and penalties on uncertain tax positions as a component of income tax expense and we recognized $0.1 million and $0.3 million of interest expense for the years ended December 31, 2016 and 2015 , respectively. As of December 31, 2015 and 2014 , $0.7 million and $0.9 million of the unrecognized tax benefits, if recognized, would have affected our effective income tax rate. We believe it is reasonably possible that approximately $4.1 million of unrecognized tax benefits may be recognized within the next twelve months.

The following summarizes the changes in our gross unrecognized income tax benefits.

	For the years ended December 31,		
(In thousands)	2016	2015	2014
Unrecognized tax benefits at beginning of period	$ 8,595	$ 5,890	$ 9,231
Gross increases – tax positions in prior period	1,443	955	524
Gross increases – tax positions in current period	18,472	2,543	193
Gross decreases – tax positions in prior period	(671)	(176)	(396)
Lapse of Statute of Limitations	(294)	(617)	(472)
Settlements	—	—	(3,190)
Unrecognized tax benefits at end of period	$ 27,545	$ 8,595	$ 5,890

Other Income Tax Disclosures

The significant elements contributing to the difference between the federal statutory tax rate and the effective tax rate are as follows:

	For the years ended December 31,		
	2016	2015	2014
Federal statutory rate	35.0 %	35.0 %	35.0 %
State income taxes, net of federal benefit	5.2 %	2.8 %	2.5 %
Foreign income tax	1.2 %	(7.8)%	(10.3)%
Research and development tax credits	5.4 %	— %	1.1 %
Non-Deductible components of Convertible Debt	2.2 %	(9.4)%	(3.8)%
Valuation allowance	9.5 %	61.1 %	(25.3)%
Rate change effect	21.2 %	— %	— %
Non-deductible foreign stock compensation	(1.9)%	(0.7)%	— %
Other	(8.7)%	(1.0)%	0.8 %
Total	69.1 %	80.0 %	— %

The following table reconciles our losses before income taxes between U.S. and foreign jurisdictions:

	For the years ended December 31,		
(In thousands)	2016	2015	2014
Pre-tax income (loss):			
U.S.	$ (92,175)	$ (113,612)	$ (84,075)
Foreign	10,977	(30,091)	(87,567)
Total	$ (81,198)	$ (143,703)	$ (171,642)

We intend to indefinitely reinvest the earnings from our foreign subsidiaries, primarily for purposes of continuing significant research and development activities related to intellectual property owned and developed by our foreign subsidiaries. The accumulated earnings are the most significant component of the basis difference which is indefinitely reinvested. The aggregate undistributed earnings of our foreign subsidiaries for which no deferred tax liability has been recorded is approximately $31.2 million as of December 31, 2016. Determination of the amount of unrecognized deferred tax liability on these undistributed earnings is not practicable because of the complexities of the hypothetical calculation.

Note 11 Related Party Transactions

We hold investments in Zebra (ownership 28%), Sevion (3%), Neovasc (4%), ChromaDex Corporation (2%), MabVax (4%), COCP (8%), ARNO (5%), NIMS 1% and BioCardia (5%). These investments were considered related party transactions as a result of our executive management's ownership interests and/or board representation in these entities. See further discussion of our investments in Note 4. In July 2015, we made an additional $0.5 million investment in a private placement transaction with Sevion pursuant to which we acquired 66,667 shares of Series C Convertible Preferred Stock convertible into 666,667 shares of common stock and warrants to purchase 333,333 shares of common stock. In October 2015, we made an additional $0.4 million investment in MabVax pursuant to which we acquired 340,909 shares of common stock at $1.10 and 170,454 warrants to purchase shares of common stock. In November 2015, we made an additional $1.0 million investment in Zebra pursuant to which we acquired 420,000 shares of Series A-2 Preferred Stock. In January 2016, we invested an additional $0.3 million in ARNO for 714,285 shares of its common stock and in August 2016, we invested an additional $0.3 million in ARNO for 714,285 shares of its common stock and warrants to purchase 357,142 shares of its common stock. In August 2016 we invested an additional $1.0 million in MabVax for 207,900 shares of its common stock and warrants to purchase 415,800 shares of its common stock. In September 2016, we invested an additional $2.0 million in COCP for 4,878,050 shares of its common stock.

In October 2016, we entered into a consulting agreement to provide strategic advisory services to BioCardia. In connection with the consulting agreement, BioCardia granted us 5,027,726 common stock options. In December 2016, we purchased 19,230,769 shares of BioCardia from Dr. Frost for $2.5 million . We have also purchased shares of BioCardia in the open market. BioCardia is a related party as a result of our executive management's ownership interest and board representation in BioCardia and its predecessor, Tiger X Medical, Inc. In October 2016, BioCardia completed its merger with Tiger X Medical, Inc., to which Tiger X Medical, Inc. was the surviving entity and the name of the issuer was changed to BioCardia.

In November 2016, we made a $0.2 million loan to Sevion which was considered a related party transaction as a result of our executive management's ownership interests and board representation in Sevion.

In November 2016, we entered into a Pledge Agreement with the Museum of Science, Inc. and the Museum of Science Endowment Fund, Inc. pursuant to which we will contribute an aggregate of $1.0 million over a four-year period for constructing, equipping and the general operation of the Frost Science Museum. Dr. Frost and Mr. Pfenniger serve on the Board of Trustees of the Frost Science Museum and Mr. Pfenniger is the Vice Chairman of the Board of Trustees.

We lease office space from Frost Real Estate Holdings, LLC ("Frost Holdings") in Miami, Florida, where our principal executive offices are located. Effective May 28, 2015, we entered into an amendment to our lease agreement with Frost Holdings. The lease, as amended, is for approximately 25,000 square feet of space. The lease provides for payments of approximately $66 thousand per month in the first year increasing annually to $75 thousand per month in the fifth year, plus applicable sales taxes. The rent is inclusive of operating expenses, property taxes and parking. The rent was reduced by $0.2 million for the cost of tenant improvements.

Our wholly-owned subsidiary, Bio-Reference, purchases and uses certain products acquired from InCellDx, Inc., a company in which we hold a 27% minority interest.

We reimburse Dr. Frost for Company-related use by Dr. Frost and our other executives of an airplane owned by a company that is beneficially owned by Dr. Frost. We reimburse Dr. Frost for out-of-pocket operating costs for the use of the airplane by Dr. Frost or Company executives for Company-related business. We do not reimburse Dr. Frost for personal use of the airplane by Dr. Frost or any other executive. For the years ended December 31, 2016 , 2015 , and 2014 , we recognized approximately $298 thousand , $595 thousand , and $175 thousand , respectively, for Company-related travel by Dr. Frost and other OPKO executives.

Note 12 Employee Benefit Plans

Effective January 1, 2007, the OPKO Health Savings and Retirement Plan (the "Plan") permits employees to contribute up to 100% of qualified pre-tax annual compensation up to annual statutory limitations. The discretionary company match for employee contributions to the Plan is 100% up to the first 4% of the participant's earnings contributed to the Plan. Our matching contributions to the Plan were approximately $0.7 million , $0.8 million and $0.6 million for the years ended December 31, 2016 , 2015 , and 2014 respectively.

Bio-Reference Laboratories, Inc. sponsors a 401(k) Profit-Sharing Plan (the "Bio-Reference Plan"). Employees become eligible for participation after attaining the age of eighteen and completing one year of service. Participants may elect to contribute up to 60% of their compensation, as defined in the Bio-Reference Plan, to a maximum allowed by the Internal Revenue Service. Bio-Reference makes a matching contribution to the plan for each participant who has elected to make tax-deferred contributions. The discretionary company match for employee contributions to the Bio-Reference Plan is 100% up to the first 3% of the participant's earnings contributed to the Bio-Reference Plan, with an annual maximum match of $1 thousand . Bio-Reference Laboratories, Inc. elected to make a matching contribution which amounted to $1.8 million for the year ended December 31, 2016 .

GeneDx, Inc. sponsors a 401(k) Profit-Sharing Plan (the "GeneDx Plan"). Employees become eligible for participation after attaining the age of eighteen and completing one month of service. Participants may elect to contribute up to 100% of their compensation, as defined in the GeneDx Plan, to a maximum allowed by the Internal Revenue Service. GeneDx, Inc. makes a matching contribution to the plan for each participant who has elected to make tax-deferred contributions. The discretionary company match for employee contributions to the GeneDx Plan is 100% up to the first 3% , plus 50% of the next 2% of the participant's earnings contributed to the GeneDx Plan. GeneDx, Inc. elected to make a matching contribution which amounted to $1.0 million for the year ended December 31, 2016 .

Note 13 Commitments and Contingencies

In connection with our acquisitions of CURNA, OPKO Diagnostics, OPKO Health Europe and OPKO Renal, we agreed to pay future consideration to the sellers upon the achievement of certain events. As a result, as of December 31, 2016 , we recorded $45.1 million as contingent consideration, with $0.3 million recorded within Accrued expenses and $44.8 million recorded within Other long-term liabilities in the accompanying Consolidated Balance Sheet. Refer to Note 5. During the year ended December 31, 2016, we satisfied a $25.0 million contingent payment to the former owners of OPKO Renal through the issuance of 2,611,648 shares of our common stock. During the year ended December 31, 2015 , we satisfied a $20.0 million contingent payment to the former owners of OPKO Renal through the issuance of 1,194,337 shares of our common stock.

On or around October 21, 2014, we received a Civil Investigative Demand ("Demand") from the U.S. Attorney's Office for the Middle District of Tennessee ("Attorney's Office"). The Demand concerns an investigation of allegations that the Company or one of its affiliated entities or other parties submitted false claims for payment related to services provided to government healthcare program beneficiaries in violation of the False Claims Act, 31 U.S.C. Section 3729. We entered into a settlement agreement resolving the matter in May 2016, and it did not have a financial impact on the Company.

Following the announcement of entry into an agreement and plan of merger with Bio-Reference, four putative class action complaints challenging the merger were filed in the Superior Court of New Jersey in Bergen County (the "Court"). In September 2015, the parties executed a stipulation and agreement of compromise, settlement and release resolving all matters between them. In January 2016, the Court entered an order finally approving the settlement. The settlement did not have a material impact on our business, financial condition, results of operations or cash flows.

Under a license agreement one of our subsidiaries has with Washington University in St. Louis, we are obligated to pay Washington University a single digit percentage of any sublicensing payment we receive in connection with a sublicense of our rights to Washington University patents subject to certain exceptions. In connection with the Pfizer Transaction, we sublicensed to Pfizer the sole remaining patent licensed to us by Washington University and paid to Washington University the sublicensing payment we believe is due under the license agreement. Washington University disagreed with the computation of the sublicense payment and notified us that it wanted to review additional information relating to the sublicense and the Pfizer Transaction to determine whether additional amounts were owed to it. In May 2016, the parties entered into a settlement agreement resolving the matter. The settlement did not have a material impact on our business, financial condition, results of operations or cash flows.

On December 18, 2013, Bio-Reference filed an action in the Superior Court of New Jersey against Horizon, captioned Bio-Reference Laboratories, Inc. v. Horizon Healthcare Services, Inc. d/b/a Horizon Blue Cross Blue Shield of New Jersey, Docket No. BER L-009748-13 (N.J. Super. Ct. Bergen County). Bio-Reference has been an in-network provider with Horizon's PPO network for more than 20 years and filed the lawsuit after attempts to resolve its dispute with Horizon were unsuccessful.

The parties have agreed to a full and final settlement of the matter with an effective date of March 31, 2016, based on an execution date of May 11, 2016. Among other consideration, under the terms of the settlement, Horizon paid Bio-Reference a negotiated settlement for the disputed claims and Bio-Reference's current PPO contract will remain in effect through December 31, 2018. The settlement was not material to Revenue from services in our Consolidated Statement of Operations for the year ended December 31, 2016 .

We accrue a liability for legal contingencies when we believe that it is both probable that a liability has been incurred and that we can reasonably estimate the amount of the loss. We review these accruals and adjust them to reflect ongoing negotiations, settlements, rulings, advice of legal counsel and other relevant information. To the extent new information is obtained and our views on the probable outcomes of claims, suits, assessments, investigations or legal proceedings change, changes in our accrued liabilities would be recorded in the period in which such determination is made. For the matters referenced in the paragraph below, the amount of liability is not probable or the amount cannot be reasonably estimated; and, therefore, accruals have not been made. In addition, in accordance with the relevant authoritative guidance, for matters which the likelihood of material loss is at least reasonably possible, we provide disclosure of the possible loss or range of loss; however, if a reasonable estimate cannot be made, we will provide disclosure to that effect.

From time to time, we may receive inquiries, document requests, or subpoenas from the Department of Justice, the Office of Inspector General and Office for Civil Rights ("OCR") of the Department of Health and Human Services, the Centers for Medicare and Medicaid Services, various payors and fiscal intermediaries, and other state and federal regulators regarding investigations, audits and reviews. In addition to the matters discussed in this note, we are currently responding to subpoenas or document requests for various matters relating to our laboratory operations. In addition, we are subject to other claims and lawsuits arising in the ordinary course of our business. Some pending or threatened proceedings against us may involve potentially substantial amounts as well as the possibility of civil, criminal, or administrative fines, penalties, or other sanctions, which could be material. Settlements of suits involving the types of issues that we routinely confront may require monetary payments as well as corporate integrity agreements. Additionally, qui tam or "whistleblower" actions initiated under the civil False Claims Act may be pending but placed under seal by the court to comply with the False Claims Act's requirements for filing such suits. Also, from time to time, we may detect issues of non-compliance with federal healthcare laws pertaining to claims submission and reimbursement practices and/or financial relationships with physicians, among other things. We may avail ourselves of various mechanisms to address these issues, including participation in voluntary disclosure protocols. Participating in voluntary disclosure protocols can have the potential for significant settlement obligations or even enforcement action. The Company generally has cooperated, and intends to continue to cooperate, with appropriate regulatory authorities as and when investigations, audits and inquiries arise. We are a party to other litigation in the ordinary course of business. We do not believe that any such litigation will have a material adverse effect on our business, financial condition, results of operations or cash flows.

We expect to continue to incur substantial research and development expenses, including expenses related to the hiring of personnel and additional clinical trials. We expect that selling, general and administrative expenses will also increase as we expand our sales, marketing and administrative staff and add infrastructure, particularly as it relates to the launch of *Rayaldee* . We do not anticipate that we will generate substantial revenue from the sale of proprietary pharmaceutical products or certain of our diagnostic products for some time and we have generated only limited revenue from our pharmaceutical operations in Chile, Mexico, Israel, Spain, and Ireland, and from sale of the *4Kscore* test. If we acquire additional assets or companies, accelerate our product development programs or initiate additional clinical trials, we will need additional funds. If we are not able to secure additional funding when needed, we may have to delay, reduce the scope of, or eliminate one or more of our clinical trials or research and development programs or possible acquisitions.

We have employment agreements with certain executives of Bio-Reference which provide for compensation and certain other benefits and for severance payments under certain circumstances. During the year ended December 31, 2016 , we recognized $17.9 million of severance costs pursuant to these employment agreements as a component of Selling, general and administrative expense.

At December 31, 2016 , we were committed to make future purchases for inventory and other items in 2017 that occur in the ordinary course of business under various purchase arrangements with fixed purchase provisions aggregating $90.3 million .

Note 14 Strategic Alliances

Vifor Fresenius Medical Renal Care Pharma Ltd

We plan to develop a portfolio of product candidates through a combination of internal development and external partnerships. In May 2016, EirGen, our wholly-owned subsidiary, and Vifor Fresenius Medical Renal Care Pharma Ltd ("VFMCRP"), entered into a Development and License Agreement (the "VFMCRP Agreement") for the development and

marketing of *Rayaldee* (the "Product") worldwide, except for (i) the United States, (ii) any country in Central America or South America (excluding Mexico), (iii) Russia, (iv) China, (v) Japan, (vi) Ukraine, (vii) Belorussia, (viii) Azerbaijan, (ix) Kazakhstan, and (x) Taiwan (the "Territory"). The license to VFMCRP potentially covers all therapeutic and prophylactic uses of the Product in human patients (the "Field"), provided that initially the license is for the use of the Product for the treatment or prevention of secondary hyperparathyroidism related to patients with stage 3 or 4 chronic kidney disease and vitamin D insufficiency/deficiency (the "Initial Indication").

Under the terms of the VFMCRP Agreement, EirGen granted to VFMCRP an exclusive license in the Territory in the Field to use certain EirGen patents and technology to make, have made, use, sell, offer for sale, and import Products and to develop, commercialize, have commercialized, and otherwise exploit the Product. EirGen received a non-refundable and non-creditable initial payment of $50 million . EirGen is also eligible to receive up to an additional $37 million in regulatory milestones ("Regulatory Milestones") and $195 million in launch and sales-based milestones ("Sales Milestones"), and will receive tiered, double digit royalty payments or a minimum royalty, whichever is greater, upon the commencement of sales of the Product within the Territory and in the Field.

As part of the arrangement, the companies will share responsibility for the conduct of trials specified within an agreed-upon development plan, with each company leading certain activities within the plan. EirGen will lead the manufacturing activities within and outside the Territory and the commercialization activities outside the Territory and outside the Field in the Territory and VFMCRP will lead the commercialization activities in the Territory and the Field. For the initial development plan, the companies have agreed to certain cost sharing arrangements. VFMCRP will be responsible for all other development costs that VFMCRP considers necessary to develop the Product for the use of the Product for the Initial Indication in the Territory in the Field except as otherwise provided in the VFMCRP Agreement.

The VFMCRP Agreement will remain in effect with respect to the Product in each country of the Territory, on a country by country basis, until the date on which VFMCRP shall have no further payment obligations to EirGen under the terms of the VFMCRP Agreement, unless earlier terminated pursuant to the VFMCRP Agreement. VFMCRP's royalty obligations expire on a country-by-country and product-by-product basis on the later of (i) expiration of the last to expire valid claim covering the Product sold in such country, (ii) expiration of all regulatory and data exclusivity applicable to the Product in the country of sale, and (c) ten (10) years after the Product first commercial sale in such country. In addition to termination rights for material breach and bankruptcy, VFMCRP is permitted to terminate the VFMCRP Agreement in its entirety, or with respect to one or more countries in the Territory, after a specified notice period, provided that VFMCRP shall not have the right to terminate the VFMCRP Agreement with respect to certain major countries without terminating the entire VFMCRP Agreement. If the VFMCRP Agreement is terminated by EirGen or VFMCRP, provision has been made for transition of product and product responsibilities to EirGen.

In connection with the VFMCRP Agreement, the parties entered into a letter agreement (the "Letter Agreement") pursuant to which EirGen granted to VFMCRP an exclusive option (the "Option") to acquire an exclusive license under certain EirGen patents and technology to use, import, offer for sale, sell, distribute and commercialize the Product in the United States solely for the treatment of secondary hyperparathyroidism in dialysis patients with chronic kidney disease and vitamin D insufficiency (the "Dialysis Indication"). Upon exercise of the Option, VFMCRP will reimburse EirGen for all of the development costs incurred by EirGen with respect to the Product for the Dialysis Indication in the United States. VFMCRP would also pay EirGen up to an additional aggregate amount of $555 million upon the achievement of certain milestones and would be obligated to pay certain double digit royalties on VFMCRP's sales in the United States for the Dialysis Indication.

The Option is exercisable until the earlier of (i) the date that EirGen submits a new drug application or supplemental new drug application or their then equivalents to the U.S. Food and Drug Administration for the Product for the Dialysis Indication in the United States, (ii) the parties mutually agree to discontinue development of Product for the Dialysis Indication, or (iii) VFMCRP provides notice to OPKO that it has elected not to exercise the Option.

OPKO has guaranteed the performance of certain of EirGen's obligations under the VFMCRP Agreement and the Letter Agreement.

For revenue recognition purposes, we evaluated the various agreements with Vifor to determine whether there were multiple deliverables in the arrangement. The VFMCRP Agreement provides for the following: (1) an exclusive license in the Territory in the Field to use certain patents and technology to make, have made, use, sell, offer for sale, and import Products and to develop, commercialize, have commercialized, and otherwise exploit the Product; (2) EirGen will supply Products to support the development, sale and commercialization of the Products to VFMCRP in the Territory (the "Manufacturing Services"); and (3) the Option to acquire an exclusive license under certain EirGen patents and technology to use, import, offer for sale, sell, distribute and commercialize the Product in the United States solely for the Dialysis Indication. Based on our evaluation, the exclusive license is the only deliverable at the outset of the arrangement. We concluded the Manufacturing

Services were a contingent deliverable dependent on the future regulatory and commercial action by VFMCRP and the Option was substantive and not considered a deliverable under the license arrangement.

We recognized the $50.0 million upfront license payment in Revenue from transfer of intellectual property in our Consolidated Statement of Operations for the year ended December 31, 2016 . Revenues related to the Manufacturing Services will be recognized as Product is sold to VFMCRP. No revenue related to the Option will be recognized unless and until VFMCRP exercises its Option under the Letter Agreement.

We determined that the cost sharing arrangement for development of the Dialysis Indication is not a deliverable in the VFMCRP Agreement. Payments for the Dialysis Indication will be recorded as Research and development expense as incurred.

EirGen is also eligible to receive up to an additional $37 million in Regulatory Milestones and $195 million in Sales Milestones. Payments received for Regulatory Milestones and Sales Milestones are non-refundable. The Regulatory Milestones are payable if and when VFMCRP obtains approval from certain regulatory authorities and will be recognized as revenue in the period in which the associated milestone is achieved, assuming all other revenue recognition criteria are met. We account for the Sales Milestones as royalties and Sales Milestones payments will be recognized as revenue in full in the period in which the associated milestone is achieved, assuming all other revenue recognition criteria are met. To date, no revenue has been recognized related to the achievement of the milestones.

Pfizer Inc.

In December 2014, we entered into an exclusive worldwide agreement with Pfizer Inc. (“Pfizer”) for the development and commercialization of our long-acting hGH-CTP for the treatment of growth hormone deficiency (“GHD”) in adults and children, as well as for the treatment of growth failure in children born small for gestational age (“SGA”) (the “Pfizer Transaction”).

The Pfizer Transaction closed in January 2015 following the termination of the waiting period under the Hart-Scott-Rodino Act. Under the terms of the Pfizer Transaction, we received non-refundable and non-creditable upfront payments of $295.0 million and are eligible to receive up to an additional $275.0 million upon the achievement of certain regulatory milestones. Pfizer received the exclusive license to commercialize hGH-CTP worldwide. In addition, we are eligible to receive initial tiered royalty payments associated with the commercialization of hGH-CTP for Adult GHD with percentage rates ranging from the high teens to mid-twenties. Upon the launch of hGH-CTP for Pediatric GHD in certain major markets, the royalties will transition to regional, tiered gross profit sharing for both hGH-CTP and Pfizer’s Genotropin®.

The agreement with Pfizer will remain in effect until the last sale of the licensed product, unless earlier terminated as permitted under the agreement. In addition to termination rights for material breach and bankruptcy, Pfizer is permitted to terminate the Agreement in its entirety, or with respect to one or more world regions, without cause after a specified notice period. If the Agreement is terminated by us for Pfizer’s uncured material breach, or by Pfizer without cause, provision has been made for transition of product and product responsibilities to us for the terminated regions, as well as continued supply of product by Pfizer or transfer of supply to us in order to support the terminated regions.

We will lead the clinical activities and will be responsible for funding the development programs for the key indications, which includes Adult and Pediatric GHD and Pediatric SGA. Pfizer will be responsible for all development costs for additional indications as well as all post-marketing studies. In addition, Pfizer will fund the commercialization activities for all indications and lead the manufacturing activities covered by the global development plan.

For revenue recognition purposes, we viewed the Pfizer Transaction as a multiple-element arrangement. Multiple-element arrangements are analyzed to determine whether the various performance obligations, or elements, can be separated or whether they must be accounted for as a single unit of accounting. We evaluated whether a delivered element under an arrangement has standalone value and qualifies for treatment as a separate unit of accounting. Deliverables that do not meet these criteria are not evaluated separately for the purpose of revenue recognition. For a single unit of accounting, payments received are recognized in a manner consistent with the final deliverable. We determined that the deliverables under the Pfizer Transaction, including the licenses granted to Pfizer, as well as our obligations to provide various research and development services, will be accounted for as a single unit of account. This determination was made because the ongoing research and development services to be provided by us are essential to the overall arrangement as we have significant knowledge and technical know-how that is important to realizing the value of the licenses granted. The performance period over which the revenue will be recognized is expected to continue from the first quarter of 2015 through 2019, when we anticipate completing the various research and development services that are specified in the Pfizer Transaction and our performance obligations are completed. We will continue to review the timing of when our research and development services will be completed in order to assess that the estimated performance period over which the revenue is to be recognized is appropriate. Any significant changes in the timing of the performance period will result in a change in the revenue recognition period.

We are recognizing the non-refundable $295.0 million upfront payments on a straight-line basis over the performance period. We recognized $70.6 million of revenue related to the Pfizer Transaction in Revenue from transfer of intellectual property in our Consolidated Statement of Operations during the year ended December 31, 2016 , and had deferred revenue related to the Pfizer Transaction of $158.9 million at December 31, 2016 . As of December 31, 2016 , $70.6 million of deferred revenue related to the Pfizer Transaction was classified in Accrued expenses and $88.3 million was classified in Other long-term liabilities in our Consolidated Balance Sheet. During the year ended December 31, 2016 , we incurred $45.9 million in research and development expenses related to hGH-CTP.

The Pfizer Transaction includes milestone payments of $275.0 million upon the achievement of certain milestones. The milestones range from $20.0 million to $90.0 million each and are based on achievement of regulatory approval in the U.S. and regulatory approval and price approval in other major markets. We evaluated each of these milestone payments and believe that all of the milestones are substantive as (i) there is substantive uncertainty at the close of the Pfizer Transaction that the milestones would be achieved as approval from a regulatory authority must be received to achieve the milestones which would be commensurate with the enhancement of value of the underlying intellectual property, (ii) the milestones relate solely to past performance and (iii) the amount of the milestone is reasonable in relation to the effort expended and the risk associated with the achievement of the milestone. The milestone payments will be recognized as revenue in full in the period in which the associated milestone is achieved, assuming all other revenue recognition criteria are met. To date, no revenue has been recognized related to the achievement of the milestones.

In the first quarter of 2015, we made a payment of $25.9 million to the Office of the Chief Scientist of the Israeli Ministry of Economy (“OCS”) in connection with repayment obligations resulting from grants previously made by the OCS to OPKO Biologics to support development of hGH-CTP and the outlicense of the technology outside of Israel. We recognized the $25.9 million payment in Grant repayment expense in our Consolidated Statement of Operations during the year ended December 31, 2015.

TESARO

In November 2009, we entered into an asset purchase agreement (the “NK-1 Agreement”) under which we acquired VARUBI™ (rolapitant) and other neurokinin-1 (“NK-1”) assets from Merck. In December 2010, we entered into an exclusive license agreement with TESARO, in which we out-licensed the development, manufacture, commercialization and distribution of our lead NK-1 candidate, VARUBI™ (the “TESARO License”). Under the terms of the license, we received a $6.0 million upfront payment from TESARO and are eligible to receive milestone payments of up to $30.0 million upon achievement of certain regulatory and commercial sale milestones (of which $20.0 million has been received to date) and additional commercial milestone payments of up to $85.0 million if specified levels of annual net sales are achieved. During the years ended December 31, 2016, 2015 and 2014 , $0.0 million , $15.0 million and $5.0 million of revenue, respectively, has been recognized related to the achievement of the milestones under the TESARO License. TESARO is also obligated to pay us tiered royalties on annual net sales achieved in the United States and Europe at percentage rates that range from the low double digits to the low twenties, and outside of the United States and Europe at low double-digit percentage rates. TESARO assumed responsibility for clinical development and commercialization of licensed products at its expense. Under the Agreement, we will continue to receive royalties on a country-by-country and product-by-product basis until the later of the date that all of the patent rights licensed from us and covering VARUBI™ expire, are invalidated or are not enforceable and 12 years from the first commercial sale of the product.

If TESARO elects to develop and commercialize VARUBI™ in Japan through a third-party licensee, TESARO will share equally with us all amounts it receives in connection with such activities, subject to certain exceptions and deductions.

The term of the license will remain in force until the expiration of the royalty term in each country, unless we terminate the license earlier for TESARO's material breach of the license or bankruptcy. TESARO has a right to terminate the license at any time during the term for any reason on three months' written notice.

TESARO's New Drug Application ("NDA") for approval of oral VARUBI™, a neurokinin-1 receptor antagonist in development for the prevention of chemotherapy-induced nausea and vomiting, was approved by the U.S. FDA in September 2015, and in November 2015, TESARO announced the commercial launch of VARUBI™ in the United States. Under the terms of the NK-1 Agreement, upon approval by the FDA of the TESARO's NDA for oral VARUBI™, we were required to pay Merck a $5.0 million milestone payment. In addition, $5.0 million will be due and payable each year thereafter for the next four (4) years on the anniversary date of the NDA approval. We recognized the present value of the milestone payments on FDA approval of $23.0 million as an intangible asset which will be amortized to expense over the expected useful life of the asset, which is approximately 13 years. The present value of the future payments to Merck of $14.0 million at December 31, 2016 is recorded as a liability in our Consolidated Balance Sheet with $4.9 million in Accrued expenses and $9.1 million in Other long-term liabilities.

Pharmsynthez

In April 2013, we entered into a series of concurrent transactions with Pharmsynthez, a Russian pharmaceutical company traded on the Moscow Stock Exchange pursuant to which we acquired an equity method investment in Pharmsynthez (ownership 17%). We also granted rights to certain technologies in the Russian Federation, Ukraine, Belarus, Azerbaijan and Kazakhstan (the "Territories") to Pharmsynthez and agreed to perform certain development activities. We will receive from Pharmsynthez royalties on net sales of products incorporating the technologies in the Territories, as well as a percentage of any sublicense income from third parties for the technologies in the Territories.

In July 2015, we entered into a Note Purchase Agreement with Pharmsynthez pursuant to which we delivered $3.0 million to Pharmsynthez in exchange for a $3.0 million note (the "Pharmsynthez Note Receivable"). The Pharmsynthez Note Receivable will be settled in 2017 and Pharmsynthez may satisfy the note either in cash or shares of its capital stock. We recorded the Pharmsynthez Note Receivable within Other current assets and prepaid expenses in our Consolidated Balance Sheet.

RXi Pharmaceuticals Corporation

In March 2013, we completed the sale to RXi of substantially all of our assets in the field of RNA interference (the "RNAi Assets") (collectively, the "Asset Purchase Agreement"). Pursuant to the Asset Purchase Agreement, RXi will be required to pay us up to $50.0 million in milestone payments upon the successful development and commercialization of each drug developed by RXi, certain of its affiliates or any of its or their licensees or sublicensees utilizing patents included within the RNAi Assets (each, a "Qualified Drug"). In addition, RXi will also be required to pay us royalties equal to: (a) a mid single-digit percentage of "Net Sales" (as defined in the Asset Purchase Agreement) with respect to each Qualified Drug sold for an ophthalmologic use during the applicable "Royalty Period" (as defined in the Asset Purchase Agreement); and (b) a low single-digit percentage of net sales with respect to each Qualified Drug sold for a non-ophthalmologic use during the applicable Royalty Period.

Other

We have completed strategic deals with numerous institutions and commercial partners. In connection with these agreements, upon the achievement of certain milestones we are obligated to make certain payments and have royalty obligations upon sales of products developed under the license agreements. At this time, we are unable to estimate the timing and amounts of payments as the obligations are based on future development of the licensed products.

Note 15 Leases

Operating leases

We conduct certain of our operations under operating lease agreements. Rent expense under operating leases was approximately $18.8 million , $7.8 million , and $2.6 million for the years ended December 31, 2016 , 2015 , and 2014 , respectively.

As of December 31, 2016 , the aggregate future minimum lease payments under all non-cancelable operating leases with initial or remaining lease terms in excess of one year are as follows:

Year Ending	(In thousands)
2017	$ 16,751
2018	12,396
2019	9,967
2020	4,761
2021	2,964
Thereafter	6,173
Total minimum operating lease commitments	$ 53,012

Capital leases

We acquired various assets under capital leases in connection with our acquisition of Bio-Reference in 2015. Capital leases are included within Property, plant and equipment, net in our Consolidated Balance Sheet with imputed interest rates of approximately 2% as follows:

Capital leases	Year ended December 31, 2016
Automobiles	$ 10,342
Less: Accumulated Depreciation	(3,291)
Net capital leases in Property, plant and equipment	$ 7,051

As of December 31, 2016 , the aggregate future minimum lease payments under all non-cancelable capital leases with initial or remaining lease terms in excess of one year are as follows:

Year Ending	(In thousands)
2017	$ 3,143
2018	2,720
2019	2,184
2020	1,426
2021	488
Thereafter	570
Total minimum capital lease commitments	10,531
Less: Amounts representing interest	290
Net capital liability	$ 10,241

Current	$ 3,025
Long-term	$ 7,216

Note 16 Segments

We manage our operations in two reportable segments, pharmaceutical and diagnostics. The pharmaceutical segment consists of our pharmaceutical operations we acquired in Chile, Mexico, Ireland, Israel and Spain and our pharmaceutical research and development. The diagnostics segment primarily consists of our clinical laboratory operations we acquired through the acquisitions of Bio-Reference and OPKO Lab and our point-of-care operations. There are no significant inter-segment sales. We evaluate the performance of each segment based on operating profit or loss. There is no inter-segment allocation of interest expense and income taxes.

Information regarding our operations and assets for our operating segments and the unallocated corporate operations as well as geographic information are as follows:

(In thousands)	For the years ended December 31, 2016	2015	2014
Revenue from services:			
Pharmaceutical	$ —	$ —	$ —
Diagnostics	1,012,129	329,599	8,426
Corporate	—	140	240
	$ 1,012,129	$ 329,739	$ 8,666
Revenue from products:			
Pharmaceutical	$ 83,467	$ 80,146	$ 76,983
Diagnostics	—	—	—
Corporate	—	—	—
	$ 83,467	$ 80,146	$ 76,983
Revenue from transfer of intellectual property:			
Pharmaceutical	$ 126,065	$ 81,853	$ 5,285
Diagnostics	—	—	191
Corporate	—	—	—
	$ 126,065	$ 81,853	$ 5,476
Operating (loss) income:			
Pharmaceutical	$ (9,841)	$ (40,395)	$ (94,401)
Diagnostics	(3,393)	(10,294)	(21,647)
Corporate	(60,041)	(46,512)	(27,725)
Less: Operating loss attributable to noncontrolling interests	—	(1,280)	(2,042)
	$ (73,275)	$ (98,481)	$ (145,815)
Depreciation and amortization:			
Pharmaceutical	$ 18,254	$ 10,245	$ 7,936
Diagnostics	78,233	31,918	6,894
Corporate	89	85	97
	$ 96,576	$ 42,248	$ 14,927
Loss from investment in investees:			
Pharmaceutical	$ (7,665)	$ (7,105)	$ (3,587)
Diagnostics	13	—	—
Corporate	—	—	—
	$ (7,652)	$ (7,105)	$ (3,587)
Revenues:			
United States	$ 1,014,389	$ 344,464	$ 14,142
Ireland	137,785	78,989	—
Chile	35,364	29,885	29,154
Spain	15,812	16,622	21,323
Israel	15,317	18,107	20,638
Mexico	2,988	3,671	5,807
Other	6	—	61
	$ 1,221,661	$ 491,738	$ 91,125

(In thousands)	December 31, 2016	December 31, 2015
Assets:		
Pharmaceutical	$ 1,294,916	$ 1,258,011
Diagnostics	1,408,522	1,479,841
Corporate	63,181	61,336
	$ 2,766,619	$ 2,799,188
Goodwill:		
Pharmaceutical	$ 251,817	$ 251,225
Diagnostics	452,786	492,123
Corporate	—	—
	$ 704,603	$ 743,348

During the year ended December 31, 2016 , no customer represented more than 10% of our total consolidated revenue. During the year ended December 31, 2015 , revenue recognized under the Pfizer Transaction represented 13% of our total consolidated revenue. During the year ended December 31, 2014, one customer of our pharmaceutical segment represented 13% of our total consolidated revenue. As of both December 31, 2016 and December 31, 2015, one customer represented more than 10% of our accounts receivable balance.

The following table reconciles our Property, plant and equipment, net between U.S. and foreign jurisdictions:

(In thousands)	December 31, 2016	December 31, 2015
PP&E:		
U.S.	$ 100,716	$ 113,307
Foreign	22,115	18,491
Total	$ 122,831	$ 131,798

Note 17 Fair Value Measurements

We record fair values at an exit price, representing the amount that would be received to sell an asset or paid to transfer a liability in an orderly transaction between market participants. As such, fair value is a market-based measurement determined based on assumptions that market participants would use in pricing an asset or liability. We utilize a three-tier fair value hierarchy, which prioritizes the inputs used in measuring fair value. These tiers include: Level 1, defined as observable inputs such as quoted prices in active markets; Level 2, defined as inputs other than quoted prices in active markets that are either directly or indirectly observable; and Level 3, defined as unobservable inputs in which little or no market data exists, therefore requiring an entity to develop its own assumptions.

A summary of our investments classified as available for sale and carried at fair value, is as follows:

	As of December 31, 2016			
(In thousands)	Amortized Cost	Gross unrealized gains in Accumulated OCI	Gross unrealized losses in Accumulated OCI	Fair value
Common stock investments, available for sale	$ 3,409	$ 1,313	$ (194)	$ 4,528
Total assets	$ 3,409	$ 1,313	$ (194)	$ 4,528

(In thousands)	As of December 31, 2015			
	Amortized Cost	Gross unrealized gains in Accumulated OCI	Gross unrealized losses in Accumulated OCI	Fair value
Common stock investments, available for sale	$ 2,978	$ 904	$ (267)	$ 3,615
Total assets	$ 2,978	$ 904	$ (267)	$ 3,615

Any future fluctuation in fair value related to our available for sale investments that is judged to be temporary, and any recoveries of previous write-downs, will be recorded in Accumulated other comprehensive income (loss). If we determine that any future valuation adjustment was other-than-temporary, we will record a loss during the period such determination is made.

As of December 31, 2016 , we have money market funds that qualify as cash equivalents, forward foreign currency exchange contracts for inventory purchases (Refer to Note 18) and contingent consideration related to the acquisitions of CURNA, OPKO Diagnostics, OPKO Health Europe, and OPKO Renal that are required to be measured at fair value on a recurring basis. In addition, in connection with our investment and our consulting agreements with Neovasc and BioCardia, we record the related Neovasc and BioCardia options at fair value as well as the warrants from COCP, ARNO, Sevion, MabVax, InCellDx, Inc., Xenetic and RXi.

Our financial assets and liabilities measured at fair value on a recurring basis are as follows:

(In thousands)	Fair value measurements as of December 31, 2016			
	Quoted prices in active markets for identical assets (Level 1)	Significant other observable inputs (Level 2)	Significant unobservable inputs (Level 3)	Total
Assets:				
Money market funds	$ 5,314	$ —	$ —	$ 5,314
Common stock investments, available for sale	4,528	—	—	4,528
Common stock options/warrants	—	4,017	—	4,017
Forward contracts	—	39	—	39
Total assets	$ 9,842	$ 4,056	$ —	$ 13,898
Liabilities:				
Embedded conversion option	$ —	$ —	$ 16,736	$ 16,736
Contingent consideration:	$ —	$ —	$ 45,076	45,076
Total liabilities	$ —	$ —	$ 61,812	$ 61,812

(In thousands)	Fair value measurements as of December 31, 2015			
	Quoted prices in active markets for identical assets (Level 1)	Significant other observable inputs (Level 2)	Significant unobservable inputs (Level 3)	Total
Assets:				
Money market funds	$ 84,421	$ —	$ —	$ 84,421
Common stock investments, available for sale	3,615	—	—	3,615
Common stock options/warrants	—	5,338	—	5,338
Forward contracts	—	9	—	9
Total assets	$ 88,036	$ 5,347	$ —	$ 93,383
Liabilities:				
Embedded conversion option	$ —	$ —	$ 23,737	$ 23,737
Contingent consideration:	—	—	54,422	54,422
Total liabilities	$ —	$ —	$ 78,159	$ 78,159

The carrying amount and estimated fair value of our 2033 Senior Notes without the embedded conversion option, as well as the applicable fair value hierarchy tiers, are contained in the table below. The fair value of the 2033 Senior Notes is determined using a binomial lattice approach in order to estimate the fair value of the embedded derivative in the 2033 Senior Notes. Refer to Note 6.

	December 31, 2016				
(In thousands)	Carrying Value	Total Fair Value	Level 1	Level 2	Level 3
2033 Senior Notes	$ 27,238	$ 28,468	$ —	$ —	$ 28,468

	December 31, 2015				
(In thousands)	Carrying Value	Total Fair Value	Level 1	Level 2	Level 3
2033 Senior Notes	$ 25,676	$ 24,647	$ —	$ —	$ 24,647

There have been no transfers between Level 1 and Level 2 and no transfers to or from Level 3 of the fair value hierarchy.

As of December 31, 2016 and 2015 , the carrying value of our other assets and liabilities approximates their fair value due to their short-term nature or variable rates of interest.

The following tables reconcile the beginning and ending balances of our Level 3 assets and liabilities as of December 31, 2016 and 2015 :

	December 31, 2016	
(In thousands)	Contingent consideration	Embedded conversion option
Balance at December 31, 2015	$ 54,422	$ 23,737
Total losses (gains) for the period:		
Included in results of operations	16,954	(7,001)
Foreign currency impact	(1)	—
Payments	(26,299)	—
Conversion	—	—
Balance at December 31, 2016	$ 45,076	$ 16,736

	December 31, 2015	
(In thousands)	Contingent consideration	Embedded conversion option
Balance at December 31, 2014	$ 71,567	$ 65,947
Total losses (gains) for the period:		
Included in results of operations	5,050	36,587
Foreign currency impact	(269)	—
Payments	(21,926)	—
Conversion	—	(78,797)
Balance at December 31, 2015	$ 54,422	$ 23,737

The estimated fair values of our financial instruments have been determined by using available market information and what we believe to be appropriate valuation methodologies. We use the following methods and assumptions in estimating fair value:

Contingent consideration – We estimate the fair value of the contingent consideration utilizing a discounted cash flow model for the expected payments based on estimated timing and expected revenues. We use several discount rates depending on each type of contingent consideration related to OPKO Diagnostics, CURNA, OPKO Health Europe and OPKO Renal transactions. If estimated future sales were to decrease by 10% , the contingent consideration related to OPKO Renal, which represents the majority of our contingent consideration liability, would decrease by $2.7 million . As of December 31, 2016 , of

the $45.1 million of contingent consideration, $0.3 million is recorded in Accrued expenses and $44.8 million is recorded in Other long-term liabilities. As of December 31, 2015 , of the $54.4 million of contingent consideration, $22.2 million is recorded in Accrued expenses and $32.3 million is recorded in Other long-term liabilities.

Embedded conversion option – We estimate the fair value of the embedded conversion option related to the 2033 Senior Notes using a binomial lattice model. Refer to Note 6 for detail description of the binomial lattice model and the fair value assumptions used.

Note 18 Derivative Contracts

The following table summarizes the fair values and the presentation of our derivative financial instruments in the Consolidated Balance Sheets:

(In thousands)	Balance Sheet Component	December 31, 2016	December 31, 2015
Derivative financial instruments:			
Common stock options/warrants	Investments, net	$ 4,017	$ 5,338
Embedded conversion option	2033 Senior Notes, net of discount and estimated fair value of embedded derivatives	$ 16,736	$ 23,737
Forward contracts	Unrealized gains on forward contracts are recorded in Other current assets and prepaid expenses. Unrealized (losses) on forward contracts are recorded in Accrued expenses.	$ 39	$ 9

We enter into foreign currency forward exchange contracts to cover the risk of exposure to exchange rate differences arising from inventory purchases on letters of credit. Under these forward contracts, for any rate above or below the fixed rate, we receive or pay the difference between the spot rate and the fixed rate for the given amount at the settlement date.

To qualify the derivative instrument as a hedge, we are required to meet strict hedge effectiveness and contemporaneous documentation requirements at the initiation of the hedge and assess the hedge effectiveness on an ongoing basis over the life of the hedge. At December 31, 2016 and 2015 , our derivative financial instruments do not meet the documentation requirements to be designated as hedges. Accordingly, we recognize the changes in Fair value of derivative instruments, net in our Consolidated Statement of Operations. The following table summarizes the losses and gains recorded for the years ended December 31, 2016 , 2015 and 2014 :

	For the years ended December 31,		
(In thousands)	2016	2015	2014
Derivative gain (loss):			
Common stock options/warrants	$ (4,262)	$ (2,854)	$ 1,193
2033 Senior Notes	7,001	(36,588)	(12,213)
Forward contracts	$ 39	$ 359	$ 388
Total	$ 2,778	$ (39,083)	$ (10,632)

Note 19 Selected Quarterly Financial Data (Unaudited)

(In thousands, except per share data)	For the 2016 Quarters Ended			
	March 31	June 30	September 30	December 31
Total revenues	$ 291,037	$ 357,100	$ 298,035	$ 275,489
Total costs and expenses	318,555	328,834	321,658	325,889
Net income (loss)	(11,978)	15,533	(14,977)	(13,661)
Net income (loss) attributable to common shareholders	(11,978)	15,533	(14,977)	(13,661)
Earnings (loss) per share, basic	$ (0.02)	$ 0.03	$ (0.03)	$ (0.02)
Earnings (loss) per share, diluted	$ (0.02)	$ 0.02	$ (0.03)	$ (0.04)

(In thousands, except per share data)	For the 2015 Quarters Ended			
	March 31	June 30	September 30	December 31
Total revenues	$ 30,084	$ 42,429	$ 143,034	$ 276,191
Total costs and expenses	86,998	67,838	151,257	284,126
Net income (loss)	(118,037)	(43,241)	128,247	1,603
Net income (loss) attributable to common shareholders	(117,112)	(42,766)	128,247	1,603
Earnings (loss) per share, basic	$ (0.26)	$ (0.09)	$ 0.26	$ —
Earnings (loss) per share, diluted	$ (0.26)	$ (0.09)	$ 0.18	$ —

Note 20 Subsequent Events

On January 3, 2017, we announced that our 2033 Senior Notes continue to be convertible by holders of such 2033 Senior Notes through March 31, 2017. We have elected to satisfy the conversion obligation in shares of our Common Stock. This conversion right has been extended because the closing price per share of our Common Stock has exceeded $9.19 , or 130% of the applicable conversion price of $7.07 , for at least 20 of 30 consecutive trading days during the quarter ended on December 31, 2016 . We previously announced that this conversion right had been triggered each quarter during the quarters ended March 31, 2015 through September 30, 2016. The 2033 Senior Notes will continue to be convertible until March 31, 2017, and may be convertible thereafter, if one or more of the conversion conditions specified in the Indenture is satisfied during future measurement periods. Pursuant to the Indenture, a holder who elects to convert the 2033 Senior Notes will receive 141.4827 shares of our Common Stock plus such number of additional shares as is applicable on the conversion date per $1,000 principal amount of 2033 Senior Notes based on the early conversion provisions in the Indenture.

We have reviewed all subsequent events and transactions that occurred after the date of our December 31, 2016 Consolidated Balance Sheet date, through the time of filing this Annual Report on Form 10-K.

ITEM 9. CHANGES IN AND DISAGREEMENTS WITH ACCOUNTANTS ON ACCOUNTING AND FINANCIAL DISCLOSURE

None.

ITEM 9A. CONTROLS AND PROCEDURES

Disclosure Controls and Procedures

Our management, with the participation of our Chief Executive Officer and Chief Financial Officer, have evaluated the effectiveness of the Company's disclosure controls and procedures (as defined in Rules 13a-15(e) and 15d-15(e) under the Securities Exchange Act of 1934, as amended (the "Exchange Act")) as of December 31, 2016 . Our disclosure controls and procedures are designed to provide reasonable assurance that information required to be disclosed by us in the reports that we file or submit under the Exchange Act is recorded, processed, summarized and reported, within the time periods specified in the rules and forms of the Securities and Exchange Commission. Disclosure controls and procedures include, without limitation, controls and procedures designed to ensure that information required to be disclosed by a company in the reports that it files or submits under the Exchange Act is accumulated and communicated to the company's management, including its principal executive and principal financial officers, as appropriate to allow timely decisions regarding required disclosure. Based on this evaluation, management concluded that our disclosure controls and procedures were effective as of December 31, 2016 .

Management's Annual Report on Internal Control Over Financial Reporting

Our management is responsible for establishing and maintaining adequate internal control over financial reporting, as such term is defined in Rules 13a-15(e) and 15d-15(e) under the Securities Exchange Act of 1934, as amended. Our internal control over financial reporting is a process designed to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles. All internal control systems, no matter how well designed, have inherent limitations. Therefore, even those systems determined effective could provide only reasonable assurance with respect to financial statement preparation and presentation.

Our management conducted an evaluation of the effectiveness of our internal control over financial reporting as of December 31, 2016 , based on the framework in the Internal Control - Integrated Framework (2013) issued by the Committee of Sponsoring Organizations of the Treadway Commission (the "2013 Internal Control-Integrated Framework"). Based on our evaluation under the 2013 Internal Control-Integrated Framework, our management concluded that our internal control over financial reporting was effective as of December 31, 2016 . As permitted, our management's assessment of and conclusion on the effectiveness of our internal control over financial reporting did not include the internal controls of Transition Therapeutics, Inc. ("Transition Therapeutics"), because Transition Therapeutics was acquired by us in a business combination in August 2016. Transition Therapeutics' assets excluded from the annual assessment process were 2% of consolidated total assets as of December 31, 2016 and 0% of consolidated revenues for the year then ended as a result of the closing of the acquisition in August 2016.

The effectiveness of the Company's internal control over financial reporting as of December 31, 2016 has been audited by Ernst & Young LLP, our independent registered public accounting firm, who also audited our Consolidated Financial Statements included in this Annual Report on Form 10-K, as stated in their report which appears with our accompanying Consolidated Financial Statements.

Changes to the Company's Internal Control Over Financial Reporting

In connection with the acquisitions of EirGen in May 2015, Bio-Reference in August 2015 and Transition Therapeutics in August 2016, we began implementing standards and procedures at EirGen, Bio-Reference and Transition Therapeutics, including establishing controls over accounting systems and establishing controls over the preparation of financial statements in accordance with generally accepted accounting principles to ensure that we have in place appropriate internal control over financial reporting at EirGen, Bio-Reference and Transition Therapeutics. We are continuing to integrate the acquired operations of EirGen, Bio-Reference and Transition Therapeutics into our overall internal control over financial reporting process.

We implemented a new billing system for our laboratory business in October 2016 and we are in the process of implementing a new comprehensive enterprise resource planning ("ERP") system on a company-wide basis. We use both the billing system and the ERP system for financial reporting. The implementation of these systems involves changes to our financial systems and other systems and accordingly, necessitated changes to our internal controls over financial reporting.

These changes to the Company's internal control over financial reporting that occurred during the most recent quarter ended December 31, 2016 have materially affected, or are reasonably likely to materially affect, the Company's internal control over financial reporting.

ITEM 9B. OTHER INFORMATION

None.

PART III

The information required in Items 10 (Directors, Executive Officers and Corporate Governance), Item 11 (Executive Compensation), Item 12 (Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters), Item 13 (Certain Relationships and Related Transactions, and Director Independence), and Item 14 (Principal Accounting Fees and Services) is incorporated by reference to the Company's definitive proxy statement for the 2017 Annual Meeting of Stockholders to be filed with the Securities and Exchange Commission within 120 days of December 31, 2016 .

PART IV.

Item 15. EXHIBITS, FINANCIAL STATEMENT SCHEDULES.

(a) (1) Financial Statements: See Part II, Item 8 of this report.

Schedule I - Condensed Financial Information of Registrant. Additionally, the financial statement schedule entitled "Schedule II – Valuation and Qualifying Accounts" has been omitted since the information required is included in the consolidated financial statements and notes thereto. Other schedules are omitted because they are not required.

(2) Exhibits: See below.

Exhibit Number	Description
1.1 (12)	Underwriting Agreement, dated March 9, 2011, by and among OPKO Health, Inc., Jefferies & Company, Inc. and J.P. Morgan Securities LLC, as representatives for the underwriters named therein.
2.1 (1)	Merger Agreement and Plan of Reorganization, dated as of March 27, 2007, by and among Acuity Pharmaceuticals, Inc., Froptix Corporation, eXegenics, Inc., e-Acquisition Company I-A, LLC, and e-Acquisition Company II-B, LLC.
2.2 (3)+	Securities Purchase Agreement, dated May 2, 2008, by and among Vidus Ocular, Inc., OPKO Instrumentation, LLC, OPKO Health, Inc., and the individual sellers and noteholders named therein.
2.3 (9)	Purchase Agreement, dated February 17, 2010, by and among Ignacio Levy García and José de Jesús Levy García, Inmobiliaria Chapalita, S.A. de C.V., Pharmacos Exakta, S.A. de C.V., OPKO Health, Inc., OPKO Health Mexicana S. de R.L. de C.V., and OPKO Manufacturing Facilities S. de R.L. de C.V.
2.4 (14)+	Agreement and Plan of Merger, dated January 28, 2011, by and among CURNA Inc., KUR, LLC, OPKO Pharmaceuticals, LLC, OPKO CURNA, LLC, and certain individuals named therein.
2.5 (15)	Agreement and Plan of Merger, dated October 13, 2011, by and among OPKO Health, Inc., Claros Merger Subsidiary, LLC, Claros Diagnostics, Inc., and Ellen Baron, Marc Goldberg and Michael Magliochetti on behalf of the Shareholder Representative Committee.
2.6 (17)+	Stock Purchase Agreement, dated December 20, 2011, by and among FineTech Pharmaceutical Ltd., Arie Gutman, OPKO Holdings Israel Ltd., and OPKO Health, Inc.
2.7 (18)	Purchase Agreement, dated January 20, 2012, by and among OPKO Health, Inc., OPKO Chile S.A., Samuel Alexandre Arama, Inversiones SVJV Limitada, Bruno Sergiani, Inversiones BS Limitada, Pierre-Yves LeGoff, and Inversiones PYTT Limitada.
2.8 (19)+	Stock Purchase Agreement, dated August 2, 2012, by and among Farmadiet Group Holding, S.L., the Sellers party thereto, OPKO Health, Inc., and Shebeli XXI, S.L.U.
2.9 (21)+	Agreement and Plan of Merger, dated October 18, 2012, by and among Prost-Data, Inc. d/b/a OurLab, Our Labs, Endo Labs and Gold Lab, Jonathan Oppenheimer, M.D., OPKO Health, Inc., OPKO Laboratories Inc., and OPKO Labs, LLC.
2.10 (22)+	Share Purchase Agreement, dated January 8, 2013, by among Cytochroma Inc., Cytochroma Holdings ULC, Cytochroma Canada Inc., Cytochroma Development Inc., Proventiv Therapeutics, LLC, Cytochroma Cayman Islands, Ltd., OPKO Health, Inc., and OPKO IP Holdings, Inc.
2.11 (23)	Asset Purchase Agreement, dated March 1, 2013, by and between RXi Pharmaceuticals Corporation and OPKO Health, Inc.

2.12 [24]	Agreement and Plan of Merger, dated April 23, 2013, by and among OPKO Health, Inc., POM Acquisition Inc., and PROLOR Biotech, Inc.
2.13 [27]+	Agreement for the Sale and Purchase of Shares in EirGen Pharma Limited, dated May 5, 2015 by and among OPKO Ireland Limited, OPKO Health, Inc. and the Sellers named therein.
2.14 [27]+	Form of Additional Agreement for the Sale and Purchase of Shares in EirGen Pharma Limited, dated May 5, 2015 by and among OPKO Ireland Limited and the Sellers named therein.
2.15 [28]+	Agreement and Plan of Merger by and among the Company, Bamboo Acquisition, Inc. and Bio-Reference Laboratories, Inc. dated as of June 3, 2015.
2.16 [35]	Arrangement Agreement by and among the Company, OPKO Global Holdings, Inc. and Transition Therapeutics Inc. dated as of June 29, 2016.
3.1 [26]	Amended and Restated Certificate of Incorporation, as amended.
3.2 [2]	Amended and Restated Bylaws.
3.3 [7]	Certificate of Designation of Series D Preferred Stock.
4.1 [1]	Form of Common Stock Warrant.
4.2 [7]	Form of Common Stock Warrant.
4.3 [25]	Indenture, dated January 30, 2013, between OPKO Health, Inc. and Wells Fargo Bank, National Association.
10.1 [1]	Form of Lockup Agreement.
10.2 [2]	Stock Purchase Agreement, dated December 4, 2007, by and between OPKO Health, Inc. and the members of The Frost Group, LLC.
10.3 [3]	Form of Director Indemnification Agreement.
10.4 [3]	Form of Officer Indemnification Agreement.
10.5 [4]	Stock Purchase Agreement, dated August 8, 2008 by and between OPKO Health, Inc. and the Purchasers named therein.
10.6 [5]	Stock Purchase Agreement, dated February 23, 2009 by and between OPKO Health, Inc. and Frost Gamma Investments Trust.
10.7 [6]	Form of Stock Purchase Agreement for transactions between OPKO Health, Inc. and Nora Real Estate SA., Vector Group Ltd., Oracle Partners LP, Oracle Institutional Partners, LP., Chung Chia Company Limited, Gold Sino Assets Limited, and Grandtime Associates Limited.
10.8 [6]	Stock Purchase Agreement, dated June 10, 2009, by and among OPKO Health, Inc. and Sorrento Therapeutics, Inc.
10.9 [7]	Form of Securities Purchase Agreement for Series D Preferred Stock.
10.10 [8]*	Form of Restricted Share Award Agreement for Directors.

10.11 [8]	Cocrystal Discovery, Inc. Agreements.
10.12 [11]	Stock Purchase Agreement, dated October 1, 2009, by and among the Laboratoria Volta S.A., Farmacias Ahumada S.A., FASA Chile S.A., OPKO Chile Limitada and Inversones OPKO Limitada, subsidiaries of OPKO Health, Inc.
10.13 [10]+	Asset Purchase Agreement, dated October 12, 2009, by and between OPKO Health, Inc. and Schering Corporation.
10.14 [10]	Letter Agreement, dated June 29, 2010, by and between OPKO Health, Inc. and Schering Corporation.
10.15 [16]+	Exclusive License Agreement by and between TESARO, Inc. and OPKO Health, Inc. dated December 10, 2010.
10.16 [13]	Third Amended and Restated Subordinated Note and Security Agreement, dated February 22, 2011, between OPKO Health, Inc. and The Frost Group, LLC.
10.17 [15]+	Asset Purchase Agreement dated September 21, 2011, by and among Optos plc, Optos Inc., OPKO Health, Inc., OPKO Instrumentation, LLC, Ophthalmic Technologies, Inc., and OTI (UK) Limited.
10.18 [20]	Form of Note Purchase Agreement, dated as of January 25, 2013, by and among OPKO Health, Inc. and each purchaser a party thereto.
10.19 [29]+	Development and Commercialization License Agreement by and between OPKO Ireland, Ltd., a subsidiary of OPKO Health, Inc., and Pfizer, Inc. dated December 13, 2014.
10.20 [34]	Credit Agreement by and between Bio-Reference Laboratories, Inc. and certain of its subsidiaries and JPMorgan Chase Bank, N.A. dated November 5, 2015.
10.21 [35]	OPKO Health, Inc. 2016 Equity Incentive Plan.
10.22 [36]	Development and License Agreement between OPKO Health, Inc. and Vifor Fresenius Medical Care Renal Pharma Ltd., dated May 8, 2016.
21	Subsidiaries of the Company.
23.1	Consent of Ernst & Young LLP.
23.2	Consent of MSPC Certified Public Accountants and Advisors, P.C. relating to Bio-Reference Laboratories, Inc.'s financial statements.
31.1	Certification by Phillip Frost, Chief Executive Officer, pursuant to Rule 13a-14(a) and 15d-14(a) of the Securities and Exchange Act of 1934 as adopted pursuant to Section 302 of the Sarbanes-Oxley Act of 2002 for the year ended December 31, 2016.
31.2	Certification by Adam Logal, Chief Financial Officer, pursuant to Rule 13a-14(a) and 15d-14(a) of the Securities and Exchange Act of 1934 as adopted pursuant to Section 302 of the Sarbanes-Oxley Act of 2002 for the year ended December 31, 2016.
32.1	Certification by Phillip Frost, Chief Executive Officer pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002 for the year ended December 31, 2016.
32.2	Certification by Adam Logal, Chief Financial Officer, pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002 for the year ended December 31, 2016.

99.1 (31)	The audited consolidated balance sheets of Bio-Reference Laboratories, Inc. and its subsidiaries as of October 31, 2014 and 2013, and the related consolidated statements of operations, shareholders' equity, and cash flows for each of the years in the three-year period ended October 31, 2014, and the notes and the independent auditor's reports thereto.
99.2 (32)	The unaudited consolidated balance sheet of Bio-Reference Laboratories, Inc. and its subsidiaries as of April 30, 2015, the related unaudited consolidated statements of operations, and statements of cash flows for the three and six months ended April 30, 2015, and the notes thereto.
99.3 (33)	The unaudited pro forma condensed combined financial statements of the Company and Bio-Reference Laboratories, Inc.
101.INS	XBRL Instance Document
101.SCH	XBRL Taxonomy Extension Schema Document
101.CAL	XBRL Taxonomy Extension Calculation Linkbase Document
101.DEF	XBRL Taxonomy Extension Definition Linkbase Document
101.LAB	XBRL Taxonomy Extension Label Linkbase Document
101.PRE	XBRL Taxonomy Extension Presentation Linkbase Document

* Denotes management contract or compensatory plan or arrangement.

\+ Certain confidential material contained in the document has been omitted and filed separately with the Securities and Exchange Commission.

(1) Filed with the Company's Current Report on Form 8-K filed with the Securities and Exchange Commission on April 2, 2007, and incorporated herein by reference.

(2) Filed with the Company's Annual Report on Form 10-K filed with the Securities and Exchange Commission on March 31, 2008 and incorporated herein by reference.

(3) Filed with the Company's Quarterly Report on Form 10-Q filed with the Securities and Exchange Commission on August 8, 2008 for the Company's three-month period ended June 30, 2008, and incorporated herein by reference.

(4) Filed with the Company's Quarterly Report on Form 10-Q filed with the Securities and Exchange Commission on November 12, 2008 for the Company's three-month period ended September 30, 2008, and incorporated herein by reference.

(5) Filed with the Company's Quarterly Report on Form 10-Q filed with the Securities and Exchange Commission on May 8, 2009 for the Company's three-month period ended March 31, 2009, and incorporated herein by reference.

(6) Filed with the Company's Quarterly Report on Form 10-Q filed with the Securities and Exchange Commission on August 7, 2009 for the Company's three-month period ended June 30, 2009, and incorporated herein by reference.

(7) Filed with the Company's Current Report on Form 8-K filed with the Securities and Exchange Commission on September 24, 2009, and incorporated herein by reference.

(8) Filed with the Company's Quarterly Report on Form 10-Q filed with the Securities and Exchange Commission on November 9, 2009 for the Company's three-month period ended September 30, 2009, and incorporated herein by reference.

(9) Filed with the Company's Quarterly Report on Form 10-Q filed with the Securities and Exchange Commission on May 10, 2010 for the Company's three-month period ended March 31, 2010, and incorporated herein by reference.

(10) Filed with the Company's Amendment to Annual Report on Form 10-K filed with the Securities and Exchange Commission on February 3, 2011.

(11) Filed with the Company's Annual Report on Form 10-K filed with the Securities and Exchange Commission on March 17, 2010.

(12) Filed with the Company's Current Report on Form 8-K filed with the Securities and Exchange Commission on March 10, 2011, and incorporated herein by reference.

(13) Filed with the Company's Quarterly Report on Form 10-Q filed with the Securities and Exchange Commission on May 10, 2011 for the Company's three-month period ended March 31, 2011, and incorporated herein by reference.

(14) Filed with the Company's Quarterly Report on Form 10-Q/A filed with the Securities and Exchange Commission on July 5, 2011, and incorporated herein by reference.

(15) Filed with the Company's Quarterly Report on Form 10-Q filed with the Securities and Exchange Commission on November 9, 2011 for the Company's three-month period ended September 30, 2011, and incorporated herein by reference.

(16) Filed with the Company's Annual Report on Form 10-K/A filed with the Securities and Exchange Commission on July 28, 2011.

(17) Filed with the Company's Annual Report on Form 10-K filed with the Securities and Exchange Commission on March 15, 2012.

(18) Filed with the Company's Quarterly Report on Form 10-Q filed with the Securities and Exchange Commission on May 10, 2012 for the Company's three-month period ended March 31, 2012, and incorporated herein by reference.

(19) Filed with the Company's Quarterly Report on Form 10-Q filed with the Securities and Exchange Commission on November 9, 2012 for the Company's three-month period ended September 30, 2012, and incorporated herein by reference.

(20) Filed with the Company's Current Report on Form 8-K filed with the Securities and Exchange Commission on January 29, 2013, and incorporated herein by reference.

(21) Filed with the Company's Annual Report on Form 10-K filed with the Securities and Exchange Commission on March 18, 2013.

(22) Filed with the Company's Quarterly Report on Form 10-Q filed with the Securities and Exchange Commission on May 10, 2013 for the Company's three-month period ended March 31, 2013, and incorporated herein by reference.

(23) Filed with the Company's Schedule 13D filed with the Securities and Exchange Commission on March 22, 2013, and incorporated herein by reference.

(24) Filed as Annex A to the Company's Preliminary Joint Proxy Statement/Prospectus, Form S-4, with the Securities Exchange Commission on June 27, 2013, as amended, and incorporated herein by reference.

(25) Filed with the Company's Current Report on Form 8-K filed with the Securities and Exchange Commission on February 5, 2013, and incorporated herein by reference.

(26) Filed with the Company's Quarterly Report on Form 10-Q filed with the Securities and Exchange Commission on November 12, 2013 for the Company's three month period ended September 30, 2013, and incorporated herein by reference.

(27) Filed with the Company's Quarterly Report on Form 10-Q filed with the Securities and Exchange Commission on August 5, 2015 for the Company's three month period ended June 30, 2015, and incorporated herein by reference.

(28) Filed with the Company's Current Report on Form 8-K filed with the Securities and Exchange Commission on June 4, 2015, and incorporated herein by reference.

(29) Filed with the Company's Annual Report on Form 10-K filed with the Securities and Exchange Commission on February 27, 2015, and incorporated herein by reference.

(30) Filed under Part II, Item 8, of the Bio-Reference Laboratories, Inc. Form 10-K filed with the Securities and Exchange Commission on January 13, 2015 (File No. 0-15266), and incorporated herein by reference.

(31) Filed under Part I, Item 1, of the Bio-Reference Laboratories, Inc. Form 10-Q filed with the Securities and Exchange Commission on June 9, 2015 (File No. 0-15266), and incorporated herein by reference.

(32) Filed under the heading "Unaudited Pro Forma Condensed Combined Financial Statements" beginning on page 27 of the Company's Registration Statement on Form S-4/A filed with the Securities and Exchange Commission on July 15, 2015 (File No. 333-205480), and incorporated herein by reference.

(33) Filed with the Company's Current Report on Form 8-K filed with the Securities and Exchange Commission on June 30, 2016 and incorporated herein by reference.

(34) Filed with the Company's Annual Report on Form 10-K filed with the Securities and Exchange Commission on February 29, 2016, and incorporated herein by reference.

(35) Filed with the Company's Definitive Proxy Statement on Schedule 14A filed with the Securities and Exchange Commission on March 25, 2016, and incorporated herein by reference.

(36) Filed with the Company's Quarterly Report on Form 10-Q filed with the Securities and Exchange Commission on August 8, 2016 for the Company's three month period ended June 30, 2016, and incorporated herein by reference.

Schedule I - Condensed Financial Information of Registrant

OPKO Health, Inc.
PARENT COMPANY CONDENSED BALANCE SHEETS
(In thousands, except share and per share data)

	December 31,	
	2016	2015
ASSETS		
Current assets:		
Cash and cash equivalents	$ 15,744	$ 97,647
Other current assets and prepaid expenses	12,446	4,306
Total current assets	28,190	101,953
Property, plant and equipment, net	503	225
Investments	2,114,473	1,932,731
Other assets	176	—
Total assets	$ 2,143,342	$ 2,034,909
LIABILITIES AND EQUITY		
Current liabilities:		
Accounts payable	$ 1,070	$ 1,266
Accrued expenses	5,769	4,341
Current portion of notes payable	522	522
Total current liabilities	7,361	6,129
2033 Senior Notes and estimated fair value of embedded derivatives, net of discount	43,701	48,986
Deferred tax liabilities, net	472	—
Total long-term liabilities	44,173	48,986
Total liabilities	51,534	55,115
Equity:		
Common Stock - $0.01 par value, 750,000,000 shares authorized; 558,576,051 and 546,188,516 shares issued at December 31, 2016 and 2015, respectively	5,586	5,462
Treasury Stock, at cost - 586,760 and 1,120,367 shares at December 31, 2016 and 2015, respectively	(1,911)	(3,645)
Additional paid-in capital	2,845,096	2,705,385
Accumulated other comprehensive loss	(27,009)	(22,537)
Accumulated deficit	(729,954)	(704,871)
Total shareholders' equity	2,091,808	1,979,794
Total liabilities and equity	$ 2,143,342	$ 2,034,909

The accompanying Notes to Parent Company Condensed Financial Statements are an integral part of these statements.

OPKO Health, Inc.
PARENT COMPANY CONDENSED STATEMENTS OF INCOME
(In thousands)

	For the years ended December 31,		
	2016	2015	2014
Revenues:			
Revenue from products	$ —	$ 140	$ 240
Revenue from transfer of intellectual property and other	—	154	—
Total revenues	—	294	240
Costs and expenses:			
Costs of revenue	875	798	252
Selling, general and administrative	60,819	47,708	27,809
Research and development	3,791	8,496	5,227
Total costs and expenses	65,485	57,002	33,288
Operating loss	(65,485)	(56,708)	(33,048)
Other income and (expense), net:			
Interest income	440	5	42
Interest expense	(3,585)	(5,347)	(11,325)
Fair value changes of derivative instruments, net	2,738	(39,442)	(11,019)
Other income (expense), net	(2,387)	2,141	2,832
Other income and (expense), net	(2,794)	(42,643)	(19,470)
Loss before income taxes and investment losses	(68,279)	(99,351)	(52,518)
Income tax benefit (provision)	(686)	—	—
Loss before investment losses	(68,965)	(99,351)	(52,518)
Loss from investments in investees	(7,665)	(7,105)	(3,587)
Net income (loss) from subsidiaries, net of taxes	51,547	76,428	(115,561)
Net loss attributable to common shareholders	$ (25,083)	$ (30,028)	$ (171,666)

The accompanying Notes to Parent Company Condensed Financial Statements are an integral part of these statements.

OPKO Health, Inc.
PARENT COMPANY CONDENSED STATEMENTS OF COMPREHENSIVE INCOME
(In thousands)

	For the years ended December 31,		
	2016	2015	2014
Net loss	$ (25,083)	$ (30,028)	$ (171,666)
Other comprehensive income (loss), net of tax:			
Change in foreign currency translation and other comprehensive income (loss)	(4,955)	(15,074)	(8,088)
Available for sale investments:			
Change in unrealized gain (loss), net of tax	(3,810)	(2,378)	(8,044)
Less: reclassification adjustments for losses included in net loss, net of tax	4,293	7,307	322
Comprehensive loss attributable to common shareholders	$ (29,555)	$ (40,173)	$ (187,476)

The accompanying Notes to Parent Company Condensed Financial Statements are an integral part of these statements.

OPKO Health, Inc.
PARENT COMPANY CONDENSED STATEMENTS OF CASH FLOWS
(In thousands)

	For the years ended December 31,		
	2016	2015	2014
Cash flows from operating activities:			
Net loss	$ (25,083)	$ (30,028)	$ (171,666)
Adjustments to reconcile net loss to net cash used in operating activities:			
Depreciation and amortization	89	85	97
Non-cash interest	1,866	2,612	5,662
Amortization of deferred financing costs	149	1,212	2,007
Losses from investments in investees	7,665	7,105	3,587
(Income) loss from subsidiaries	(51,546)	(76,428)	115,561
Equity-based compensation – employees and non-employees	42,693	26,074	14,779
Realized loss (gain) on equity securities and disposal of fixed assets	(2,738)	7,091	167
Gain on conversion of 3.00% convertible senior notes	284	(943)	(2,668)
Change in fair value of derivative instruments	2,347	39,442	11,019
Gain on deconsolidation of SciVac	—	(15,940)	—
Changes in other assets and liabilities	(6,844)	(15,640)	(5,627)
Net cash used in operating activities	(31,118)	(55,358)	(27,082)
Cash flows from investing activities:			
Investments in investees	(14,424)	(4,375)	(589)
Subsidiary financing	(44,569)	62,471	(85,386)
Proceeds from sale of equity securities	—	—	1,331
Acquisition of businesses, net of cash	—	(138)	(231)
Capital expenditures	(368)	(92)	(18)
Net cash provided by (used in) investing activities	(59,361)	57,866	(84,893)
Cash flows from financing activities:			
Proceeds from the exercise of Common Stock options and warrants	8,576	25,921	12,928
Net cash provided by financing activities	8,576	25,921	12,928
Net increase (decrease) in cash and cash equivalents	(81,903)	28,429	(99,047)
Cash and cash equivalents at beginning of period	97,647	69,218	168,265
Cash and cash equivalents at end of period	$ 15,744	$ 97,647	$ 69,218
SUPPLEMENTAL INFORMATION:			
Interest paid	$ 966	$ 2,175	$ 3,686
Pharmsynthez common stock received	$ —	$ —	$ 6,264

	For the years ended December 31,		
	2016	2015	2014
Non-cash financing:			
Shares issued upon the conversion of:			
2033 Senior Notes	$ 583	$ 120,299	$ 95,665
Common Stock options and warrants, surrendered in net exercise	$ 350	$ 14,369	$ 3,494
Issuance of capital stock to acquire or contingent consideration settlement:			
Transition Therapeutics, Inc.	$ 58,530	$ —	$ —
Bio-Reference Laboratories, Inc.	$ —	$ 950,148	$ —
EirGen Pharma Limited	$ —	$ 33,569	$ —
OPKO Renal	$ 25,986	$ 20,113	$ 21,155
OPKO Health Europe	$ 313	$ 1,813	$ —
OPKO Uruguay Ltda.	$ —	$ —	$ 159
Inspiro	$ —	$ —	$ 8,566
Issuance of stock for investment in Xenetic	$ 4,856	$ —	$ —

The accompanying Notes to Parent Company Condensed Financial Statements are an integral part of these statements.

OPKO Health, Inc.
Notes to Parent Company Condensed Financial Statements

Note 1. Organization and Basis of Presentation

We are a diversified healthcare company that seeks to establish industry-leading positions in large and rapidly growing medical markets. The parent company condensed financial statements included in this Schedule I represent the financial statements of OPKO Health, Inc., the parent company (or "OPKO"), on a stand-alone basis and do not include results of operations from our consolidated subsidiaries. The parent company condensed financial statements should be read in conjunction with our audited consolidated financial statements included in Item 8 of Part II of this Form 10-K. As of December 31, 2016 and 2015, approximately $2.1 billion and $1.9 billion , respectively, of our Investments, net have not been eliminated in the parent company condensed financial statements.

The parent company condensed financial statements included herein have been prepared in accordance with Rule 12-04, Schedule I of Regulation S-X, as substantially all the assets of Bio-Reference, a wholly owned subsidiary, and its subsidiaries are restricted from sale, transfer, lease, disposal or distributions to OPKO under the credit agreement with JPMorgan Chase Bank, N.A. (the "Credit Agreement"), subject to certain exceptions. Bio-Reference and its subsidiaries' net assets as of December 31, 2016 were approximately $1.0 billion , which includes goodwill of $401.8 million and intangible assets of $488.7 million . Bio-Reference's restricted net assets exceeds 25% of OPKO's consolidated net assets of $2.8 billion as of December 31, 2016.

Note 2 Debt

In January 2013, we entered into note purchase agreements (the “2033 Senior Notes”) with qualified institutional buyers and accredited investors (collectively, the “Purchasers”) in a private placement in reliance on exemptions from registration under the Securities Act of 1933, (the “Securities Act”). The 2033 Senior Notes were issued on January 30, 2013 . The 2033 Senior Notes, which totaled $175.0 million in original principal amount, bear interest at the rate of 3.00% per year, payable semiannually on February 1 and August 1 of each year. The 2033 Senior Notes will mature on February 1, 2033 , unless earlier repurchased, redeemed or converted. Upon a fundamental change as defined in the Indenture, dated as of January 30, 2013, by and between the Company and Wells Fargo Bank N.A., as trustee, governing the 2033 Senior Notes (the "Indenture"), subject to certain exceptions, the holders may require us to repurchase all or any portion of their 2033 Senior Notes for cash at a repurchase price equal to 100% of the principal amount of the 2033 Senior Notes being repurchased, plus any accrued and unpaid interest to but not including the fundamental change repurchase date.

The following table sets forth information related to the 2033 Senior Notes which is included our Consolidated Balance Sheet as of December 31, 2016 :

(In thousands)	Embedded conversion option	2033 Senior Notes	Discount	Debt Issuance Cost	Total
Balance at December 31, 2015	$ 23,737	$ 32,200	$ (6,525)	$ (426)	$ 48,986
Amortization of debt discount	—	—	1,913	153	2,066
Change in fair value of embedded derivative	(7,001)	—	—	—	(7,001)
Conversion	—	(350)	—	—	(350)
Balance at December 31, 2016	$ 16,736	$ 31,850	$ (4,612)	$ (273)	$ 43,701

The following table sets forth information related to the 2033 Senior Notes which is included our Consolidated Balance Sheet as of December 31, 2015 :

(In thousands)	Embedded conversion option	2033 Senior Notes	Discount	Debt Issuance Cost	Total
Balance at December 31, 2014	$ 65,947	$ 87,642	$ (22,135)	$ (1,638)	$ 129,816
Amortization of debt discount	—	—	2,613	233	2,846
Change in fair value of embedded derivative	36,587	—	—	—	36,587
Conversion	(78,797)	(55,442)	12,997	979	(120,263)
Balance at December 31, 2015	$ 23,737	$ 32,200	$ (6,525)	$ (426)	$ 48,986

The 2033 Senior Notes will be convertible at any time on or after November 1, 2032, through the second scheduled trading day immediately preceding the maturity date, at the option of the holders. Additionally, holders may convert their 2033 Senior Notes prior to the close of business on the scheduled trading day immediately preceding November 1, 2032, under the following circumstances: (1) conversion based upon satisfaction of the trading price condition relating to the 2033 Senior Notes; (2) conversion based on the Common Stock price; (3) conversion based upon the occurrence of specified corporate events; or (4) if we call the 2033 Senior Notes for redemption. The 2033 Senior Notes will be convertible into cash, shares of our Common Stock, or a combination of cash and shares of Common Stock, at our election unless we have made an irrevocable election of net share settlement. The initial conversion rate for the 2033 Senior Notes will be 141.48 shares of Common Stock per $1,000 principal amount of 2033 Senior Notes (equivalent to an initial conversion price of approximately $7.07 per share of Common Stock), and will be subject to adjustment upon the occurrence of certain events. In addition, we will, in certain circumstances, increase the conversion rate for holders who convert their 2033 Senior Notes in connection with a make-whole fundamental change (as defined in the Indenture) and holders who convert upon the occurrence of certain specific events prior to February 1, 2017 (other than in connection with a make-whole fundamental change). Holders of the 2033 Senior Notes may require us to repurchase the 2033 Senior Notes for 100% of their principal amount, plus accrued and unpaid interest, on February 1, 2019, February 1, 2023 and February 1, 2028, or following the occurrence of a fundamental change as defined in the indenture governing the 2033 Senior Notes.

We may not redeem the 2033 Senior Notes prior to February 1, 2017. On or after February 1, 2017 and before February 1, 2019, we may redeem for cash any or all of the 2033 Senior Notes but only if the last reported sale price of our Common Stock exceeds 130% of the applicable conversion price for at least 20 trading days during the 30 consecutive trading day period ending on the trading day immediately prior to the date on which we deliver the redemption notice. The redemption price will equal 100% of the principal amount of the 2033 Senior Notes to be redeemed, plus any accrued and unpaid interest to but not including the redemption date. On or after February 1, 2019, we may redeem for cash any or all of the 2033 Senior Notes at a redemption price of 100% of the principal amount of the 2033 Senior Notes to be redeemed, plus any accrued and unpaid interest up to but not including the redemption date.

The terms of the 2033 Senior Notes, include, among others: (i) rights to convert into shares of our Common Stock, including upon a fundamental change; and (ii) a coupon make-whole payment in the event of a conversion by the holders of the 2033 Senior Notes on or after February 1, 2017 but prior to February 1, 2019. We have determined that these specific terms are considered to be embedded derivatives. Embedded derivatives are required to be separated from the host contract, the 2033 Senior Notes, and carried at fair value when: (a) the embedded derivative possesses economic characteristics that are not clearly and closely related to the economic characteristics of the host contract; and (b) a separate, stand-alone instrument with the same terms would qualify as a derivative instrument. We have concluded that the embedded derivatives within the 2033 Senior Notes meet these criteria and, as such, must be valued separate and apart from the 2033 Senior Notes and recorded at fair value each reporting period.

For accounting and financial reporting purposes, we combine these embedded derivatives and value them together as one unit of accounting. At each reporting period, we record these embedded derivatives at fair value which is included as a component of the 2033 Senior Notes on our Consolidated Balance Sheet.

In August 2013, one of the conversion rights in the 2033 Senior Notes was triggered. Holders of the 2033 Senior Notes converted $16.9 million principal amount into 2,396,145 shares of the Company’s Common Stock. In June 2014, we entered into an exchange agreement with a holder of the Company’s 2033 Senior Notes pursuant to which such holder exchanged $70.4 million in aggregate principal amount of 2033 Senior Notes for 10,974,431 shares of the Company’s Common Stock and approximately $0.8 million in cash representing accrued interest through the date of completion of the exchange. During 2015, pursuant to a conversion right or through exchange agreements we entered with certain holders of our 2033 Senior Notes, holders of our 2033 Senior Notes converted or exchanged $55.4 million in aggregate principal amount of 2033 Senior Notes for 8,118,062 shares of the Company’s Common Stock.

On April 1, 2015, we initially announced that our 2033 Senior Notes were convertible through June 2015 by holders of such notes. This conversion right was triggered because the closing price per share of our Common Stock exceeded $9.19 , or 130% of the initial conversion price of $7.07 , for at least 20 of 30 consecutive trading days during the applicable measurement period. We have elected to satisfy our conversion obligation under the 2033 Senior Notes in shares of our Common Stock. Our 2033 Senior Notes continued to be convertible by holders of such notes for the remainder of 2015 and 2016 and continue to be convertible for the first quarter of 2017, and may be convertible thereafter, if one or more of the conversion conditions specified in the Indenture is satisfied during future measurement periods. Pursuant to the Indenture, a holder who elects to convert the 2033 Senior Notes will receive 141.4827 shares of our Common Stock plus such number of additional shares as is applicable on the conversion date per $1,000 principal amount of 2033 Senior Notes based on the early conversion provisions in the Indenture. See further discussion in Note 14.

In November 2015, Bio-Reference and certain of its subsidiaries entered into the Credit Agreement with JPMorgan Chase Bank, which provides for a $175.0 million secured revolving credit facility and includes a $20.0 million sub-facility for swingline loans and a $20.0 million sub-facility for the issuance of letters of credit. The Credit Agreement matures on November 5, 2020 and is secured by substantially all assets of Bio-Reference and its domestic subsidiaries, as well as a non-recourse pledge by us of our equity interest in Bio-Reference.

Note 3 Commitments and Contingencies

We have no significant direct commitments and contingencies, but our subsidiaries do. See Note 13 of our consolidated financial statements in Item 8 of Part II of this Form 10-K.

Note 4 Dividends

We did not receive any dividend payments from our consolidated subsidiaries for the years ended December 31, 2016, 2015 and 2014.

Note 5 Income Taxes

The parent company condensed financial statements recognize the current and deferred income tax consequences that result from our activities during the current and preceding periods pursuant to the provisions of Accounting Standards Codification Topic 740, Income Taxes (ASC 740), as if we were a separate taxpayer rather than a member of the consolidated income tax return group. The tax expense and benefit recorded in OPKO's consolidated financial statements was the result of activity at the subsidiaries and therefore all tax benefit and expense was reported in the Net income (loss) from subsidiaries, net of taxes line in the Condensed Statement of Income.

SIGNATURES

Pursuant to the requirements of Section 13 or 15(d) of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned, thereunto duly authorized.

Date: March 1, 2017

OPKO HEALTH, INC.

By: /s/ Phillip Frost, M.D.
Phillip Frost, M.D.
Chairman of the Board and
Chief Executive Officer

Pursuant to the requirements of the Securities Exchange Act of 1934, this report has been signed below by the following persons on behalf of the registrant and in the capacities and on the dates indicated.

Signature	Title	Date
/s/ Phillip Frost, M.D. Phillip Frost, M.D.	Chairman of the Board and Chief Executive Officer (Principal Executive Officer)	March 1, 2017
/s/ Jane H. Hsiao, Ph.D., MBA Jane H. Hsiao, Ph.D., MBA	Vice Chairman and Chief Technical Officer	March 1, 2017
/s/ Steven D. Rubin Steven D. Rubin	Director and Executive Vice President – Administration	March 1, 2017
/s/ Adam Logal Adam Logal	Senior Vice President, Chief Financial Officer, Chief Accounting Officer and Treasurer (Principal Financial Officer)	March 1, 2017
/s/ Richard Krasno, Ph.D. Richard Krasno, Ph.D.	Director	March 1, 2017
/s/ Thomas E. Beier Thomas E. Beier	Director	March 1, 2017
/s/ Dmitry Kolosov Dmitry Kolosov	Director	March 1, 2017
/s/ Richard A. Lerner, M.D. Richard A. Lerner, M.D.	Director	March 1, 2017
/s/ John A. Paganelli John A. Paganelli	Director	March 1, 2017
/s/ Richard C. Pfenniger, Jr. Richard C. Pfenniger, Jr.	Director	March 1, 2017
/s/ Alice Lin-Tsing Yu, M.D., Ph.D. Alice Lin-Tsing Yu, M.D., Ph.D.	Director	March 1, 2017

Exhibit Index

Exhibit Number	Description
21	Subsidiaries of the Company.
23.1	Consent of Ernst & Young LLP.
23.2	Consent of MSPC Certified Public Accountants and Advisors, P.C. relating to Bio-Reference Laboratories, Inc.'s financial statements.
31.1	Certification by Phillip Frost, Chief Executive Officer, pursuant to Rule 13a-14(a) and 15d-14(a) of the Securities and Exchange Act of 1934 as adopted pursuant to Section 302 of the Sarbanes-Oxley Act of 2002 for the year ended December 31, 2016.
31.2	Certification by Adam Logal, Chief Financial Officer, pursuant to Rule 13a-14(a) and 15d-14(a) of the Securities and Exchange Act of 1934 as adopted pursuant to Section 302 of the Sarbanes-Oxley Act of 2002 for the year ended December 31, 2016.
32.1	Certification by Phillip Frost, Chief Executive Officer pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002 for the year ended December 31, 2016.
32.2	Certification by Adam Logal, Chief Financial Officer, pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002 for the year ended December 31, 2016.
101.INS	XBRL Instance Document
101.SCH	XBRL Taxonomy Extension Schema Document
101.CAL	XBRL Taxonomy Extension Calculation Linkbase Document
101.DEF	XBRL Taxonomy Extension Definition Linkbase Document
101.LAB	XBRL Taxonomy Extension Label Linkbase Document
101.PRE	XBRL Taxonomy Extension Presentation Linkbase Document

Exhibit 21

SUBSIDIARIES OF OPKO HEALTH, INC.

NAME	JURISDICTION OF INCORPORATION
OPKO Instrumentation, LLC	Delaware
OPKO Pharmaceuticals, LLC	Delaware
OPKO Diagnostics, LLC	Delaware
OPKO Chile, S.A.	Chile
Arama Natural Products Distribuidora, Ltda	Chile
Pharmacos Exakta S.A. de C.V.	Mexico
FineTech Pharmaceutical Ltd	Israel
Farmadiet Group Holdings, S.C.	Spain
OPKO Biologics, Ltd	Israel
OPKO Ireland Global Holdings, Ltd	Ireland
OPKO Ireland, Ltd	Ireland
OPKO Canada Corp, ULC	Canada
OPKO Renal, LLC	Canada
Curna, Inc.	Delaware
Bio-Reference Laboratories, Inc.	New Jersey
GeneDX, Inc.	New Jersey
Genome Diagnostics, Ltd	Canada
EirGen Pharma Limited	Ireland
Transition Therapeutics, Inc.	Canada

Exhibit 23.1

Consent of Independent Registered Certified Public Accounting Firm

We consent to the incorporation by reference in the following Registration Statements:

1. Registration Statement (Form S-8 No. 333-211209) pertaining to the 2016 Equity Incentive Plan of OPKO Health, Inc. and subsidiaries,
2. Registration Statement (Form S-8 No. 333-144040) pertaining to the 2007 Equity Incentive Plan of OPKO Health, Inc. and subsidiaries,
3. Registration Statement (Form S-8 No. 333-190899) pertaining to the 2005 Stock Incentive Plan and 2007 Equity Incentive Plan of PROLOR Biotech, Inc. (formerly Modigene Inc.),
4. Registration Statement (Form S-8 No. 333-190900) pertaining to the 2007 Equity Incentive Plan of OPKO Health, Inc. and subsidiaries, and
5. Registration Statement (Form S-8 No. 333-206489) pertaining to the 2003 Employee Incentive Stock Option Plan of Bio-Reference Laboratories, Inc.

of our reports dated March 1, 2017, with respect to the consolidated financial statements and schedule of OPKO Health, Inc. and subsidiaries and the effectiveness of internal control over financial reporting of OPKO Health, Inc. and subsidiaries included in this Annual Report (Form 10-K) of OPKO Health, Inc. and subsidiaries for the year ended December 31, 2016.

/s/ Ernst & Young LLP

Miami, Florida
March 1, 2017

Exhibit 23.2

Consent of Independent Registered Public Accounting Firm

March 1, 2017

OPKO Health, Inc.
4400 Biscayne Blvd.
Miami, FL 33137

We consent to the incorporation by reference in the following Registration Statements:

1. Registration Statement on Form S-8 (No. 333-211209) of OPKO Health, Inc. and subsidiaries;

2. Registration Statement on Form S-3 (No. 333-144040) of OPKO Health, Inc. and subsidiaries,

3. Registration Statement on Form S-8 (No. 333-190899) of OPKO Health, Inc. and subsidiaries;

4. Registration Statement on Form S-8 (No. 333-190900) of OPKO Health, Inc. and subsidiaries; and

5. Registration Statement on Form S-8 (No. 333-206489) of OPKO Health, Inc. and subsidiaries;

of our reports dated January 13, 2015, with respect to the consolidated financial statements and internal controls over financial reporting of Bio-Reference Laboratories, Inc. and its subsidiaries which is incorporated by reference in this Annual Report on Form 10-K of OPKO Health, Inc.

/s/ MSPC
MSPC
Certified Public Accountants and Advisors
A Professional Corporation

Cranford, New Jersey
March 1, 2017

Exhibit 31.1

CERTIFICATIONS

I, Phillip Frost, certify that:

(1) I have reviewed this Annual Report on Form 10-K of OPKO Health, Inc.;

(2) Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

(3) Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

(4) The registrant's other certifying officer(s) and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

(a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

(b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

(c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

(d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

(5) The registrant's other certifying officer(s) and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

(a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

(b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: March 1, 2017

/s/Phillip Frost, M.D.

Phillip Frost, M.D.
Chief Executive Officer

Exhibit 31.2

CERTIFICATIONS

I, Adam Logal, certify that:

(1) I have reviewed this Annual Report on Form 10-K of OPKO Health, Inc.;

(2) Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

(3) Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

(4) The registrant's other certifying officer(s) and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

(a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

(b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

(c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

(d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

(5) The registrant's other certifying officer(s) and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

(a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

(b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: March 1, 2017

/s/ Adam Logal

Adam Logal

Senior Vice President, Chief Financial Officer,
Chief Accounting Officer and Treasurer

Exhibit 32.1

Certification Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002

(Subsections (a) and (b) of Section 1350, Chapter 63 of Title 18, United States Code)

Pursuant to 18 U.S.C. Section 1350, as adopted pursuant section 906 of the Sarbanes-Oxley Act of 2002, I, Phillip Frost, Chief Executive Officer of OPKO Health, Inc. (the "Company"), hereby certify that:

The Annual Report on Form 10-K for the year ended December 31, 2016 (the "Form 10-K") of the Company fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934, and the information contained in the Form 10-K fairly presents, in all material respects, the financial condition and results of operations of the Company.

Date: March 1, 2017

/s/ Phillip Frost, M.D.

Phillip Frost, M.D.
Chief Executive Officer

Exhibit 32.2

Certification Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002

(Subsections (a) and (b) of Section 1350, Chapter 63 of Title 18, United States Code)

Pursuant to 18 U.S.C. Section 1350, as adopted pursuant section 906 of the Sarbanes-Oxley Act of 2002, I, Adam Logal, Chief Financial Officer of OPKO Health, Inc. (the "Company"), hereby certify that:

The Annual Report on Form 10-K for the year ended December 31, 2016 (the "Form 10-K") of the Company fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934, and the information contained in the Form 10-K fairly presents, in all material respects, the financial condition and results of operations of the Company.

Date: March 1, 2017

/s/ Adam Logal

Adam Logal

Senior Vice President, Chief Financial Officer
Chief Accounting Officer and Treasurer