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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, 2017.

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 Website, 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, smaller reporting company or an emerging growth company. See the definitions of "large accelerated filer," "accelerated filer," "smaller reporting company," and "emerging growth company" in Rule 12b-2 of the Exchange Act.

(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	☐

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

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the 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: $2,182,572,438.

As of February 20, 2018, the registrant had 559,473,568 shares of Common Stock outstanding.

Documents Incorporated by Reference

Portions of the registrant's definitive proxy statement for its 2018 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, BioReference, EirGen and other acquired businesses;
- changes in regulation and policies in the United States and other countries, including increasing downward pressure on healthcare 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 and collect for our services;
- failure in our information technology systems, including cybersecurity attacks or other data security or privacy 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 BioReference Laboratories ("BioReference"), the nation's third-largest clinical laboratory with a core genetic testing business and an almost 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 IV formulation launched in November 2017), OPK88004, a selective androgen receptor modulator being developed for benign prostate hypertrophy (BPH) and other urologic and metabolic conditions, and OPK88003, 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. Our pharmaceutical business also features hGH-CTP, a once-weekly human growth hormone injection (in Phase 3 for pediatric 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 BioReference 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 BioReference'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 operate 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 acquisition of BioReference in 2015 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

BioReference Laboratories

Through BioReference, the third largest full service clinical laboratory in the United States, we 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. BioReference has an almost 400-person sales and marketing team and operates a network of approximately 275 patient service centers .

Our BioReference 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 BioReference, we operate in the following highly specialized laboratory divisions:

- *BioReference Laboratories.* BioReference 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.

BioReference provides us with a significant diagnostics commercial infrastructure for marketing and sales that reached almost 11 million patients in 2017. 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 BioReference, along with its almost 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 BioReference 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 BioReference 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, Digital Rectal Exam (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 and mortality 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. and in a clinical study of 366 predominantly African American men at 8 VA centers in the U.S. African Americans are at 1.7 times more likely to be diagnosed with prostate cancer than Caucasian men, and 2.2 times more likely to die from the disease. 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, regardless of race. The full data from the blinded, prospective U.S. clinical validation study and the VA study have been published in peer reviewed medical journals.

The clinical data from both studies 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 greater than 0.80 and is significantly higher than previously developed tests. Furthermore, the *4Kscore* test demonstrated excellent risk calibration, indicating the accuracy of the result for an individual patient, both Caucasian and African American. 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 utility 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",* was published in a peer reviewed medical journal. The study, 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 more than a dozen 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 (CPT Code 81539). A CPT code is used by insurance companies and government payers to describe health care services and procedures. A Category I CPT code is critical to facilitate reimbursement in government programs such as Medicare and Medicaid, as well as private insurance programs.

The National Comprehensive Cancer Network ("NCCN") included the *4Kscore* test as a recommended test in their 2015, 2016, and 2017 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. We expect to significantly expand our efforts to obtain broad reimbursement for the *4Kscore* test throughout 2018 and beyond.

Point-of-Care Diagnostics

OPKO Diagnostics, LLC ("OPKO Diagnostics"), formerly Claros Diagnostics, Inc., has developed a novel diagnostic instrument system to provide rapid, high performance blood test results in the point-of-care setting. The technology only requires a finger stick drop of blood introduced into the test cassette that can then run a quantitative test. The instrument performs the tests on a consumable cassette that is a microfluidics-based diagnostic test system. The credit card-sized test cassette works with a sophisticated desktop analyzer to provide 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.

We completed a multi-center clinical trial for the PSA test in mid-2017 and later filed the pre-marketing authorization ("PMA") for the Claros Analyzer and Sangia Total PSA Test with the FDA. The key clinical study with patients who were suspicious for prostate cancer found that the Sangia Total PSA test improved the sensitivity of a digital rectal exam ("DRE") to 91%, detecting 2.9 times the prostate cancers compared to DRE alone.We submitted our PMA for the PSA test in November 2017 and are actively engaged with FDA in the review of the PMA. We also intend to commence a clinical trial of a testosterone diagnostic test for our point-of-care system. We expect to fully leverage BioReference'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 parathyroid hormone (PTH) and 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 64-person highly specialized sales and marketing team dedicated to the launch and commercialization of *Rayaldee* as of December 31, 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 seventy percent (70%) of U.S. covered lives as of the end of 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 at percentage rates that range from the mid-teens to the mid-twenties or a minimum royalty, whichever is greater, upon commencement of 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.

On October 12, 2017, we entered into a Development and License Agreement (the "JT Agreement") with Japan Tobacco Inc. ("JT") granting JT the exclusive rights for the development and commercialization of *Rayaldee* in Japan (the "JT Territory"). The license grant to JT covers the therapeutic and preventative use of the product for (i) SHPT in non-dialysis and dialysis patients with CKD, (ii) rickets, and (iii) osteomalacia, as well as such additional indications as may be added to the scope of the license subject to the terms of the JT Agreement. Under the terms of the JT Agreement, OPKO received an initial upfront payment of $6 million. OPKO will receive another $6 million upon the initiation of OPKO's planned phase 2 study for *Rayaldee* in dialysis patients in the U.S. OPKO is also eligible to receive up to an additional aggregate amount of $31 million upon the achievement of certain regulatory and development milestones by JT for *Rayaldee* in the JT Territory, and $75 million upon the achievement of certain sales based milestones by JT in the JT Territory. OPKO will also receive tiered, double digit royalty payments at rates ranging from low double digits to mid-teens on net product sales within the JT Territory. JT will, at its sole cost and expense, be responsible for performing all development activities necessary to obtain all regulatory approvals for *Rayaldee* in Japan and for all commercial activities pertaining to *Rayaldee* in Japan, except for certain preclinical expenses which OPKO has agreed to reimburse JT up to a capped amount.

The FDA approval for *Rayaldee* was supported by successful 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.

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 of a higher dose product is expected to commence during the first half of 2018 for end stage renal disease patients on *Rayaldee*.

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 currentlyconsidering a single additional Phase 3 clinical trial 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 OPK88004, an orally administered selective androgen receptor modulator (SARM) which we are developing for the treatment of BPH and other urologic and metabolic conditions. The selective and antagonistic properties of OPK88004 on the prostate appear to be well suited to potentially reduce prostate hyperplasia and volume, as well as provide anabolic therapeutic benefits such as increased lean body mass and physical function, and decreased fat mass in specific patient populations.

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. OPK88004 is currently being studied in a Phase 2 study in prostate cancer patients who have undergone radical prostatectomy. The main objective of the study is to examine the effect of OPK88004 on sexual function and quality of life issues associated with this patient population. An additional Phase 2b study to determine the optimal dose to treat patients with Benign Prostatic Hypertrophy (BPH) commenced in November 2017 and is expected to enroll 126 patients in the U.S. The main focus of the study is to determine the optimal dose of OPK88004 that will reduce prostate volume and PSA levels, and increase anabolic effects such lean body and decreased fat mass in BPH patients.

Oxyntomodulin

Our internal product development program is also currently focused on developing a once weekly administered oxyntomodulin for type 2 diabetes and obesity. Our most advanced oxyntomodulin product candidate, OPK88003, 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, OPK88003 has the potential to regulate blood glucose.

OPK88003 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 OPK88003 (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 OPK88003 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. OPK88003 also provided a reduction in HbA1c, a marker of sugar metabolism, similar to exenatide at weeks 12 and 24.

We plan to evaluate OPK88003 in a dose escalation Phase 2b trial in 110 type 2 diabetics where patients will be treated with a dose escalation regimen over 3 months intended to optimize dose levels, and increase body weight loss and reduce the adverse event profile, such as nausea and vomiting. The patients will be treated for a total of 30 weeks in the study. The key primary endpoint will be HbA1c and secondary endpoints such as weight loss, lipid profile and safety will also be analyzed.

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.

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.

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.

Our Phase 3 trial of hGH-CTP in pediatric patients was initiated in December 2016 and patient enrollment is ongoing. 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 is delivered in a pen device in this multi-regional study in over 30 countries. The GHD subjects will be treated weekly for 12 months. In addition to the Phase 3 pediatric study, we have continued without interruption our ongoing Phase 2 pediatric open label extension study for hGH-CTP. The Phase 2 pediatric patients have been treated with hGH-CTP for over 3 years, and some patients for over 4 years. We are currently switching all of the pediatric patients in this study to the disposable pen device. We have also initiated 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.

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 have now completed post-hoc sensitivity analyses to evaluate the influence of outliers on the primary endpoint results using multiple statistical approaches. Analyses that excluded outliers showed a statistically significant difference between hGH-CTP and placebo on the change in trunk fat mass. Additional analyses that did not exclude outliers showed mixed results. Following completion of the analyses, OPKO and Pfizer have agreed that OPKO may communicate with the FDA regarding a potential BLA submission. In addition, we have continued the adult phase 3 study extension to monitor and accumulate long term safety of hGH-CTP treatment in the adult GDH patient population.

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. 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.

In February 2016, we commenced a Phase 2a dose escalation study and a phase 1 dose escalating subcutaneous study in healthy volunteers to determine safety 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.

We believe that the CTP technology may also be broadly applicable to other therapeutic proteins in the market and provide a reduction in the number of injections.

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. We expect to initiate a phase 1 study for Dravet Syndrome during the first half of 2018.

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 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 oral VARUBI™ in the United States. TESARO's IV formulation of VARUBI™ was approved by the FDA in October 2017 and commercial sales commenced in November 2017. In January 2018, the package insert for VARUBI™ was updated to include mention of new adverse effects, including anaphylaxis, anaphylactic shock and other serious hypersensitivity reactions which were reported following its introduction to the market in November 2017. In late February 2018, TESARO announced it would suspend distribution of VARUBI™ IV, but would continue to support the oral product.

Under the terms of the license, we received a $6.0 million upfront payment from TESARO and we received $30.0 million of milestone payments upon achievement of certain regulatory and commercial sale milestones.We are eligible to receive 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.

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. 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, 2017, 2016, and 2015, we incurred $125.2 million, $111.2 million, and $99.5 million, respectively, of research and development expenses related to our various product candidates. During the years ended December 31, 2017, 2016, and 2015, 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 patents and 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.

OPKO and/or its affiliates have entered into two exclusive license agreements with respect to *Rayaldee* patents in certain territories outside of North America with VFMCRP (Europe plus) and JT (Japan).

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 the IV formulation of rolapitant are granted and/or currently pending in multiple jurisdictions. In addition to the patents covering rolapitant, OPKO has an additional patent family granted worldwide covering another NK-1 antagonist (SCH900978) and also has method patent applications filed covering its use in 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.

OPK88003 and OPK88004

In 2016, we acquired Transition Therapeutics, Inc. which is developing multiple drug candidates that include OPK88003 (a long acting oxyntomodulin) and OPK88004 (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 OPK88003 and expires in December 2030, without extension. U.S. Pat. No. 7968587 covers OPK88004 and expires, without extension, in November 2027. In addition, Transition and its affiliates have patented compounds (scyllo-inositol) 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 October 2017, we entered into a license and development agreement with JT for the development and commercialization of *Rayaldee* in Japan for the treatment of SHPT in non-dialysis and dialysis patients with CKD. 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 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 commercializing our *4Kscore* product in the U.S., Europe and Mexico in a laboratory setting and seek 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 BioReference's national marketing, sales and distribution resources, along with its almost 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 CMS under 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, failure to meet anticipated clinical success, patient safety concerns, 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. Since the early 1990s, FDA has managed a user fee program whereby sponsors of drug applications pay a fee to the agency and the agency commits to meeting a series of performance goals designed to reduce drug review times. 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.

In addition to clinical trial rules, FDA imposes other requirements on applicants including obligations related to Good Manufacturing Practices (GMPs), proper labeling, and other issues related to manufacturing and marketing a drug.

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.

In December of 2016, Congress enacted the 21st Century Cures Act (P.L. 114-255) which contained provisions establishing a new Breakthrough Device pathway to allow faster patient access to devices and breakthrough technologies that provide for more effective treatment or diagnosis for life-threatening or irreversibly debilitating diseases, for which no approved or cleared treatment exists or that offer significant advantages over existing approved or cleared alternatives. FDA has just begun to implement this program and it is not clear if any of our products would be eligible.

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, since 2012, the FDA has collected 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 and the regulatory situation remains fluid. 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 drug or device 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 payors 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 payors, such as the government or private insurance plans. Third party payors 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 are established by calculating a weighted mean of private payer rates with new rates. On November 17, 2017, CMS released the new clinical laboratory fee schedule which took effect on January 1, 2018. The new Medicare rates are lower than rates paid in 2017 for many of our 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.

Additionally, as we operate in Europe, we may be subject to laws governing the collection, use, disclosure and transmission of personal and/or patient information. In December 2015, the European Union approved a General Data Protection Regulation ("GDPR") to replace the current data protection directive, Directive 95/46/EC, which will take effect May 25, 2018. The GDPR governs the use and transfer of personal data and imposes enhanced penalties for noncompliance. We are currently evaluating how to adjust our operations so as to comply with the GDPR.

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.

Open Payments Program

With the launch of *Rayaldee*, part of our business is now subject to the federal Physician Payments Sunshine Act under the Affordable Care Act, and its implementing regulations, which is implemented though the Open Payments Program(the "Open Payments Program"). The Open Payments Program 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 continue 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 BioReference's almost 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 64-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, 2017, we had 6,030 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 BioReference 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 BioReference and our other commercial businesses. If we are unable to generate profits and cash flow from BioReference 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, 2017, we have cash and cash equivalents of $91.5 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 relationships with Pfizer, VFMCRP and JT and the success of our integration of BioReference 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 relationships with Pfizer, VFMCRP, and JT, cash flow generated by BioReference and costs associated with the integration of the BioReference 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.

Safety concerns with drug products over the years 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. 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 licensing agreements with Vifor Fresenius Medical Renal Care Pharma Ltd ("VFMCRP") and Japan Tobacco ("JT") for the international development and marketing of Rayaldee. Failure to maintain these license agreements 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.

In October 2017, we entered into a Development and License Agreement (the "JT Agreement") with JT under which JT was granted the exclusive rights for the development and commercialization of *Rayaldee* in Japan. The license grant to JT covers

the therapeutic and preventative use of the product for (i) SHPT in non-dialysis and dialysis patients with CKD, (ii) rickets, and (iii) osteomalacia, as well as such additional indications as may be added to the scope of the license subject to the terms of the JT Agreement. Under the terms of the JT Agreement, we received an initial upfront payment of $6 million and we will receive an additional $6 million upon the initiation of our planned phase 2 study for *Rayaldee* in dialysis patients in the U.S. We are also eligible to receive up to an additional aggregate amount of $31 million upon the achievement of certain regulatory and development milestones by JT for *Rayaldee* in Japan, and $75 million upon the achievement of certain sales based milestones by JT. We will also receive tiered, double digit royalty payments at rates ranging from low double digits to mid-teens on net sales within Japan. JT will, at its sole cost and expense, be responsible for performing all development activities necessary to obtain all regulatory approvals for *Rayaldee* in Japan and for all commercial activities pertaining to *Rayaldee* in Japan, except for certain preclinical expenses which we have agreed to reimburse JT up to a capped amount. If JT, for any reason, including but not limited to early termination of the JT Agreement, fails to devote sufficient resources to successfully develop and market *Rayaldee* in Japan, our ability to earn milestone payments or receive royalty payments would be adversely affected, which could 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 completed post-hoc sensitivity analyses to evaluate the influence of outliers on the primary endpoint results using multiple statistical approaches. Analyses that excluded outliers showed a statistically significant difference between hGH-CTP and placebo on the change in trunk fat mass. Additional analyses that did not exclude outliers showed mixed results. There can be no assurance that the FDA will consider the sensitivity analysis or consider the product for approval for adults with GHD. 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 BioReference 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 BioReference, 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 BioReference. 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, specimens submitted by existing clients, or payment rates, 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 or develop 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 contracting with third party payors, 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;
- delay or failure to obtain institutional review board ("IRB") approval to conduct or renew a clinical trial at a prospective site; and
- insufficient liquidity to fund our preclinical and clinical studies.

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;
- inability to monitor patients adequately during or after treatment; and
- insufficient liquidity to fund ongoing studies.

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 sixty-four 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 64 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 other employees. 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, as well as our ability to obtain in network status with such 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 restricting in network status of laboratory providers. 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 or approve our laboratory for in network status.

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. Private health plans, such as managed care plans and pharmacy benefit management (PBM) programs may also not include our products on formularies, use other techniques that may restrict access to our products or set a lower reimbursement rate than anticipated.

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.

In 2017, Congress reauthorized the Generic Drug User Fee Act (GDUFA). The generic drug user fee program, established in 2012, is designed to speed the approval of new generic drugs. In addition, over the past few months, FDA has used its regulatory authority to enact other programs to streamline the path to market for generic drugs. In addition, a regulatory pathway for biosimilars was established in 2012 including a new user fee program to promote the development of these products that show no clinically meaningful differences from innovator biologics. Though they have their own statutory market pathway, like generic drugs, biosimilars can receive FDA approval by providing less clinical data than the innovator product. Biosimilars are expected to be less expensive competitors to innovator biologics reducing prices overall. We anticipate several new biosimilars reaching the market over the next year.

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 as required by applicable laws 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 and collect for our services could have a material adverse effect on our revenues and 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 and payor practices 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 and the World Health Organization establishes diagnostic codes using a data set called International Statistical Classification of Diseases, or ICD-10, 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 the ICD-10 code selected by the ordering or performing physician. 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.

In addition to the items described above, third-party payers, including government programs, may decide to deny payment or recoup payments for testing that they contend was improperly billed or not medically necessary, against their coverage determinations, or for which they believe they have otherwise overpaid (including as a result of their own error), and we may be required to refund payments already received. Our revenues may be subject to retroactive adjustment as a result of these factors among others, including without limitation, differing interpretations of billing and coding guidance and changes by government agencies and payors in interpretations, requirements, and "conditions of participation" in various programs.

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. As an integral part of our billing compliance program, we assess our billing and coding practices in the ordinary course of business, respond to payor audits on a routine basis, and investigate reported failures or suspected failures to comply with federal and state healthcare reimbursement requirements, as well as overpayment claims which may arise from time to time without fault on the part of the Company. We have in the ordinary course of business been the subject of recoupments by payors and have from time to time identified and reimbursed payors for overpayments.

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Incorrect or incomplete documentation and billing information, as well as the other items described above, among other factors, 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 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 limit the laboratory network to only a single national or regional laboratory to obtain improved fee-for-service pricing. There is 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.

We expect continuing efforts to limit the number of participating laboratories in payor networks, 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 failing to become a contracted provider 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, 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 and other payors 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.

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.* We submitted our PMA for the PSA test in November 2017 and are actively engaged with FDA in the review of the PMA. 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, BLA, 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 regulatory situation is fluid. 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 and non-US laws, including the General Data Protection Regulation;
- 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 implementation and/or repeal of part or all of 2010 Health Care Reform Legislation; 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. Under the FCA, whistleblower or qui tam provisions 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 and we may be subject to such suits. Violations of the FCA could result in enormous economic liability and could have a material impact on the Company. 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.

Tax reform may significantly affect the Company and its stockholders.

On December 22, 2017, President Trump signed into law the Tax Cuts and Jobs Act (the "Tax Act") that significantly reforms the Internal Revenue Code of 1986, as amended (the "Code"). The Tax Act, among other things, includes changes to U.S. federal tax rates, including reduction of the corporate tax rate from a top marginal rate of 35% to a flat rate of 21%, limitations of the tax deduction for interest expense to 30% of adjusted earnings (except for certain small businesses), limitations of the deduction for net operating losses to 80% of current year taxable income and elimination of net operating loss

carrybacks, one time taxation of offshore earnings at reduced rates regardless of whether they are repatriated, elimination of U.S. tax on foreign earnings (subject to certain important exceptions), immediate deductions for certain new investments instead of deductions for depreciation expense over time, modifying or repealing many business deductions and credits and putting into effect the migration from a "worldwide" system of taxation to a territorial system. Notwithstanding the reduction in the corporate income tax rate, the overall impact of the new federal tax law is uncertain and our business and financial condition could be adversely affected. In addition, it is uncertain if and to what extent various states will adjust their policies in response to the newly enacted federal tax law. The impact of this tax reform as well as other tax laws and regulations in the U.S. or other countries where we do business on holders of our common stock and our operating results and financial position is uncertain and could be adverse.

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.

The Company may also be required to comply with the data privacy and security laws of other countries in which it operates or from which it receives data transfers. The European Union enacted the General Data Protection Regulation (GDPR) to replace the current data protection directive, Directive 95/46/EC, which will take effect May 25, 2018, and which has a broader application and enhanced penalties for noncompliance. The GDPR, which is wide-ranging in scope, governs the collection and use of personal data in the EU and will impose operational requirements for companies that receive or process personal data of residents of the European Union that are different than those currently in place in the European Union. The GDPR will apply to our European operations and possibly to our laboratory and clinical development operations. The Company is evaluating the scope of work required to comply with the new EU regulations.

In March 2014, CareEvolve, BioReference'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. BioReference self-reported this incident to the appropriate government agency, the Office of Civil Rights ("OCR"). OCR notified BioReference that it has initiated an investigation of the breach report, and the Company is awaiting further discussion, investigation and action by OCR. Since March 2014, BioReference has taken meaningful steps to further improve its HIPAA and cybersecurity platform, including 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. We have had other data and security breaches in the ordinary course and such breaches may continue to happen from time to time despite our best efforts to prevent such breaches and safeguard private information. Some of these other data and security breaches have been reported to OCR and we are awaiting discussion, investigation or action by OCR. Any action by OCR may require us to pay fines or take remedial actions that may be expensive and require the attention of management, any of which may have a material adverse effect on the Company and our results of operations.

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 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 for clinical laboratory testing and from the interpreting pathologist for anatomic pathology services. 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. Under the FCA, whistleblower or qui tam provisions 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 and we may be subject to such suits. 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 $21,916. 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 services that are paid under the physician fee schedule. 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.

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. 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 payors 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 is established by calculating a weighted mean of private payer rates. On November 17, 2017, CMS released the new clinical laboratory fee schedule which took effect on January 1, 2018.The new Medicare rates are lower than rates paid in 2017 for many of our 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. However, as discussed in further detail below, the current Presidential administration has attempted to repeal and replace the 2010 Health Care Reform Legislation.

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 beginning in January 2013. However, a two-year moratorium on the tax was issued on December 18, 2015. The moratorium was extended for an additional two-year period on January 22, 2018. As such, the excise tax does not apply to sales in 2016 through 2019. The return of the tax in January 2020 will likely increase our expense in the future.

Additionally, the 2010 Health Care Reform Legislation included significant fraud and abuse measures, including (i) required disclosures under the Open Payments Program (which implements the requirements of the Physician Payments Sunshine Act), which in conjunction with its implementing regulations, requires certain manufacturers of certain drugs, biologics, and devices that are reimbursed by Medicare and Medicaid to report annually certain payments or "transfers of value" provided to physicians and teaching hospitals and to report annually ownership and investment interests held by physicians and their immediate family members during the preceding calendar year, (ii) lower thresholds for violations, and (iii) 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.

Prior to the 2016 U.S. elections (including the current Presidential administration), regulations under the 2010 Health Care Reform Legislation were expected to continue being drafted, released and finalized throughout the next several years. In 2017, the President and members of Congress sought to repeal and replace the 2010 Health Care Reform Legislation. It is uncertain whether such repeal and replace legislation will be enacted into law, and if enacted, what the impact might be on our business. It is also uncertain whether regulatory changes to the implementation of the 2010 Health Care Reform Legislation

will restrict patient access to affordable insurance and impact their access to novel, biosimilar and complex generic products. The full effects of any repeal and replacement of the 2010 Health Care Reform Legislation, or regulatory changes to its implementation, cannot be known until a new law is enacted or existing law is implemented through regulations or guidance issued by the CMS and other federal and state health care agencies. 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. In addition, litigation may prevent some or all of the legislation from taking effect. 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.

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.

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. 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 BioReference, 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 BioReference 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 BioReference 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 BioReference in the expected time frame may adversely affect our future results.

Historically, we and BioReference have operated as independent companies. There can be no assurances that our and BioReference's businesses can be integrated successfully. It is possible that the integration process could result in the loss of our or BioReference'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 BioReference'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 BioReference'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, 2017, we have goodwill and other intangible assets of $2.0 billion, or approximately 79% 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 26, 2018, our directors, executive officers, principal stockholders, and affiliated entities beneficially owned, in the aggregate 41.13% 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 32.95% of our Common Stock as of February 27, 2018. 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 also 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, 2018, investors held a short position of approximately 57,503,433 million shares of our common stock which represented approximately 10.3% 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 BioReference 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.

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 29,500 square feet, which encompasses space for our corporate offices and administrative services. Effective January 1, 2017, we entered into an amendment to our lease agreement with Frost Real-Estate Holdings. The lease, as amended, is for a three-year term. The lease provides for payments of approximately $81 thousand per month in the first year increasing annually to $86 thousand per month in the third year, plus applicable sale tax.

The table below summarizes certain information as to our significant physical properties as of December 31, 2017:

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.

We are involved from time to time in various claims and legal actions arising in the ordinary course of business.

As previously reported, in April 2017, the Civil Division of the United States Attorney's Office for the Southern District of New York (the "SDNY") informed BioReference that it believes that, from 2006 to the present, BioReference had, in violation of the False Claims Act, improperly billed Medicare and TRICARE (both are federal government health care programs) for clinical laboratory services provided to hospital inpatient beneficiaries at certain hospitals. BioReference is reviewing and assessing the allegations made by the SDNY, and, at this point, BioReference has not determined whether there is any merit to the SDNY's claims nor can it determine the extent of any potential liability. While management cannot predict the outcome of these matters at this time, the ultimate outcome could be material to our business, financial condition, results of operations, and cash flows.

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:

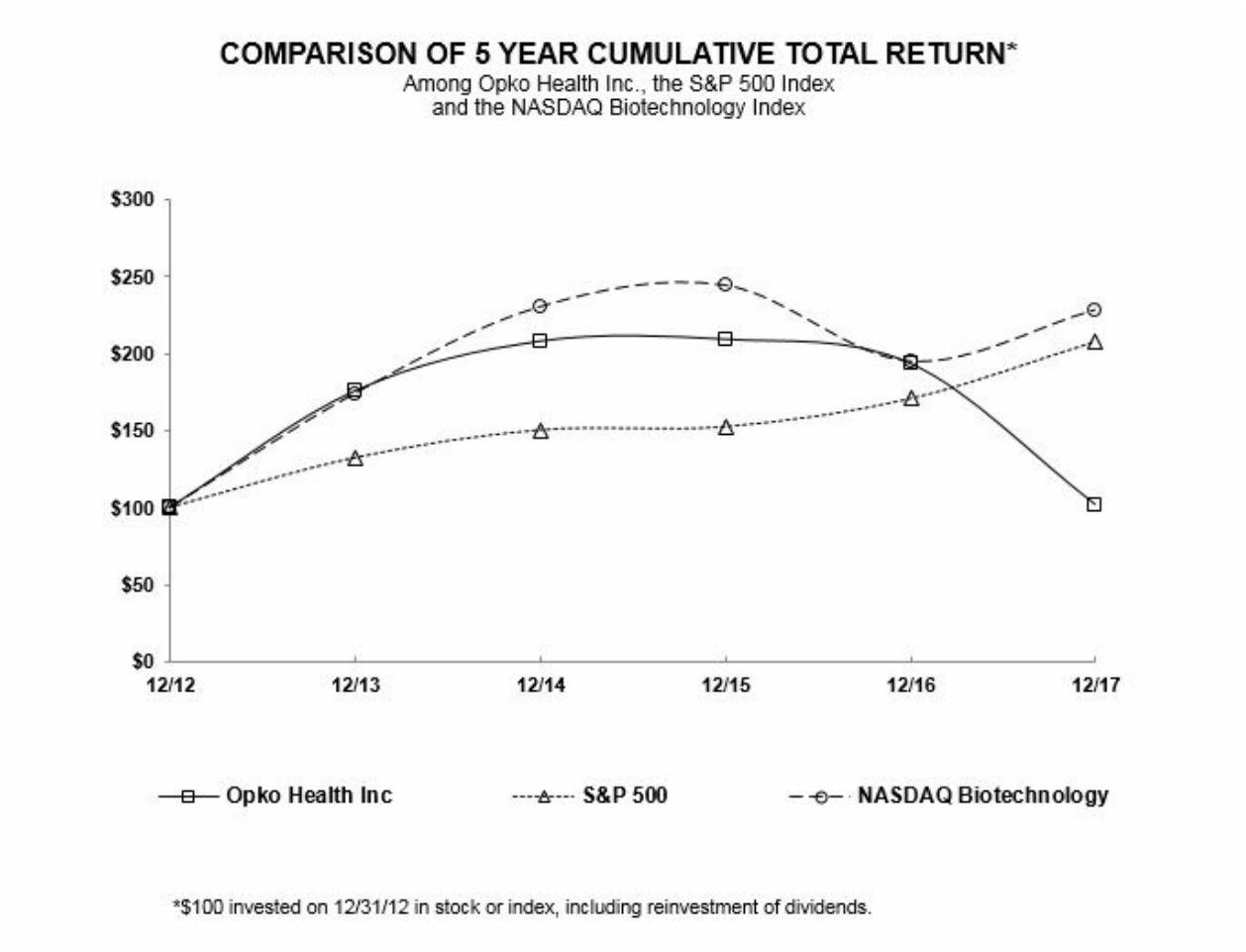
	High	Low
2017		
First Quarter	$ 9.55	$ 7.13
Second Quarter	8.04	5.99
Third Quarter	7.24	5.85
Fourth Quarter	7.08	4.50
2016		
First Quarter	$ 11.85	$ 7.12
Second Quarter	11.39	8.71
Third Quarter	11.31	8.91
Fourth Quarter	12.15	8.92

As of February 20, 2018, there were approximately 620 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 2018.

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, 2012 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.



	12/31/2012	12/31/2013	12/31/2014	12/31/2015	12/31/2016	12/31/2017
OPKO Health, Inc.	$ 100.00	$ 175.47	$ 207.69	$ 208.94	$ 193.35	$ 101.87
S&P 500	100.00	132.39	150.51	152.59	170.84	208.14
NASDAQ Biotechnology	100.00	174.05	230.33	244.29	194.95	228.29

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, 2017, 2016, 2015, 2014 and 2013 and the consolidated balance sheet data as of December 31, 2017, 2016, 2015, 2014 and 2013, 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)	2017	2016	2015	2014	2013
Statement of operations data:					
Revenues	$ 1,067,503	$ 1,221,661	$ 491,738	$ 91,125	$ 96,530
Costs and expenses:					
Cost of revenue	620,130	611,482	235,239	48,009	48,860
Operating expenses	727,435	683,454	354,980	188,931	127,302
Total costs and expenses	1,347,565	1,294,936	590,219	236,940	176,162
Operating loss	(280,062)	(73,275)	(98,481)	(145,815)	(79,632)
Other income and (expense), net	4,518	(271)	(39,517)	(25,212)	(24,586)
Income tax benefit (provision)	(18,855)	56,115	113,675	(24)	(1,672)
Net loss	(308,870)	(25,083)	(31,428)	(174,638)	(117,346)
Net loss attributable to common shareholders	$ (308,870)	$ (25,083)	$ (30,028)	$ (171,666)	$ (114,827)
Loss per share, basic and diluted:					
Net loss per share	$ (0.55)	$ (0.05)	$ (0.06)	$ (0.41)	$ (0.32)
Weighted average number of common shares outstanding basic and diluted:	559,160,565	550,846,553	488,065,908	422,014,039	355,095,701
Balance sheet data:					
Total assets	$ 2,584,556	$ 2,766,619	$ 2,799,188	$ 1,267,664	$ 1,391,516
Long-term liabilities	$ 397,843	$ 411,515	$ 567,492	$ 348,812	$ 426,687
Total shareholders' equity	$ 1,885,378	$ 2,091,808	$ 1,979,794	$ 835,741	$ 872,979

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 BioReference Laboratories ("BioReference"), the nation's third-largest clinical laboratory with a core genetic testing business and an almost 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 IV formulation launched in November 2017), OPK88004, a selective androgen receptor modulator being developed for benign prostatic hyperplasia and other urologic and metabolic conditions, and OPK88003, 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). Our pharmaceutical business also features hGH-CTP, a once-weekly human growth hormone injection (in Phase 3 and partnered with Pfizer), and a once-daily Factor VIIa drug for hemophilia (Phase 2a).

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

On October 12, 2017, EirGen, our wholly-owned subsidiary, and Japan Tobacco Inc. ("JT") entered into a Development and License Agreement (the "JT Agreement") granting JT the exclusive rights for the development and commercialization of *Rayaldee* in Japan (the "JT Territory"). The license grant to JT covers the therapeutic and preventative use of *Rayaldee* for (i) SHPT in non-dialysis and dialysis patients with CKD, (ii) rickets, and (iii) osteomalacia (the "JT Initial Indications"), as well as such additional indications as may be added to the scope of the license subject to the terms of the JT Agreement (the "JT Additional Indications", and together with the JT Initial Indications, the "JT Field").

OPKO received an initial upfront payment of $6 million. OPKO will receive another $6 million upon the initiation of OPKO's planned phase 2 study for *Rayaldee* in dialysis patients in the U.S. OPKO is also eligible to receive up to an additional aggregate amount of $31 million upon the achievement of certain regulatory and development milestones by JT for *Rayaldee* in the JT Territory, and $75 million upon the achievement of certain sales based milestones by JT in the JT Territory. OPKO will also receive tiered, double digit royalty payments at rates ranging from low double digits to mid-teens on sales of *Rayaldee* within the JT Territory and in the JT Field. JT will, at its sole cost and expense, be responsible for performing all development activities necessary to obtain all regulatory approvals for *Rayaldee* in Japan and for all commercial activities pertaining to *Rayaldee* in Japan, except for certain preclinical expenses which OPKO has agreed to reimburse JT up to a capped amount.

RESULTS OF OPERATIONS

For The Years Ended December 31, 2017 and December 31, 2016

Revenues	For the years ended December 31,		
(In thousands)	2017	2016	Change
Revenue from services	$ 889,076	$ 1,012,129	$ (123,053)
Revenue from products	107,759	83,467	24,292
Revenue from transfer of intellectual property and other	70,668	126,065	(55,397)
Total revenues	$ 1,067,503	$ 1,221,661	$ (154,158)

The decrease in Revenue from services is attributable to decreased reimbursement at BioReference's GeneDx division and decreased volume and overall reimbursement at BioReference. Revenue from services for the year ended December 31, 2017 was also affected by adjustments to the estimated payment amounts from third-party payors and claims of overpayment, including as a result of payor error. The increase in Revenue from products principally reflects an increase in revenue from OPKO Chile, Spain and EirGen. Revenue from products in 2017 also reflects $9.1 million of revenue from sales of *Rayaldee,* which was launched in the U.S. in November 2016. Revenue from transfer of intellectual property decreased as a result of $50.0 million of revenue from the initial payment in the VFMCRP Agreement for the year ended December 31, 2016, which was partially offset by $10.0 million of revenue from a milestone payment from our licensee, TESARO, for the year ended December 31, 2017. Revenue from transfer of intellectual property for the years ended December 31, 2017 and 2016 also reflects $57.8 million and $70.6 million, respectively, of revenue related to the Pfizer Transaction.

Costs of revenue. Costs of revenue for the year ended December 31, 2017 increased $8.6 million compared to the prior year. The decrease in cost of service revenue is attributable to decreased revenue at BioReference. The increase in cost of product revenue is attributable to an increase in revenue at OPKO Chile, Spain and EirGen and to cost of revenue related to sales of *Rayaldee*, which was launched in the U.S. in November 2016. Also included in cost of product revenue for the year ended December 31, 2017 is $5.4 million of inventory obsolescence expense related primarily to the launch of *Rayaldee*. Cost of revenue for the years ended December 31, 2017 and 2016 were as follows:

Cost of Revenue	For the years ended December 31,		
(In thousands)	2017	2016	Change
Cost of service revenue	$ 558,953	$ 564,103	$ (5,150)
Cost of product revenue	61,177	47,379	13,798
Total cost of revenue	$ 620,130	$ 611,482	$ 8,648

Selling, general and administrative expenses. Selling, general and administrative expenses for the years ended December 31, 2017 and 2016 were $521.0 million and $490.9 million, respectively. The increase in selling, general and administrative expenses was primarily due to costs related to the launch of *Rayaldee* and increased selling, general and administrative expenses at BioReference, which was partially offset by a decrease in severance costs. Included in selling, general and administrative expenses for the years ended December 31, 2017 and 2016 are $5.8 million and $17.9 million, respectively, of net severance costs for certain BioReference executives. These severance costs include $2.8 million and $8.9 million of expense related to the acceleration of stock option vesting for certain BioReference executives in 2017 and 2016, respectively. Selling, general and administrative expenses for the year ended December 31, 2017 also include $8.8 million of expense to write-off certain other current assets.

Selling, general and administrative expenses during the years ended December 31, 2017 and 2016, include equity-based compensation expense of $21.2 million and $33.4 million, respectively, including the expense related to the acceleration of stock option vesting for certain BioReference executives.

Research and development expenses. Research and development expenses for the years ended December 31, 2017 and 2016 were $125.2 million and $111.2 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 PMAs for diagnostics tests, if any. Internal expenses include

employee-related expenses including 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.

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

	For the years ended December 31,	
	2017	2016
External expenses:		
Phase 3 clinical trials	$ 15,339	$ 12,161
Manufacturing expense for biological products	47,737	35,985
PMA studies	1,089	—
Earlier-stage programs	7,620	6,297
Research and development employee-related expenses	29,970	28,676
Other internal research and development expenses	24,680	30,752
Third-party grants and funding from collaboration agreements	(1,249)	(2,666)
Total research and development expenses	$ 125,186	$ 111,205

The increase in research and development expenses is primarily 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 the acquisition of Transition Therapeutics in August 2016. In addition, during the years ended December 31, 2017 and 2016, we recorded, as an offset to research and development expenses, $1.2 million and $2.7 million, respectively, related to research and development grants received from our collaboration and funding agreements. Research and development expenses for the years ended December 31, 2017 and 2016 include equity-based compensation expenses of $5.1 million and $7.5 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 income (expense) for the years ended December 31, 2017 and 2016, were $3.4 million of income and $17.0 million of expense, respectively. The change in contingent consideration income (expense) was attributable to contingent consideration for OPKO Renal during the year ended December 31, 2017 due to changes in assumptions regarding the timing of achievement of future milestones of *Rayaldee*. The contingent consideration liabilities of $41.4 million at December 31, 2017 relate to potential amounts payable to former stockholders of CURNA, OPKO Diagnostics and OPKO Renal pursuant to our acquisition agreements in January 2011, October 2011 and March 2013, respectively.

Amortization of intangible assets. Amortization of intangible assets was $84.7 million and $64.4 million, respectively, for the years ended December 31, 2017 and 2016. Amortization expense reflects the amortization of acquired intangible assets with defined useful lives. Amortization of intangible assets for the years ended December 31, 2017 and 2016 includes $16.0 million and $8.0 million, respectively, 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 Sheets and began to amortize that asset. Our indefinite lived 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. Amortization of intangible assets for the year ended December 31, 2017 also includes an impairment charge of $13.2 million to write our intangible asset for VARUBI™ down to its estimated fair value.

Interest income. Interest income for the years ended December 31, 2017 and 2016, 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, 2017 and 2016, was $6.6 million and $7.4 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 BioReference's outstanding debt under its credit facility.

Fair value changes of derivative instruments, net. Fair value changes of derivative instruments, net for the years ended December 31, 2017 and 2016, were $0.1 million and $2.8 million of income, respectively. Fair value changes of derivative instruments, net reflects non-cash income related to the changes in the fair value of the embedded derivatives in the 2033 Senior Notes of $3.2 million and $7.0 million for the years ended December 31, 2017 and 2016, respectively. For the year ended December 31, 2017, we observed a decrease in the market price of our Common Stock which resulted in the decrease in

the estimated fair value of our embedded derivatives in the 2033 Senior Notes through the last valuation on February 1, 2017. Fair value changes of derivative instruments, net for the year ended December 31, 2017 also reflects $2.9 million of expense related to the change in the fair value of warrants and options to purchase additional shares of Neovasc, Inc. ("Neovasc") and Xenetic Biosciences, Inc. ("Xenetic"). 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. ("Cocrystal"), ARNO Therapeutics, Inc. ("ARNO") and MabVax Therapeutics Holdings, Inc. ("MabVax").

Other income and (expense), net. Other income and (expense), net for the years ended December 31, 2017 and 2016, were $10.5 million and $3.9 million of income, respectively. Other income for the year ended December 31, 2017 primarily consists of a $3.0 million gain on the sale of non-strategic assets at a wholly-owned BioReference subsidiary, a $1.5 million gain on the sale of certain available for sale investments, a $2.5 million gain in connection with the acquisition transaction between Eloxx Pharmaceuticals, Inc. and Sevion Therapeutics, Inc., and a $1.9 million gain in connection with the dilution of our equity method investment in VBI Vaccines Inc. ("VBI"). 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 SciVac Therapeutics Inc. ("STI") and VBI, 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 Pharmaceuticals Corporation ("RXi") down to their respective fair values.

Income tax benefit (provision). Our income tax benefit (provision) for the years ended December 31, 2017 and 2016 was $(18.9) million, and $56.1 million, respectively. The change in income tax provision is primarily due to the establishment of valuation allowance against certain U.S. and non-U.S. deferred tax assets. As of December 31, 2017, the Company determined that it is more likely than not that certain U.S. and non-U.S. deferred tax assets will not be realized and recorded a valuation allowance of $28.7 million. On December 22, 2017, the Tax Act was enacted into law and the new legislation reduced the corporate income tax rate from 35% to 21% which required us to remeasure our U.S. deferred tax assets and liabilities and recognize the effect in the period of enactment, resulting in $31.8 million of expense, with an equal offset to valuation allowance.

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 report a net loss. Loss from investments in investees was $14.5 million and $7.7 million for the years ended December 31, 2017 and 2016, respectively. The increase in Loss from investments in investees is attributable to losses recognized on our investment in Pharmsynthez in 2017.

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	For the years ended December 31,		
(In thousands)	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 BioReference 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.

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 BioReference 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	For the years ended December 31,		
(In thousands)	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 BioReference 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 BioReference 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 BioReference 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 BioReference 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 BioReference 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.

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 BioReference'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 BioReference'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 of income and $36.6 million of expense 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, ARNO and MabVax.

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, 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 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 BioReference 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.

LIQUIDITY AND CAPITAL RESOURCES

At December 31, 2017, we had cash and cash equivalents of approximately $91.5 million. Cash used in operations of $92.1 million during 2017 principally reflects expenses related to general and administrative activities of our corporate operations, research and development activities and our launch activities related to *Rayaldee*. Cash used in investing activities primarily reflects capital expenditures of $46.5 million. Cash provided by financing activities primarily reflects net borrowings on lines of credit of $58.9 million. 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.

On October 12, 2017, EirGen, our wholly-owned subsidiary, and Japan Tobacco Inc. ("JT") entered into a Development and License Agreement (the "JT Agreement") granting JT the exclusive rights for the development and commercialization of *Rayaldee* in Japan (the "JT Territory"). The license grant to JT covers the therapeutic and preventative use of *Rayaldee* for (i) SHPT in non-dialysis and dialysis patients with CKD, (ii) rickets, and (iii) osteomalacia, as well as such additional indications as may be added to the scope of the license subject to the terms of the JT Agreement. In connection with the transaction, OPKO received an initial upfront payment of $6 million, and OPKO will receive another $6 million upon the initiation of OPKO's planned phase 2 study for *Rayaldee* in dialysis patients in the U.S. OPKO is also eligible to receive up to an additional aggregate amount of $31 million upon the achievement of certain regulatory and development milestones by JT for *Rayaldee* in the JT Territory, and $75 million upon the achievement of certain sales based milestones by JT in the JT Territory. OPKO will also receive tiered, double digit royalty payments at rates ranging from low double digits to mid-teens on sales of *Rayaldee* within the JT Territory. JT will, at its sole cost and expense, be responsible for performing all development activities necessary to obtain all regulatory approvals for *Rayaldee* in Japan and for all commercial activities pertaining to *Rayaldee* in Japan, except for certain preclinical expenses which OPKO has agreed to reimburse JT up to a capped amount.

In August 2017, we entered into a Commitment Letter (the "Commitment Letter") with Veterans Accountable Care Group, LLC ("VACG") in connection with submission of a bid by its affiliate, the Veterans Accountable Care Organization, LLC ("VACO") in response to a request for proposal ("RFP") from the Veterans Health Administration ("VA") regarding its Community Care Network. If VACO is successful in its bid, we will acquire a fifteen percent (15%) membership interest in VACO. In addition, BioReference, our wholly-owned subsidiary, will provide laboratory services for the Community Care Network, a region which currently includes approximately 2,133,000 veterans in the states of Massachusetts, Maine, New Hampshire, Vermont, New York, Pennsylvania, New Jersey, Rhode Island, Connecticut, Maryland, Virginia, West Virginia, and North Carolina.

Pursuant to the Commitment Letter, we committed to provide, or to arrange from a third party lender, a line of credit for VACG in the amount of $50.0 million (the "Facility"). Funds drawn under the Facility would be contributed by VACG to VACO in order to satisfy the financial stability requirement of VACO in connection with its submission of the RFP. VACG would not be permitted to draw down on the Facility unless and until the VHA awards a contract to VACO. The Facility would have a maturity of five (5) years. Interest on the Facility would be payable at a rate equal to six and one-half percent (6.5%) per annum, payable quarterly in arrears. The Facility is subject to the negotiation of definitive documentation conditions customary for transactions of such type and otherwise acceptable to VACG and the lender under the Facility.

We currently anticipate that a decision by the VHA with respect to the RFP will occur during 2018, although there can be no assurance that a decision will be made by such time or that, if favorable, such decision will not be challenged by participants in the RFP process or otherwise.

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 increased 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 commercialization 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 SHPT related to patients with stage 3 or 4 chronic kidney disease and vitamin D insufficiency/deficiency ("VFMCRP 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 royalties on sales of the product at percentage rates that range from the mid-teens to the mid-twenties 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 VFMCRP Initial Indication in the VFMCRP 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 royalties on sales of the product at percentage rates that range from the mid-teens to the mid-twenties or a minimum royalty, whichever is greater, upon commencement of sales of the product.

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 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 have completed post-hoc sensitivity analyses to evaluate the influence of outliers on the primary endpoint results using multiple statistical approaches. Analyses that excluded outliers showed a statistically significant difference between hGH-CTP and placebo on the change in trunk fat mass. Additional analyses that did not exclude outliers showed mixed results. Following completion of the analyses, OPKO and Pfizer agreed that OPKO may proceed to discuss a possible BLA submission with the FDA.

We are constructing a research, development and manufacturing center in Waterford, Ireland, for which we expect to incur between $40 million and $45 million for the construction and validation of the facility. Construction of the facility began in the fourth quarter of 2016 with 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 oral VARUBI™ in the United States. TESARO launched its IV formulation of VARUBI™ ("VARUBI™ IV") in November 2017. We received $30.0 million of milestone payments from TESARO upon achievement of certain regulatory and commercial sale milestones, which includes a $10.0 million milestone payment we received for the year ended December 31, 2017, and we are eligible to receive 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. In January 2018, the package insert for VARUBI™ was updated to include mention of new adverse effects, including anaphylaxis, anaphylactic shock and other serious hypersensitivity reactions which were reported following its introduction to the market in November 2017. In late February 2018, TESARO announced it would suspend distribution of VARUBI™ IV, but would continue to support the oral product.

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, 2017, $31.9 million principal amount of 2033 Senior Notes was outstanding.

In connection with our acquisitions of CURNA, OPKO Diagnostics 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, BioReference 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. BioReference 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 BioReference's domestic subsidiaries. The Credit Agreement is also secured by substantially all assets of BioReference and its domestic subsidiaries, as well as a non-recourse pledge by us of our equity interest in BioReference. Availability under the Credit Agreement is based on a borrowing base comprised of eligible accounts receivables of BioReference and certain of its subsidiaries, as specified therein.

On March 17, 2017, BioReference and certain of its subsidiaries entered into Amendment No. 3 to Credit Agreement, which amended the Credit Agreement to permit BioReference and its subsidiaries to dividend cash to the Company in the form of an intercompany loan, in an aggregate amount not to exceed $55.0 million. On August 7, 2017, BioReference and certain of its subsidiaries entered into Amendment No. 4 to Credit Agreement, which amended the Credit Agreement to permit BioReference and its subsidiaries to dividend cash to the Company in the form of an additional intercompany loan, in an aggregate amount not to exceed $35.0 million. On November 8, 2017, BioReference and certain of its subsidiaries entered into Amendment No. 5 to Credit Agreement, which amended the Credit Agreement to, among other things, ease certain thresholds that require increased reporting by BioReference and reduce the pro forma availability condition for BioReference to make certain cash dividends to the Company. On December 22, 2017, BioReference and certain of its subsidiaries entered into Amendment No. 6 to Credit Agreement, which amended the Credit Agreement to, among other things, permit BioReference and its subsidiaries to dividend cash to the Company in the form of intercompany loans, in an aggregate amount not to exceed $45.0 million. The other terms of the Credit Agreement remain unchanged.

On February 28, 2018, BioReference and certain of its subsidiaries entered into Amendment No. 7 to the Credit Agreement, which amended the Credit Agreement to permit BioReference and its subsidiaries to use cash on hand, up to a maximum amount set forth in the amendment, to meet the availability requirements that otherwise would trigger (i) covenants that would require BioReference to maintain a minimum fixed charge coverage ratio and provide certain increased reporting under the Credit Agreement and (ii) CB's right, as agent for the lenders under the Credit Agreement, to exercise sole dominion over funds held in certain accounts of BioReference. The other terms of the Credit Agreement remain unchanged.

As of December 31, 2017, the total availability under our Credit Agreement with CB and our lines of credit with financial institutions in Chile and Spain was $116.0 million, of which $114.7 million was used and outstanding as of December 31, 2017. The weighted average interest rate on these lines of credit is approximately 4.2%. 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, 2017, was $115.1 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, 2017, the amounts available to be borrowed under our lines of credit and the proceeds from the 5% Convertible Promissory Notes which we agreed to issue in February 2018 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 success of *Rayaldee*, BioReference'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, our success in developing markets for our product candidates and results of government investigations, payor claims, and legal proceedings that may arise. 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, 2017, with respect to the amounts and timing of our known contractual obligation payments due by period.

Contractual obligations (In thousands)	2018	2019	2020	2021	2022	Thereafter	Total
Open purchase orders	$ 80,810	$ 1,312	$ 38	$ —	$ —	$ —	$ 82,160
Operating leases	19,059	15,166	9,360	6,079	3,148	3,542	56,354
Capital leases	3,521	3,029	2,440	1,586	410	441	11,427
2033 Senior Notes	—	31,850	—	—	—	—	31,850
Deferred payments	5,000	5,000	—	—	—	—	10,000
Mortgages and other debts payable	1,632	415	415	415	415	351	3,643
Lines of credit	10,511	—	104,152	—	—	—	114,663
Severance payments	4,224	—	—	—	—	—	4,224
Interest commitments	1,020	212	39	23	19	19	1,332
Total	$ 125,777	$ 56,984	$ 116,444	$ 8,103	$ 3,992	$ 4,353	$ 315,653

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 $159.1 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, 2017 and 2016 was $2.0 billion and $2.1 billion, respectively, representing approximately 79% and 76% 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 $717.1 million and $704.6 million, respectively, at December 31, 2017 and 2016. 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, 2017 and 2016 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 $1.3 billion and $1.4 billion, including IPR&D of $647.3 million and $644.7 million, respectively, at December 31, 2017 and 2016. 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.

IPR&D is tested for impairment 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 amount. If the carrying amount of the IPR&D exceeds its fair value, an impairment loss shall be recognized in an amount equal to that excess. Intangible assets with defined lives are tested for impairment by a comparison of the carrying amount of the asset to its estimated undiscounted future cash flows expected to be generated by the asset. If the carrying amount of an asset exceeds its estimated undiscounted 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. We recorded an impairment charge of $13.2 million in Amortization of intangible assets in our Consolidated Statement of Operations for the year ended December 31, 2017 to write our intangible asset for VARUBI™ down to its estimated fair value as a result of our testing. No intangible asset impairment was recorded for the year ended December 31, 2016 as a result of our testing.

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.

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 indicators.

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 $84.7 million and $64.4 million for the years ended December 31, 2017 and 2016, 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 payor programs including various managed care organizations, as well as the Medicare and Medicaid programs. For the year ended December 31, 2017, approximately 31% of our revenues from services were derived directly from 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.

The complexities and ambiguities of billing, reimbursement regulations and claims processing, as well as issues unique to Medicare and Medicaid programs, require us to estimate the potential for retroactive adjustments in the recognition of revenue in the period the related services are rendered. Actual amounts are adjusted in the period those adjustments become known.

Third-party payers, including government programs, may decide to deny payment or recoup payments for testing they contend were improperly billed or not medically necessary, against their coverage determinations, or for which they believe they have otherwise overpaid (including as a result of their own error), and we may be required to refund payments already received. Our revenues may be subject to retroactive adjustment as a result of these factors among others, including without

limitation, differing interpretations of billing and coding guidance and changes by government agencies and payors in interpretations, requirements, and "conditions of participation" in various programs. We have processed requests for recoupment from third-party payers in the ordinary course of our business, and it is likely that we will continue to do so in the future. If a third-party payer denies payment for testing or recoups money from us in a later period, reimbursement revenue for our testing could decline.

As an integral part of our billing compliance program, we periodically assess our billing and coding practices , respond to payor audits on a routine basis, and investigate reported failures or suspected failures to comply with federal and state healthcare reimbursement requirements, as well as overpayment claims which may arise from time to time without fault on the part of the Company. We may have an obligation to reimburse Medicare, Medicaid, and third party payers for overpayments regardless of fault. We have periodically identified and reported overpayments, reimbursed payors for overpayments and taken appropriate corrective action.

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 healthcare providers and payers that provide for government-mandated and/or privately-negotiated rebates, chargebacks and discounts with respect to the purchase of *Rayaldee*.

As of December 31, 2017, allowances for Sales Deductions and product returns related to sales of *Rayaldee* are known or estimable utilizing historical information and market research projections. As a result, we recognize revenue for shipments of *Rayaldee* at the time of delivery to *Rayaldee* Customers. For the year ended December 31, 2017, we recognized $9.1 million in net product revenue from sales of *Rayaldee*, including amounts previously deferred. No revenue was recognized from sales of *Rayaldee* for the year ended December 31, 2016 as we lacked the experiential data which would allow us to estimate Sales Deductions and product returns. The related deferred revenue balance as of December 31, 2016 was $1.6 million.

The following table presents an analysis of product sales allowances and accruals for the year ended December 31, 2017:

(In thousands)	Chargebacks, discounts, rebates and fees	Governmental	Returns	Total
Balance at December 31, 2016	$ —	$ —	$ —	$ —
Provision related to current period sales	1,591	1,332	490	3,413
Credits or payments made	(1,358)	(984)	(53)	(2,395)
Balance at December 31, 2017	$ 233	$ 348	$ 437	$ 1,018
Total gross *Rayaldee* sales				$ 12,482
Provision for *Rayaldee* sales allowances and accruals as a percentage of gross *Rayaldee* sales				27%

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 healthcare programs are funded by federal and state governments, and payment is primarily dependent upon submitting appropriate documentation. At December 31, 2017 and 2016, receivable balances (net of contractual adjustments) from Medicare and Medicaid in total were 16% and 23%, respectively, of our consolidated Accounts receivable, net.

The portion of our accounts receivable due from individual patients comprises the largest portion of credit risk. At December 31, 2017 and 2016, receivables due from patients represent approximately 3.2% and 4.1%, respectively, of our consolidated Accounts receivable, net.

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 $66.4 million and $36.3 million at December 31, 2017 and 2016, 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. Valuation allowances on certain U.S. deferred tax assets and non-U.S. deferred tax assets are established, because realization of these tax benefits through future taxable income does not meet the more-likely-than-not threshold.

On December 22, 2017, the 2017 Tax Cuts and Jobs Act (the "Tax Act") was enacted into law and the new legislation contains several key tax provisions, including a reduction of the corporate income tax rate from 35% to 21% effective January 1, 2018 and a one-time mandatory transition tax on accumulated foreign earnings, among others. We are required to recognize the effect of the tax law changes in the period of enactment, such as remeasuring our U.S. deferred tax assets and liabilities, as well as reassessing the net realizability of our deferred tax assets and liabilities. In December 2017, the SEC staff issued Staff Accounting Bulletin No. 118, Income Tax Accounting Implications of the Tax Cuts and Jobs Act (SAB 118), which allows us to record provisional amounts during a measurement period not to extend beyond one year of the enactment date. Since the Tax Act was passed late in the fourth quarter of 2017, and ongoing guidance and accounting interpretation are expected over the next 12 months, our accounting of deferred tax re-measurements, the transition tax, and other items are provisional and may materially change due to the forthcoming guidance and our ongoing analysis of final year-end data and tax positions. We expect to complete our analysis within the measurement period in accordance with SAB 118.

We anticipate future impacts at a U.S. state and local tax level related to the Tax Act; however, statutory and interpretive guidance is not available from applicable state and local tax authorities to reasonably estimate the impact. Consequently, for

those jurisdictions, we have not recorded provisional amounts and have continued to apply ASC 740 based on the provisions of the tax laws that were in effect immediately prior to Tax Act enactment.

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 cash flows 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 and 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 and net realizable value. Inventories at our diagnostics segment consist primarily of purchased laboratory supplies, which is used in our testing laboratories. Inventory obsolescence for the years ended December 31, 2017 and 2016 was $5.4 million and $0.0 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.

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

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 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 plan to adopt the ASU in the first quarter of 2018 using the full retrospective approach.

We continue to assess the impact of this ASU on our financial condition, results of operations, cash flows and disclosures. Our analysis includes reviewing current accounting policies and practices to identify potential differences that would result from applying the requirements under this new standard. We have reviewed certain contracts with its customers that we believe are representative of our revenue streams and continue to review additional contracts across our global business units. ASU 2014-09 requires increased disclosure which in turn is expected to require certain new processes. The determination of the impact of adoption of ASU 2014-09 on our financial condition, results of operations, cash flows and disclosures is ongoing, and, as such, we are not able to reasonably estimate the quantitative effect that the adoption of the new standard will have on our financial statements. Based on our preliminary assessment of this ASU, for our diagnostics segment, we generally do not expect any significant changes to the timing of revenue recognition or net income, but there will be a change in the presentation in the Statement of Operations. Under the ASU, the majority of the amounts that were historically classified as provision for bad debts, primarily related to patient responsibility, will be considered an implicit price concession in determining net revenues. Accordingly, we will report uncollectible balances associated with individual patients as a reduction of the transaction price and therefore as a reduction in net revenues when historically these amounts were classified as provision for bad debts within Selling, general and administrative expenses.

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 was effective for fiscal years beginning after December 15, 2016, including interim periods within those fiscal years, with early adoption permitted. The adoption of ASU 2015-11 in the first quarter of 2017 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. 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. 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 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, 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, but the primary effect will be the recognition of changes in the fair value of our available for sale investments in net income.

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 was effective for fiscal years beginning after December 15, 2016, including interim periods within those fiscal years, with early adoption permitted. We adopted this standard in the first quarter of 2017. As required by ASU 2016-09, excess tax benefits are classified as an operating activity in our Consolidated Statement of Cash Flows and we have applied this provision prospectively. In addition, we have elected to estimate forfeitures over the course of a vesting period, rather than account for forfeitures as they occur. We adjust our forfeiture estimates based on the number of share-based awards that ultimately vest on at least an annual basis. As a result of the adoption of ASU 2016-09 in 2017, we recorded a cumulative-effect adjustment to reduce our deferred tax liabilities and reduce our accumulated deficit by $31.7 million with respect to excess tax benefits recognized in our Consolidated Balance Sheets.

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 portions 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 Statements 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, 2017, we had cash and cash equivalents of $91.5 million. The weighted average interest rate related to our cash and cash equivalents for the year ended December 31, 2017 was less than 1%. As of December 31, 2017, the principal outstanding balance under our Credit Agreement with JPMorgan Chase Bank, N.A. and our Chilean and Spanish credit lines was $114.7 million in the aggregate at a weighted average interest rate of approximately 4.2%.

Our $31.9 million aggregate principal amount of our 2033 Senior Notes has a fixed interest rate of 3.0%, 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.

ITEM 8. FINANCIAL STATEMENTS AND SUPPLEMENTARY DATA

Report of Independent Registered Certified Public Accounting Firm

To the Shareholders and the Board of Directors of OPKO Health, Inc. and subsidiaries

Opinion on the Financial Statements

We have audited the accompanying consolidated balance sheets of OPKO Health, Inc. and subsidiaries (the Company) as of December 31, 2017 and 2016, the related consolidated statements of operations, comprehensive loss, equity and cash flows for each of the three years in the period ended December 31, 2017, and the related notes and financial statements schedule included at Item 15(a)(1) (collectively referred to as the "consolidated financial statements"). In our opinion, the consolidated financial statements present fairly, in all material respects, the financial position of the Company at December 31, 2017 and 2016, and the results of its operations and its cash flows for each of the three years in the period ended December 31, 2017, in conformity with U.S generally accepted accounting principles.

We also have audited, in accordance with the standards of the Public Company Accounting Oversight Board (United States) (PCAOB), the Company's internal control over financial reporting as of December 31, 2017, 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, 2018 expressed an unqualified opinion thereon.

Basis for Opinion

These financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on the Company's financial statements based on our audits. We are a public accounting firm registered with the PCAOB and are required to be independent with respect to the Company in accordance with the U.S. federal securities laws and the applicable rules and regulations of the Securities and Exchange Commission and the PCAOB.

We conducted our audits in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement, whether due to error or fraud. Our audits included performing procedures to assess the risks of material misstatement of the financial statements, whether due to error or fraud, and performing procedures that respond to those risks. Such procedures included examining, on a test bases, evidence regarding the amounts and disclosures in the financial statements. Our audits also included evaluating the accounting principles used and significant estimates made by management, as well as evaluating the overall presentation of the financial statements. We believe that our audits provide a reasonable basis for our opinion.

/s/ Ernst & Young LLP

We have served as the Company's auditor since 2007.

Miami, Florida
March 1, 2018

Report of Independent Registered Certified Public Accounting Firm

To the Shareholders and the Board of Directors of OPKO Health, Inc. and subsidiaries

Opinion on Internal Control over Financial Reporting

We have audited OPKO Health, Inc. and subsidiaries' internal control over financial reporting as of December 31, 2017, 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). In our opinion, OPKO Health, Inc. and subsidiaries (the Company) maintained, in all material respects, effective internal control over financial reporting as of December 31, 2017, based on the COSO criteria.

We also have audited, in accordance with the standards of the Public Company Accounting Oversight Board (United States) (PCAOB), the 2017 consolidated financial statements of the Company and our report dated March 1, 2018 expressed an unqualified opinion thereon.

Basis for Opinion

The Company's 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 are a public accounting firm registered with the PCAOB and are required to be independent with respect to the Company in accordance with the U.S. federal securities laws and the applicable rules and regulations of the Securities and Exchange Commission and the PCAOB.

We conducted our audit in accordance with the standards of the PCAOB. 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.

Definition and Limitations of Internal Control Over Financial Reporting

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.

/s/ Ernst & Young LLP

Miami, Florida
March 1, 2018

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

	December 31,	
	2017	2016
ASSETS		
Current assets:		
Cash and cash equivalents	$ 91,499	$ 168,733
Accounts receivable, net	165,516	220,284
Inventory, net	49,333	47,228
Other current assets and prepaid expenses	37,113	47,356
Total current assets	343,461	483,601
Property, plant and equipment, net	146,557	122,831
Intangible assets, net	683,835	763,976
In-process research and development	647,347	644,713
Goodwill	717,099	704,603
Investments	40,642	41,139
Other assets	5,615	5,756
Total assets	$ 2,584,556	$ 2,766,619
LIABILITIES AND EQUITY		
Current liabilities:		
Accounts payable	$ 74,307	$ 53,360
Accrued expenses	215,102	197,955
Current portion of lines of credit and notes payable	11,926	11,981
Total current liabilities	301,335	263,296
2033 Senior Notes, net of discount	29,160	43,701
Deferred tax liabilities, net	148,729	165,331
Other long-term liabilities, principally deferred revenue, contingent consideration and lines of credit	219,954	202,483
Total long-term liabilities	397,843	411,515
Total liabilities	699,178	674,811
Equity:		
Common Stock - $0.01 par value, 750,000,000 shares authorized; 560,023,745 and 558,576,051 shares issued at December 31, 2017 and 2016, respectively	5,600	5,586
Treasury Stock, at cost - 549,907 and 586,760 shares at December 31, 2017 and 2016, respectively	(1,791)	(1,911)
Additional paid-in capital	2,889,256	2,845,096
Accumulated other comprehensive income (loss)	(528)	(27,009)
Accumulated deficit	(1,007,159)	(729,954)
Total shareholders' equity	1,885,378	2,091,808
Total liabilities and equity	$ 2,584,556	$ 2,766,619

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,		
	2017	2016	2015
Revenues:			
Revenue from services	$ 889,076	$ 1,012,129	$ 329,739
Revenue from products	107,759	83,467	80,146
Revenue from transfer of intellectual property and other	70,668	126,065	81,853
Total revenues	1,067,503	1,221,661	491,738
Costs and expenses:			
Cost of service revenue	558,953	564,103	193,305
Cost of product revenue	61,177	47,379	41,934
Selling, general and administrative	520,994	490,888	196,576
Research and development	125,186	111,205	99,488
Contingent consideration	(3,423)	16,954	5,050
Amortization of intangible assets	84,678	64,407	27,977
Grant repayment	—	—	25,889
Total costs and expenses	1,347,565	1,294,936	590,219
Operating loss	(280,062)	(73,275)	(98,481)
Other income and (expense), net:			
Interest income	610	478	255
Interest expense	(6,601)	(7,430)	(8,419)
Fair value changes of derivative instruments, net	52	2,778	(39,083)
Other income (expense), net	10,457	3,903	7,730
Other income and (expense), net	4,518	(271)	(39,517)
Loss before income taxes and investment losses	(275,544)	(73,546)	(137,998)
Income tax benefit (provision)	(18,855)	56,115	113,675
Net loss before investment losses	(294,399)	(17,431)	(24,323)
Loss from investments in investees	(14,471)	(7,652)	(7,105)
Net loss	(308,870)	(25,083)	(31,428)
Less: Net loss attributable to noncontrolling interests	—	—	(1,400)
Net loss attributable to common shareholders	$ (308,870)	$ (25,083)	$ (30,028)
Loss per share, basic and diluted:			
Net loss per share	$ (0.55)	$ (0.05)	$ (0.06)
Weighted average number of common shares outstanding, basic and diluted	559,160,565	550,846,553	488,065,908

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,		
	2017	2016	2015
Net loss	$ (308,870)	$ (25,083)	$ (31,428)
Other comprehensive income (loss), net of tax:			
Change in foreign currency translation and other comprehensive income (loss)	22,724	(4,955)	(15,074)
Available for sale investments:			
Change in unrealized gain (loss), net of tax	3,790	(3,810)	(2,378)
Less: reclassification adjustments for losses included in net loss, net of tax	(33)	4,293	7,307
Comprehensive loss	(282,389)	(29,555)	(41,573)
Less: Comprehensive loss attributable to noncontrolling interest	—	—	(1,400)
Comprehensive loss attributable to common shareholders	$ (282,389)	$ (29,555)	$ (40,173)

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, 2017, 2016, 2015 (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, 2017, 2016, 2015 (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 EQUITY
(In thousands, except share and per share data)
For the years ended December 31, 2017, 2016, 2015 (continued)

	Common Stock		Treasury		Additional Paid-In Capital	Accumulated Other Comprehensive Loss	Accumulated Deficit	Total
	Shares	Dollars	Shares	Dollars				
Balance at December 31, 2016	558,576,051	$ 5,586	(586,760)	$ (1,911)	$ 2,845,096	$ (27,009)	$ (729,954)	$ 2,091,808
Equity-based compensation expense	—	—	—	—	28,307	—	—	28,307
Exercise of Common Stock options and warrants	1,447,694	14	—	—	2,118	—	—	2,132
Reclassification of embedded derivatives to equity	—	—	—	—	13,551	—	—	13,551
Issuance of Treasury Stock in connection with OPKO Health Europe's Contingent Consideration	—	—	36,853	120	184	—	—	304
Adoption of ASU 2016-09	—	—	—	—	—	—	31,665	31,665
Net loss attributable to common shareholders	—	—	—	—	—	—	(308,870)	(308,870)
Other comprehensive loss	—	—	—	—	—	26,481	—	26,481
Balance at December 31, 2017	560,023,745	$ 5,600	(549,907)	$ (1,791)	$ 2,889,256	$ (528)	$ (1,007,159)	$ 1,885,378

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,		
	2017	2016	2015
Cash flows from operating activities:			
Net loss	$ (308,870)	$ (25,083)	$ (31,428)
Adjustments to reconcile net loss to net cash provided by (used in) operating activities:			
Depreciation and amortization	102,093	96,576	42,248
Non-cash interest	2,575	2,699	2,612
Amortization of deferred financing costs	224	237	1,212
Losses from investments in investees	14,471	7,652	7,105
Equity-based compensation – employees and non-employees	28,307	42,693	26,074
Impairment of intangible assets	13,194	—	—
Revenue from receipt of equity	—	—	(140)
Realized loss (gain) on equity securities and disposal of fixed assets	(8,663)	2,321	7,091
Loss (gain) on conversion of 3.00% convertible senior notes	—	284	(943)
Change in fair value of derivative instruments	(52)	(2,778)	39,083
Change in fair value of contingent consideration	(3,423)	16,954	5,050
Gain on deconsolidation of SciVac	—	—	(15,940)
Deferred income tax provision (benefit)	16,092	(66,300)	(123,536)
Changes in assets and liabilities, net of the effects of acquisitions:			
Accounts receivable, net	58,011	(25,637)	(4,845)
Inventory, net	(3,539)	(6,607)	(4,953)
Other current assets and prepaid expenses	10,171	17,262	(4,391)
Other assets	(2,372)	(1,899)	(305)
Accounts payable	20,171	(19,819)	(18,122)
Foreign currency measurement	(255)	(376)	979
Deferred revenue	(60,656)	(74,169)	227,671
Accrued expenses and other liabilities	30,441	68,036	9,502
Net cash provided by (used in) operating activities	(92,080)	32,046	164,024
Cash flows from investing activities:			
Investments in investees	(9,625)	(14,424)	(4,375)
Proceeds from sale of equity securities	2,211	—	—
Acquisition of businesses, net of cash acquired	—	15,878	(79,000)
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	7,271	1,401	—
Capital expenditures	(46,524)	(18,547)	(10,846)
Net cash used in investing activities	(46,667)	(20,702)	(99,221)
Cash flows from financing activities:			
Proceeds from the exercise of Common Stock options and warrants	2,132	8,576	25,921
Cash from non-controlling interest	—	—	100
Borrowings on lines of credit	92,421	22,407	261,339
Repayments of lines of credit	(33,510)	(66,178)	(254,355)
Net cash provided by (used in) financing activities	61,043	(35,195)	33,005
Effect of exchange rate changes on cash and cash equivalents	470	(1,014)	(1,117)
Net (decrease) increase in cash and cash equivalents	(77,234)	(24,865)	96,691
Cash and cash equivalents at beginning of period	168,733	193,598	96,907
Cash and cash equivalents at end of period	$ 91,499	$ 168,733	$ 193,598
SUPPLEMENTAL INFORMATION:			
Interest paid	$ 1,313	$ 2,890	$ 4,572
Income taxes paid, net of refunds	$ 5,416	$ (27,122)	$ 4,879
Non-cash financing:			
Shares issued upon the conversion of:			
2033 Senior Notes	$ —	$ 583	$ 120,299
Common Stock options and warrants, surrendered in net			

exercise	$ 1,546	$ 350	$ 14,369
Issuance of capital stock to acquire or contingent consideration settlement:			
Transition Therapeutics, Inc.	$ —	$ 58,530	$ —
BioReference Laboratories, Inc.	$ —	$ —	$ 950,148
EirGen Pharma Limited	$ —	$ —	$ 33,569
OPKO Renal	$ —	$ 25,986	$ 20,113
OPKO Health Europe	$ 303	$ 313	$ 1,813
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 BioReference Laboratories, Inc. ("BioReference"), the nation's third-largest clinical laboratory with a core genetic testing business and an almost 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 IV formulation launched November 2017), OPK88003, 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 OPK88004, a selective androgen receptor modulator being developed for benign prostatic hyperplasia and other urologic and metabolic conditions. Our pharmaceutical business also features hGH-CTP, a once-weekly human growth hormone injection (in Phase 3 and partnered with Pfizer), and a once-daily Factor VIIa drug for hemophilia (Phase 2a). 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 OPK88003, a once or twice weekly oxyntomodulin for type 2 diabetes and obesity, and OPK88004, a selective 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.

Through BioReference, 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.

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 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 and 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 and net realizable value. Inventories at our diagnostics segment consist primarily of purchased laboratory supplies, which is used in our testing laboratories. Inventory obsolescence for the years ended December 31, 2017 and 2016 was $5.4 million and $0.0 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, 2017 and 2016, were $2.0 billion and $2.1 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 recorded an impairment charge of $13.2 million in Amortization of intangible assets in our Consolidated Statement of Operations for the year ended December 31, 2017 to write our intangible asset for VARUBI™ down to its estimated fair value. No intangible asset impairment was recorded for the year ended December 31, 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 Sheets upon the FDA's approval of *Rayaldee* in June 2016. The assets are being 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 $84.7 million, $64.4 million and $28.0 million for the years ended December 31, 2017, 2016 and 2015, respectively. Amortization expense from operations

for our intangible assets is expected to be $66.9 million, $64.2 million, $58.2 million, $52.2 million and $51.9 million for the years ended December 31, 2018, 2019, 2020, 2021 and 2022, 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, 2017 and 2016 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, 2017 and 2016, 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 - 5-12 years, leasehold improvements - the lesser of their useful life or the lease term, buildings and improvements - 10-40 years, automobiles - 3-5 years. Expenditures for repairs and maintenance are charged to expense as incurred. Depreciation expense was $30.6 million, $33.3 million and $14.2 million for the years ended December 31, 2017, 2016 and 2015, respectively. Assets held under capital leases are included within Property, plant and equipment, net in our Consolidated Balance Sheets 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.

On December 22, 2017, the 2017 Tax Cuts and Jobs Act (the “Tax Act”) was enacted into law and the new legislation contains several key tax provisions, including a reduction of the corporate income tax rate from 35% to 21% effective January 1, 2018, and a one-time mandatory transition tax on accumulated foreign earnings, among others. The Tax Act required us to remeasure our U.S. deferred tax assets and liabilities and recognize the effect in the period of enactment, which resulted in an income tax charge of $31.8 million for the year ended December 31, 2017, with an equal offset to valuation allowance. We are

required to recognize the effect of the tax law changes in the period of enactment, such as remeasuring our U.S. deferred tax assets and liabilities, as well as reassessing the net realizability of our deferred tax assets and liabilities. In December 2017, the SEC staff issued Staff Accounting Bulletin No. 118, Income Tax Accounting Implications of the Tax Cuts and Jobs Act (SAB 118), which allows us to record provisional amounts during a measurement period not to extend beyond one year of the enactment date. Since the Tax Act was passed late in the fourth quarter of 2017, and ongoing guidance and accounting interpretation are expected over the next 12 months, our accounting of deferred tax re-measurements, the transition tax, and other items are provisional and may materially change due to the forthcoming guidance and our ongoing analysis of final year-end data and tax positions. We expect to complete our analysis within the measurement period in accordance with SAB 118.

We anticipate future impacts at a U.S. state and local tax level related to the Tax Act; however, statutory and interpretive guidance is not available from applicable state and local tax authorities to reasonably estimate the impact. Consequently, for those jurisdictions, we have not recorded provisional amounts and have continued to apply ASC 740 based on the provisions of the tax laws that were in effect immediately prior to Tax Act enactment.

We operate in various countries and tax jurisdictions globally. For the year ended December 31, 2017, 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 establishment of a valuation allowance in the U.S. and operating results in tax jurisdictions which do not result in a tax benefit.

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 payor programs including various managed care organizations, as well as the Medicare and Medicaid programs. For the year ended December 31, 2017, approximately 31% of our revenues from services were derived directly from 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.

The complexities and ambiguities of billing, reimbursement regulations and claims processing, as well as issues unique to Medicare and Medicaid programs, require us to estimate the potential for retroactive adjustments in the recognition of revenue in the period the related services are rendered. Adjustments to the estimated collection amounts are recorded upon settlement as an adjustment to revenue.

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 healthcare providers and payers that provide for government-mandated and/or privately-negotiated rebates, chargebacks and discounts with respect to the purchase of *Rayaldee*.

As of December 31, 2017, allowances for Sales Deductions and product returns related to sales of *Rayaldee* are known or estimable utilizing historical information and market research projections. As a result, we recognize revenue for shipments of *Rayaldee* at the time of delivery to *Rayaldee* Customers. For the year ended December 31, 2017, we recognized $9.1 million in net product revenue from sales of *Rayaldee*, including amounts previously deferred. No revenue was recognized from sales of *Rayaldee* for the year ended December 31, 2016 as we lacked the experiential data which would allow us to estimate Sales Deductions and product returns. The related deferred revenue balance as of December 31, 2016 was $1.6 million.

The following table presents an analysis of product sales allowances and accruals for the year ended December 31, 2017:

(In thousands)	Chargebacks, discounts, rebates and fees	Governmental	Returns	Total
Balance at December 31, 2016	$ —	$ —	$ —	$ —
Provision related to current period sales	1,591	1,332	490	3,413
Credits or payments made	(1,358)	(984)	(53)	(2,395)
Balance at December 31, 2017	$ 233	$ 348	$ 437	$ 1,018

Total gross *Rayaldee* sales	$ 12,482
Provision for *Rayaldee* sales allowances and accruals as a percentage of gross *Rayaldee* sales	27%

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, 2017, 2016 and 2015 we recorded $70.7 million, $126.1 million and $81.9 million of revenue from the transfer of intellectual property, respectively. For the year ended December 31, 2017, revenue from the transfer of intellectual property included $57.8 million related to the Pfizer Transaction and $10.0 million related to a milestone payment that TESARO, Inc. (“TESARO”) paid us under our license agreement with them. Refer to Note 14. 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. 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 paid us under our license agreement with them and $65.5 million related to the Pfizer Transaction.

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 $105.2 million and $162.4 million at December 31, 2017 and 2016, respectively. The deferred revenue balance at December 31, 2017 and 2016 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 healthcare programs are funded by federal and state governments, and payment is

primarily dependent upon submitting appropriate documentation. At December 31, 2017 and 2016, receivable balances (net of contractual adjustments) from Medicare and Medicaid in total were 16% and 23%, respectively, of our consolidated Accounts receivable, net.

The portion of our accounts receivable due from individual patients comprises the largest portion of credit risk. At December 31, 2017 and 2016, receivables due from patients represent approximately 3.2% and 4.1%, respectively, of our consolidated Accounts receivable, net.

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 $66.4 million and $36.3 million at December 31, 2017 and 2016, respectively. The provision for bad debts for the years ended December 31, 2017 and 2016 was $107.3 million and $83.5 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 cash flows 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, 2017, 2016 and 2015, we recorded $28.3 million, $42.7 million and $26.1 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 in 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 BioReference 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, 2017, 2016 and 2015, we recorded $1.4 million, $0.8 million and $(2.4) million, respectively of transaction gains (losses).

Variable interest entities. The consolidation of a variable interest entity ("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. 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 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 plan to adopt the ASU in the first quarter of 2018 using the full retrospective approach.

We continue to assess the impact of this ASU on our financial condition, results of operations, cash flows and disclosures. Our analysis includes reviewing current accounting policies and practices to identify potential differences that would result from applying the requirements under this new standard. We have reviewed certain contracts with its customers that we believe are representative of our revenue streams and continue to review additional contracts across our global business units. ASU 2014-09 requires increased disclosure which in turn is expected to require certain new processes. The determination of the impact of adoption of ASU 2014-09 on our financial condition, results of operations, cash flows and disclosures is ongoing, and, as such, we are not able to reasonably estimate the quantitative effect that the adoption of the new standard will have on our financial statements. Based on our preliminary assessment of this ASU, for our diagnostics segment, we generally do not expect any significant changes to the timing of revenue recognition or net income, but there will be a change in the presentation in the Statement of Operations. Under the ASU, the majority of the amounts that were historically classified as provision for bad debts, primarily related to patient responsibility, will be considered an implicit price concession in determining net revenues. Accordingly, we will report uncollectible balances associated with individual patients as a reduction of the transaction price and therefore as a reduction in net revenues when historically these amounts were classified as provision for bad debts within Selling, general and administrative expenses.

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 was effective for fiscal years beginning after December 15, 2016, including interim periods within those fiscal years, with early adoption permitted. The adoption of ASU 2015-11 in the first quarter of 2017 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. 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. 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 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, 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, but the primary effect will be the recognition of changes in the fair value of our available for sale investments in net income.

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 was effective for fiscal years beginning after December 15, 2016, including interim periods within those fiscal years, with early adoption permitted. We adopted this standard in the first quarter of 2017. As required by ASU 2016-09, excess tax benefits are classified as an operating activity in our Consolidated Statement of Cash Flows and we have applied this provision prospectively. In addition, we have elected to estimate forfeitures over the course of a vesting period, rather than account for forfeitures as they occur. We adjust our forfeiture estimates based on the number of share-based awards that ultimately vest on at least an annual basis. As a result of the adoption of ASU 2016-09 in 2017, we recorded a cumulative-effect adjustment to reduce our deferred tax liabilities and reduce our accumulated deficit by $31.7 million with respect to excess tax benefits recognized in our Consolidated Balance Sheets.

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, for the years ended December 31, 2016 and 2015, conversion options of the 2033 Senior Notes is determined by applying the “treasury stock” method. For the year ended December 31, 2017, the 2033 Senior Notes have been considered using the “if converted” 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 6,255,624, 9,494,999 and 14,269,717 potential shares of Common Stock have been excluded from the calculation of diluted net loss per share for the years ended December 31, 2017, 2016 and 2015, respectively, because their inclusion would be antidilutive. A full presentation of diluted earnings per share has not been provided because the required adjustments to the numerator and denominator resulted in diluted earnings per share equivalent to basic earnings per share.

During the year ended December 31, 2017, 1,720,649 Common Stock options and Common Stock warrants to purchase shares of our Common Stock were exercised, resulting in the issuance of 1,447,792 shares of Common Stock. Of the 1,720,649 Common Stock options and Common Stock warrants exercised, 272,857 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, 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.

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 final purchase price allocation and the fair value of the net assets acquired and liabilities assumed at the date of acquisition:

(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.

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.

Investments

The following table reflects the accounting method, carrying value and underlying equity in net assets of our unconsolidated investments as of December 31, 2017:

(in thousands)

Investment type	Investment Carrying Value	Underlying Equity in Net Assets
Equity method investments	$ 23,338	$ 18,210
Variable interest entity, equity method	402	—
Available for sale investments	12,461	
Cost method investment	1,108	
Warrants and options	3,333	
Total carrying value of investments	$ 40,642	

Equity method investments

Our equity method investments consist of investments in Pharmsynthez (ownership 9%), Cocrystal Pharma, Inc. ("COCP") (9%), Non-Invasive Monitoring Systems, Inc. ("NIMS") (1%), Neovasc Inc. (5%), VBI Vaccines Inc. ("VBI") (10%), InCellDx, Inc. (29%), BioCardia, Inc. ("BioCardia") (5%), and Xenetic Biosciences, Inc. ("Xenetic") (4%). The total assets, liabilities, and net losses of our equity method investees as of and for the year ended December 31, 2017 were $396.3 million, $201.8 million, and $130.9 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, 2017 is $54.8 million.

Available for sale investments

Our available for sale investments consist of investments in RXi Pharmaceuticals Corporation ("RXi") (ownership 2%), ChromaDex Corporation (1%), MabVax Therapeutics Holdings, Inc. ("MabVax") (2%) and Eloxx Pharmaceuticals, Inc. (5%). 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 investment in Xenetic, including Xenetic's decreasing stock price during the year ended December 31, 2017, we determined that the decline in fair value of our Xenetic common shares was other-than-temporary and recorded an impairment charge of $0.6 million in Other income (expense), net in our Consolidated Statement of Operations for the year ended December 31, 2017 to write our investment in Xenetic down to its fair value as of December 31, 2017.

Based on our evaluation of the value of our investments in Xenetic, RXi and ARNO, including their decreasing stock price during the year ended December 31, 2016, we determined that the decline in fair value of our common shares in Xenetic, RXi and ARNO was other-than-temporary and recorded an impairment charge of $4.8 million in Other income (expense), net in our Consolidated Statement of Operations for the year ended December 31, 2016 to write our investments in Xenetic, RXi and ARNO down to their respective fair values as of December 31, 2016.

In December 2017, Eloxx Pharmaceuticals Ltd. and Sevion Therapeutics, Inc. completed their acquisition transaction. The company will be known as Eloxx Pharmaceuticals, Inc. ("Eloxx") following completion of the transaction. We recorded a $2.5 million gain in connection with the acquisition transaction in Other income (expense), net in our Consolidated Statement of Operations for the year ended December 31, 2017. We account for our investment in Eloxx as an available for sale investment.

Sales of investments

Gains included in earnings from sale of our investments for the year ended December 31, 2017, were $1.5 million and were recorded in Other income (expense), net in our Consolidated Statement of Operations. No gains (losses) were recognized during the years ended December 31, 2016 and 2015. The cost of securities sold is based on the specific identification method.

Warrants and options

In addition to our equity method investments and available for sale investments, we hold options to purchase 0.4 million additional shares of BioCardia, 0.1 million of which are vested as of December 31, 2017, and 1.0 million, 0.7 million, 0.5 million, 0.2 million and 4.9 million of warrants to purchase additional shares of COCP, InCellDx, Inc., Xenetic, RXi and Neovasc, 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 29% at December 31, 2017). 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 have 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.

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

We recorded $8.8 million of expense in Selling, general and administrative expenses in our Consolidated Statement of Operations for the year ended December 31, 2017 to write certain Other current assets from our investees down to their estimated fair value.

Note 5 Composition of Certain Financial Statement Captions

(In thousands)	For the years ended December 31, 2017	2016
Accounts receivable, net		
Accounts receivable	$ 231,940	$ 256,552
Less: allowance for doubtful accounts	(66,424)	(36,268)
	$ 165,516	$ 220,284
Inventories, net		
Consumable supplies	$ 21,546	$ 23,448
Finished products	21,012	16,143
Work in-process	5,873	3,896
Raw materials	7,467	4,686
Less: inventory reserve	(6,565)	(945)
	$ 49,333	$ 47,228
Other current assets and prepaid expenses		
Other receivables	$ 3,398	$ 13,021
Taxes recoverable	18,138	16,187
Prepaid supplies	8,207	6,952
Prepaid insurance	3,532	3,688
Other	3,838	7,508
	$ 37,113	$ 47,356
Property, plant and equipment, net:		
Machinery, medical and other equipment	$ 112,961	$ 100,100
Leasehold improvements	34,121	30,122
Furniture and fixtures	11,540	11,247
Automobiles and aircraft	11,137	13,342
Software	12,469	10,990
Building	8,227	5,696
Land	2,552	2,264
Construction in process	39,397	5,848
Less: accumulated depreciation	(85,847)	(56,778)
	$ 146,557	$ 122,831
Intangible assets, net:		
Customer relationships	$ 448,345	$ 443,560
Technologies	340,921	340,397
Trade names	50,553	50,442
Covenants not to compete	16,372	16,348
Licenses	10,305	23,506
Product registrations	10,475	7,641
Other	5,799	5,289
Less: accumulated amortization	(198,935)	(123,207)
	$ 683,835	$ 763,976
Accrued expenses:		
Deferred revenue	$ 46,189	$ 73,434
Employee benefits	50,377	43,792
Taxes payable	4,609	4,430
Contingent consideration	11,750	259

(In thousands)	For the years ended December 31, 2017	2016
Clinical trials	12,191	5,935
Capital leases short-term	3,399	3,025
Milestone payment	4,868	4,865
Professional fees	2,355	4,035
Other	79,364	58,180
	$ 215,102	$ 197,955
Other long-term liabilities:		
Deferred revenue	$ 58,989	$ 89,016
Line of credit	104,152	38,809
Contingent consideration	29,603	44,817
Capital leases long-term	7,786	7,216
Mortgages and other debts payable	1,567	717
Other	17,857	21,908
	$ 219,954	$ 202,483

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
BioReference	$ 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 BioReference. 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.

The changes in value of the intangible assets and goodwill during 2017 are primarily due to foreign currency fluctuations between the Chilean Peso, the Euro and the Shekel against the U.S. dollar. For the year ended December 31, 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 upon the FDA's approval of *Rayaldee* in June 2016. In addition, we made certain purchase price allocation adjustments related to the BioReference acquisition during the year ended December 31, 2016.

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
2017					
Allowance for doubtful accounts	$ (36,268)	(107,256)	77,047	53	$ (66,424)
Inventory reserve	$ (945)	(5,390)	(230)	—	$ (6,565)
Tax valuation allowance	$ (55,415)	(82,358)	—	(4,289)	$ (142,062)
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)

The following table summarizes the changes in Goodwill during the years ended December 31, 2017 and 2016.

	2017				2016			
(In thousands)	Balance at January 1	Purchase Accounting Adj	Foreign exchange and other	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	78,358	—	10,868	89,226	81,139	—	(2,781)	78,358
FineTech	11,698	—	—	11,698	11,698	—	—	11,698
OPKO Biologics	139,784	—	—	139,784	139,784	—	—	139,784
OPKO Chile	4,785	—	418	5,203	4,517	—	268	4,785
OPKO Health Europe	6,936	—	962	7,898	7,191	—	(255)	6,936
OPKO Renal	2,069	—	—	2,069	2,069	—	—	2,069
Transition Therapeutics	3,360	—	248	3,608	—	3,453	(93)	3,360
Diagnostics								
BioReference	401,821	—	—	401,821	441,158	(39,337)	—	401,821
OPKO Diagnostics	17,977	—	—	17,977	17,977	—	—	17,977
OPKO Lab	32,988	—	—	32,988	32,988	—	—	32,988
	$ 704,603	$ —	$ 12,496	$ 717,099	$ 743,348	$ (35,884)	$ (2,861)	$ 704,603

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, as amended (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 3.0% 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, 2017:

(In thousands)	Embedded conversion option	2033 Senior Notes	Discount	Debt Issuance Cost	Total
Balance at December 31, 2016	$ 16,736	$ 31,850	$ (4,612)	$ (273)	$ 43,701
Amortization of debt discount and debt issuance costs	—	—	2,047	148	2,195
Change in fair value of embedded derivative	(3,185)	—	—	—	(3,185)
Reclassification of embedded derivatives to equity	(13,551)	—	—	—	(13,551)
Balance at December 31, 2017	$ —	$ 31,850	$ (2,565)	$ (125)	$ 29,160

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 and debt issuance costs	—	—	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 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.

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 determined that these specific terms were 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 concluded that the embedded derivatives within the 2033 Senior Notes meet these criteria for periods prior to February 1, 2017 and, as such, were valued separate and apart from the 2033 Senior Notes and recorded at fair value each reporting period.

For accounting and financial reporting purposes, prior to 2017 we combined these embedded derivatives and valued them together as one unit of accounting.

On February 1, 2017, certain terms of the embedded derivatives expired pursuant to the original agreement and we determined that the embedded derivatives no longer met the criteria to be separated from the host contract and, as a result, the embedded derivatives are no longer required to be valued separate and apart from the 2033 Senior Notes and are not required to be measured at fair value subsequent to February 1, 2017.

The change in derivative income for the period from January 1, 2017 to February 1, 2017 related to the embedded derivatives was $3.2 million and the fair value at that date was $13.6 million. As the embedded derivatives are no longer required to be accounted for separately each period, the embedded derivative fair value of $13.6 million as of February 1, 2017 was reclassified to additional paid in capital.

From 2013 to 2016, holders of the 2033 Senior Notes converted 143.2 million in aggregate principal amount into an aggregate of 21,539,873 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, 2016 and the first quarter of 2017. They may become convertible again 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.

Through February 1, 2017, 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:

	February 1, 2017	December 31, 2016	December 31, 2015
Stock price	$8.63	$9.30	$10.05
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%	1.22%	1.33%
Estimated stock volatility	49%	47%	50%
Estimated credit spread	761 basis points	765 basis points	1,142 basis points

On November 5, 2015, BioReference 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 BioReference'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. BioReference 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 BioReference's domestic subsidiaries. The Credit Agreement is also secured by substantially all assets of BioReference and its domestic subsidiaries, as well as a non-recourse pledge by us of our equity interest in BioReference. Availability under the Credit Agreement is based on a borrowing base comprised of eligible accounts receivables of BioReference and certain of its subsidiaries, as specified therein. As of December 31, 2017, the total availability under our Credit Agreement with CB was $104.2 million. Principal under the Credit Agreement is due upon maturity on November 5, 2020.

At BioReference'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 0.50% of the lending commitments.

On March 17, 2017, BioReference and certain of its subsidiaries entered into Amendment No. 3 to Credit Agreement, which amended the Credit Agreement to permit BioReference and its subsidiaries to dividend cash to the Company in the form of an intercompany loan, in an aggregate amount not to exceed $55.0 million. On August 7, 2017, BioReference and certain of its subsidiaries entered into Amendment No. 4 to Credit Agreement, which amended the Credit Agreement to permit BioReference and its subsidiaries to dividend cash to the Company in the form of an additional intercompany loan, in an aggregate amount not to exceed $35.0 million. On November 8, 2017, BioReference and certain of its subsidiaries entered into Amendment No. 5 to Credit Agreement, which amended the Credit Agreement to, among other things, ease certain thresholds that require increased reporting by BioReference and reduce the pro forma availability condition for BioReference to make certain cash dividends to the Company. On December 22, 2017, BioReference and certain of its subsidiaries entered into Amendment No. 6 to Credit Agreement, which amended the Credit Agreement to, among other things, permit BioReference and its subsidiaries to dividend cash to the Company in the form of intercompany loans, in an aggregate amount not to exceed $45.0 million. The other terms of the Credit Agreement remain unchanged.

The Credit Agreement contains customary covenants and restrictions, including, without limitation, covenants that require BioReference 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 BioReference 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 BioReference 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 BioReference and its subsidiaries are restricted from sale, transfer, lease, disposal or distributions to the Company, subject to certain exceptions. BioReference and its subsidiaries net assets as of December 31, 2017 were approximately $0.9 billion, which includes goodwill of $401.8 million and intangible assets of $446.5 million.

In addition to the Credit Agreement with CB, we have line of credit agreements with eleven other financial institutions as of December 31, 2017 and ten other financial institutions as of December 31, 2016 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 BioReference, Chilean and Spanish lines of credit:

(Dollars in thousands)			Balance Outstanding	
Lender	Interest rate on borrowings at December 31, 2017	Credit line capacity	December 31, 2017	December 31, 2016
JP Morgan Chase	3.27%	$ 175,000	$ 104,152	$ 38,809
Itau Bank	5.50%	1,810	446	419
Bank of Chile	6.60%	3,800	1,598	1,619
BICE Bank	5.50%	2,500	1,819	1,538
BBVA Bank	5.50%	3,250	1,665	1,063
Security Bank	5.50%	501	501	—
Estado Bank	5.50%	3,500	2,111	1,870
Santander Bank	5.50%	4,500	1,988	1,196
Scotiabank	5.00%	1,800	384	789
Corpbanca	5.00%	—	—	18
Banco Bilbao Vizcaya	2.90%	300	—	—
Santander Bank	2.67%	359	—	—
Total		$ 197,320	$ 114,664	$ 47,321

At December 31, 2017 and 2016, the weighted average interest rate on our lines of credit was approximately 4.2% and 4.7%, respectively.

At December 31, 2017 and 2016, 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, 2017	December 31, 2016
Current portion of notes payable	$ 1,632	$ 3,681
Other long-term liabilities	2,011	2,090
Total	$ 3,643	$ 5,771

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, 2017 and 2016, was 3.0% and 3.2%, 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, 2017.

	Number of warrants	Weighted average exercise price	Expiration date
Outstanding at December 31, 2016	639,598	$ 0.86	Various from January 2017 through March 2017
Exercised	(416,295)	0.86	
Expired	(223,303)	0.86	
Outstanding and Exercisable at December 31, 2017	—	$ —	

Of the 416,295 Common Stock warrants exercised, 6,895 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, 2017 and 2016, 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, 2017, 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, 2016	$ (28,128)	$ 1,119	$ (27,009)
Other comprehensive income (loss) before reclassifications	22,724	3,790	26,514
Reclassification adjustments for losses included in net loss, net of tax	—	(33)	(33)
Net other comprehensive income (loss)	22,724	3,757	26,481
Balance at December 31, 2017	$ (5,404)	$ 4,876	$ (528)

Amounts reclassified from Accumulated other comprehensive income (loss) for the year ended December 31, 2017 includes an other-than-temporary impairment charge on our investment in Xenetic 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, 2016, 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, 2015	$ (23,174)	$ 637	$ (22,537)
Other comprehensive income (loss) before reclassifications	(4,954)	(3,811)	(8,765)
Reclassification adjustments for losses included in net loss, net of tax	—	4,293	4,293
Net other comprehensive income (loss)	(4,954)	482	(4,472)
Balance at December 31, 2016	$ (28,128)	$ 1,119	$ (27,009)

Amounts reclassified from Accumulated other comprehensive income (loss) for the year ended December 31, 2016 includes an 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.

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 cash flows from operations. There were no excess tax benefits for the years ended December 31, 2017, 2016, and 2015.

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 $28.3 million, $42.7 million and $26.1 million for the years ended December 31, 2017, 2016, and 2015, respectively, all of which were reflected as operating expenses. Of the $28.3 million of equity based compensation expense recorded in the year ended December 31, 2017, $21.2 million was recorded as selling, general and administrative expenses, $5.1 million was recorded as research and development expenses and $2.0 million was recorded as a cost of revenue. 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 expense, $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, $7.9 million was recorded as research and development expenses and 0.8 million was recorded as cost of revenue.

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, 2017, there was $40.4 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, 2017	Year Ended December 31, 2016	Year Ended December 31, 2015
Expected term (in years)	3.0 - 10.0	1.0 - 10.0	1.0 - 10.0
Risk-free interest rate	1.32% - 2.41%	0.71% - 2.51%	0.26% - 2.42%
Expected volatility	38% - 55%	38% - 64%	32% - 64%
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, 2017, there were 28,901,409 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 BioReference, 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, 2017, 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, 2016	34,640,514	$ 10.18	6.79	$ 32,984
Granted	2,131,500	$ 7.50		
Exercised	(1,298,704)	$ 3.01		
Forfeited	(2,735,813)	$ 11.75		
Expired	(1,438,112)	$ 11.84		
Outstanding at December 31, 2017	31,299,385	$ 10.08	6.37	$ 1,886
Vested and expected to vest at December 31, 2017	29,484,888	$ 10.04	6.27	$ 1,886
Exercisable at December 31, 2017	18,697,466	$ 9.59	5.26	$ 1,886

The total intrinsic value of stock options exercised for the years ended December 31, 2017, 2016, and 2015 was $6.4 million, $9.9 million and $69.9 million, respectively.

The weighted average grant date fair value of stock options granted for the years ended December 31, 2017, 2016, and 2015 was $4.50, $4.78, and $5.00, respectively. The total fair value of stock options vested during the years ended December 31, 2017, 2016, and 2015 was $34 million, $30.2 million and $13.3 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)	2017	2016	2015
Current			
Federal	$ 2,398	$ —	$ 430
State	(1,737)	(2,931)	(2,157)
Foreign	(3,424)	(2,438)	(8,134)
	(2,763)	(5,369)	(9,861)
Deferred			
Federal	(10,759)	25,739	109,286
State	(2,738)	10,657	12,327
Foreign	(2,595)	25,088	1,923
	(16,092)	61,484	123,536
Total, net	$ (18,855)	$ 56,115	$ 113,675

Deferred income tax assets and liabilities as of December 31, 2017 and 2016 are comprised of the following:

(In thousands)	December 31, 2017	December 31, 2016
Deferred income tax assets:		
Federal net operating loss	$ 79,356	$ 76,792
State net operating loss	46,571	36,285
Foreign net operating loss	35,710	32,895
Research and development expense	4,038	3,246
Tax credits	20,040	20,894
Stock options	28,830	36,485
Accruals	5,719	8,306
Equity investments	8,454	7,011
Bad debts	20,302	14,283
Lease liability	2,205	3,233
Foreign credits	11,113	10,253
Available for sale securities	2,406	4,792
Other	17,448	7,795
Deferred income tax assets	282,192	262,270
Deferred income tax liabilities:		
Intangible assets	(280,962)	(354,043)
Fixed assets	(5,572)	(13,710)
Other	(2,325)	(2,121)
Deferred income tax liabilities	(288,859)	(369,874)
Net deferred income tax liabilities	(6,667)	(107,604)
Valuation allowance	(142,062)	(55,415)
Net deferred income tax liabilities	$ (148,729)	$ (163,019)

As of December 31, 2017, we have federal, state and foreign net operating loss carryforwards of approximately $488.7 million, $602.9 million and $146.9 million, respectively, that expire at various dates through 2037. Included in the foreign net operating losses is $95.8 million related to OPKO Biologics. As of December 31, 2017, we have research and development tax credit carryforwards of approximately $20.0 million that expire in varying amounts through 2037. 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. The Company has evaluated realization of its U.S. and non-U.S. deferred tax assets and has determined that certain deferred tax assets, primarily those generated in 2017, will more likely than not be unrealized. As a result, a valuation allowance of $82.4 million was recorded as of December 31, 2017.

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 $488.7 million of federal net operating loss carryforwards, at least approximately $53.4 million may not be able to be utilized.

Tax Cuts and Jobs Act

On December 22, 2017, the Tax Act was signed into law making significant changes to the Internal Revenue Code. Changes include, but are not limited to, a federal corporate tax rate decrease from 35% to 21%, effective for tax years beginning January 1, 2018, the transition of U.S. international taxation from a worldwide tax system to a territorial system, and a one-time transition tax on the mandatory deemed repatriation of cumulative foreign earnings.

In December 2017, the SEC staff issued Staff Accounting Bulletin No. 118, Income Tax Accounting Implications of the Tax Cuts and Jobs Act (SAB118), which allows us to record provisional amounts during a measurement period not to extend beyond one year of the enactment date. Since the Tax Act was passed late in the fourth quarter of 2017, and ongoing guidance and accounting interpretation are expected over the next 12 months, our accounting of deferred tax re-measurements, the transition tax, and other items are provisional and may materially change due to the forthcoming guidance and our ongoing analysis of final yearend data and tax positions. We expect to complete our analysis within the measurement period in accordance with SAB 118.

As a result of changes made by the Tax Cuts and Jobs Act, starting with compensation paid in 2018, Section 162(m) will limit us from deducting compensation, including performance-based compensation, in excess of $1.0 million paid to anyone who, starting in 2018, serves as the Chief Executive Officer or Chief Financial Officer, or who is among the three most highly compensated executive officers for any fiscal year. Because many different factors influence a well-rounded, comprehensive executive compensation program, and as a result of the changes made to Code Section 162(m) by the Tax Cuts and Jobs Act, some of the compensation we provide to our executive officers may not be deductible as a result of Code Section 162(m) if our Committee believes it will contribute to the achievement of our business objectives.

We anticipate future impacts at a U.S. state and local tax level related to the Tax Act; however, statutory and interpretive guidance is not available from applicable state and local tax authorities to reasonably estimate the impact. Consequently, we have not recorded provisional amounts and have continued to apply ASC 740 based on the provisions of the tax laws that were in effect immediately prior to Tax Act enactment.

The Tax Act affects the tax treatment of foreign earnings and profits ("E&P") and results in a one-time transition tax on our post-1986 foreign E&P that we previously deferred from U.S. income tax expense. We have provisionally determined that we will not owe any transition tax and we have not provided for additional income taxes on any remaining undistributed foreign E&P not subject to the transition tax, or any outside tax basis differences inherent in our foreign subsidiaries.

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, Quebec and Nova Scotia 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 2014. However, because we are carrying forward income tax attributes, such as net operating losses and tax credits from 2014 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 2014 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 2014.

Foreign: Under the statute of limitations applicable to our foreign operations, we are generally no longer subject to tax examination for years before 2012 in jurisdictions where we have filed income tax returns.

Unrecognized Tax Benefits

As of December 31, 2017, 2016, and 2015, the total amount of gross unrecognized tax benefits was approximately $21.3 million, $27.5 million, and $8.6 million, respectively. As of December 31, 2017, the total gross unrecognized tax benefit of $21.3 million consisted of increases of $0.0 million as a result of current year activity, and decreases of $4.5 million as a result of the lapse of statutes of limitations. As of December 31, 2017, the total amount of unrecognized tax benefits that, if recognized, would affect our effective income tax rate was $(12.4) million. We account for any applicable interest and penalties on uncertain tax positions as a component of income tax expense and we recognized $0.4 million and $0.1 million of interest expense for the years ended December 31, 2017 and 2016, respectively. As of December 31, 2016 and 2015, $6.1 million and $0.7 million of the unrecognized tax benefits, if recognized, would have affected our effective income tax rate. We believe it is reasonably possible that approximately $4.6 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)	2017	2016	2015
Unrecognized tax benefits at beginning of period	$ 27,545	$ 8,595	$ 5,890
Gross increases – tax positions in prior period	44	1,443	955
Gross increases – tax positions in current period	—	18,472	2,543
Gross decreases – tax positions in prior period	(1,724)	(671)	(176)
Lapse of Statute of Limitations	(4,518)	(294)	(617)
Unrecognized tax benefits at end of period	$ 21,347	$ 27,545	$ 8,595

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,		
	2017	2016	2015
Federal statutory rate	35.0 %	35.0 %	35.0 %
State income taxes, net of federal benefit	5.1 %	5.2 %	2.8 %
Foreign income tax	(5.2)%	1.2 %	(7.8)%
Research and development tax credits	0.6 %	5.4 %	— %
Non-Deductible components of Convertible Debt	0.1 %	2.2 %	(9.4)%
Valuation allowance	(28.4)%	9.5 %	61.1 %
Rate change effect	(10.8)%	21.2 %	— %
Non-deductible items	(1.9)%	(1.9)%	(0.7)%
Other	(1.0)%	(8.7)%	(1.0)%
Total	(6.5)%	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)	2017	2016	2015
Pre-tax income (loss):			
U.S.	$ (247,938)	$ (92,175)	$ (113,612)
Foreign	(42,077)	10,977	(30,091)
Total	$ (290,015)	$ (81,198)	$ (143,703)

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. 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 29%), Neovasc (5%), ChromaDex Corporation (1%), MabVax (2%), COCP (9%), 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 December 2017, Sevion and Eloxx completed their acquisition transaction, and the combined company is known as Eloxx Pharmaceuticals, Inc. following completion of the transaction. Subsequent to the acquisition transaction in December 2017, Eloxx Pharmaceuticals, Inc. is not a related party of OPKO. In June 2017, we invested $1.5 million in Eloxx for 99,915 Preferred C Shares and in July 2017, we invested an additional $1.5 million in Sevion for 10,000,000 shares of Sevion common stock. An entity controlled by Dr. Frost also made an investment in Eloxx. Previously, in November 2016, we made a $0.2 million loan to Sevion, and in February 2017, we entered into an agreement with Sevion pursuant to which we delivered $0.3 million cash to Sevion in exchange for a promissory note. The loan and promissory note were converted into 4.1 million shares of Sevion common stock in August 2017. In September 2017, we converted 66,667 shares of Series C Preferred Stock of Sevion into 1,250,006 shares of common stock. The agreements with Sevion were considered related party transactions as a result of our executive management's ownership interests and board representation in Sevion. Steve Rubin, a member of our Board of Directors and Executive Vice President, serves as a director of Eloxx.

In November 2017, we invested an additional $3.0 million in Neovasc for 2,054,794 shares of its common stock, 2,054,794 Series A warrants, 2,054,794 Series B warrants and 822,192 Series C warrants.

In July 2017, we invested an additional $0.1 million in MabVax for 152,143 shares of common stock and in May 2017, we invested an additional $0.5 million in MabVax for 285,714 shares of Series G Preferred Stock and 322,820 shares of Series I Preferred Stock. We had also invested an additional $1.0 million in MabVax in August 2016 for 207,900 shares of its common stock and warrants to purchase 415,800 shares of its common stock.

In April 2017, we invested an additional $1.0 million in COCP for 4,166,667 shares of its common stock, and in August 2016, we had invested an additional $2.0 million in COCP for 4,878,050 shares of its common 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 had 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 October 2016, we entered into a consulting agreement to provide strategic advisory services to BioCardia. In connection with the consulting agreement, BioCardia granted us 418,977 common stock options, after adjusting for a 1-for-12 reverse stock split in 2017. In December 2016, we purchased 1,602,564 shares of BioCardia, after adjusting for the reverse stock split, 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 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 January 1, 2017, we entered into an amendment to our lease agreement with Frost Holdings. The lease, as amended, is for approximately 29,500 square feet of space. The lease provides for payments of approximately $81 thousand per month in the first year increasing annually to $86 thousand per month in the third year, plus applicable sales tax. The rent is inclusive of operating expenses, property taxes and parking.

Our wholly-owned subsidiary, BioReference, purchases and uses certain products acquired from InCellDx, Inc., a company in which we hold a 29% 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, 2017, 2016, and 2015, we recognized approximately $361 thousand, $298 thousand, and $595 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. Effective January 1, 2017, employees of BioReference and its subsidiaries are eligible for participation in the Plan. Our matching contributions to our plans, including predecessor plans for BioReference, were approximately $8.4 million, $3.5 million and $3.1 million for the years ended December 31, 2017, 2016, and 2015 respectively.

Note 13 Commitments and Contingencies

In connection with our acquisitions of CURNA, OPKO Diagnostics 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, 2017, we have recorded $41.4 million as contingent consideration, with $11.8 million recorded within Accrued expenses and $29.6 million recorded within Other long-term liabilities in the accompanying Consolidated Balance Sheets. 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.

In August 2017, we entered into a Commitment Letter (the "Commitment Letter") with Veterans Accountable Care Group, LLC ("VACG") in connection with submission of a bid by its affiliate, the Veterans Accountable Care Organization, LLC ("VACO") in response to a request for proposal ("RFP") from the Veterans Health Administration ("VA") regarding its Community Care Network. If VACO is successful in its bid, we will acquire a fifteen percent (15%) membership interest in VACO. In addition, BioReference, our wholly-owned subsidiary, will provide laboratory services for the Community Care Network, a region which currently includes approximately 2,133,000 veterans in the states of Massachusetts, Maine, New Hampshire, Vermont, New York, Pennsylvania, New Jersey, Rhode Island, Connecticut, Maryland, Virginia, West Virginia, and North Carolina.

Pursuant to the Commitment Letter, we committed to provide, or to arrange from a third party lender, a line of credit for VACG in the amount of $50.0 million (the "Facility"). Funds drawn under the Facility would be contributed by VACG to VACO in order to satisfy the financial stability requirement of VACO in connection with its submission of the RFP. VACG would not be permitted to draw down on the Facility unless and until the VHA awards a contract to VACO. The Facility would have a maturity of five (5) years. Interest on the Facility would be payable at a rate equal to six and one-half percent (6.5%) per annum, payable quarterly in arrears. The Facility is subject to the negotiation of definitive documentation conditions customary for transactions of such type and otherwise acceptable to VACG and the lender under the Facility.

We currently anticipate that a decision by the VHA with respect to the RFP will occur during 2018, although there can be no assurance that a decision will be made by such time or that, if favorable, such decision will not be challenged by participants in the RFP process or otherwise.

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 established 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. 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.

In April 2017, the Civil Division of the United States Attorney's Office for the Southern District of New York (the "SDNY") informed BioReference that it believes that, from 2006 to the present, BioReference had, in violation of the False Claims Act, improperly billed Medicare and TRICARE (both are federal government healthcare programs) for clinical laboratory services provided to hospital inpatient beneficiaries at certain hospitals. BioReference is reviewing and assessing the allegations made by the SDNY, and, at this point, BioReference has not determined whether there is any merit to the SDNY's claims nor can it determine the extent of any potential liability. While management cannot predict the outcome of these matters at this time, the ultimate outcome could be material to our business, financial condition, results of operations, and 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 BioReference which provide for compensation and certain other benefits and for severance payments under certain circumstances. During the years ended December 31, 2017 and 2016, we recognized $5.8 million and $17.9 million, respectively, of severance costs pursuant to these employment agreements as a component of Selling, general and administrative expense.

At December 31, 2017, we were committed to make future purchases for inventory and other items in 2018 that occur in the ordinary course of business under various purchase arrangements with fixed purchase provisions aggregating $82.2 million.

Note 14 Strategic Alliances

Japan Tobacco Inc.

On October 12, 2017, EirGen, our wholly-owned subsidiary, and Japan Tobacco Inc. ("JT") entered into a Development and License Agreement (the "JT Agreement") granting JT the exclusive rights for the development and commercialization of *Rayaldee* in Japan (the "JT Territory"). The license grant to JT covers the therapeutic and preventative use of the product for (i) SHPT in non-dialysis and dialysis patients with CKD, (ii) rickets, and (iii) osteomalacia (the "Initial Indications"), as well as such additional indications as may be added to the scope of the license subject to the terms of the JT Agreement (the JT Additional Indications" and together with the JT Initial Indications, the "JT Field").

In connection with the license, OPKO received an initial upfront payment of $6 million ("JT Upfront Payment"). OPKO will receive another $6 million upon the initiation of OPKO's planned phase 2 study for *Rayaldee* in dialysis patients in the U.S. OPKO is also eligible to receive up to an additional aggregate amount of $31 million upon the achievement of certain regulatory and development milestones by JT for *Rayaldee* in the JT Territory, and $75 million upon the achievement of certain sales based milestones by JT in the JT Territory. OPKO will also receive tiered, double digit royalty payments at rates ranging from low double digits to mid-teens on net sales of *Rayaldee* within the JT Territory. JT will, at its sole cost and expense, be responsible for performing all development activities necessary to obtain all regulatory approvals for *Rayaldee* in Japan and for all commercial activities pertaining to *Rayaldee* in Japan, except for certain preclinical expenses which OPKO has agreed to reimburse JT up to a capped amount ("Preclinical Expenses").

For revenue recognition purposes, we evaluated the JT Agreement to determine whether there were multiple deliverables in the arrangement. The JT Agreement provides for the following: (1) an exclusive license in the JT Territory in the JT Field for the development and commercialization of *Rayaldee*; and (2) upon JT's request, EirGen will supply products to support the development, sale and commercialization of the products to JT in the JT Territory (the "JT Manufacturing Services"). We determined that the license granted to JT, as well as our obligation to provide additional license materials and development

services, will be accounted for as a single unit of account. This determination was made because the additional license materials and development services to be provided by us are essential to the overall arrangement. We concluded the JT Manufacturing Services were a contingent deliverable dependent on the future regulatory and commercial action by JT.

We are recognizing the non-refundable $6 million upfront payment, net of the Preclinical Expenses, on a straight-line basis over the performance period as Revenue from transfer of intellectual property in our Consolidated Statement of Operations. The performance period over which the revenue will be recognized is expected to continue from the fourth quarter of 2017 through 2021, when we anticipate completing the various services that are specified in the JT Agreement and our performance obligations are completed. The additional $6 million we will receive upon the initiation of our planned phase 2 study for *Rayaldee* in dialysis patients in the U.S. will be recognized on a straight-line basis over the remaining performance period when received. Revenues related to the JT Manufacturing Services will be recognized as product is sold to JT.

We are also eligible to receive up to $31 million in regulatory and development milestones and $75 million in sales milestones. Payments received for regulatory, development and sales milestones are non-refundable. The milestones are payable if and when the associated milestone is achieved and will be recognized as revenue 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.

Vifor Fresenius Medical Care Renal 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 Care Renal Pharma Ltd ("VFMCRP"), entered into a Development and License Agreement (the "VFMCRP Agreement") for the development and commercialization 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 "VFMCRP Territory"). The license to VFMCRP potentially covers all therapeutic and prophylactic uses of the Product in human patients (the "VFMCRP Field"), provided that initially the license is for the use of the Product for the treatment or prevention of SHPT related to patients with stage 3 or 4 chronic kidney disease and vitamin D insufficiency/deficiency (the "VFMCRP Initial Indication").

Under the terms of the VFMCRP Agreement, EirGen granted to VFMCRP an exclusive license in the VFMCRP Territory in the VFMCRP 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 royalties on sales of the product at percentage rates that range from the mid-teens to the mid-twenties or a minimum royalty, whichever is greater, upon the commencement of sales of the Product within the VFMCRP Territory and in the VFMCRP 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 VFMCRP Territory and the commercialization activities outside the VFMCRP Territory and outside the VFMCRP Field in the VFMCRP Territory and VFMCRP will lead the commercialization activities in the VFMCRP Territory and the VFMCRP 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 VFMCRP Initial Indication in the VFMCRP Territory in the VFMCRP 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 VFMCRP 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 (iii) 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 VFMCRP 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 royalties at percentage rates that range from the mid-teens to the mid-twenties on sales of the Product 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 VFMCRP to determine whether there were multiple deliverables in the arrangement. The VFMCRP Agreement provides for the following: (1) an exclusive license in the VFMCRP Territory in the VFMCRP 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 VFMCRP 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 which 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 2020, 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 increased the expected performance period over which the revenue will be recognized in 2017 by approximately one year.

We are recognizing the non-refundable $295.0 million upfront payments on a straight-line basis over the performance period. We recognized $57.8 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, 2017, and had deferred revenue related to the Pfizer Transaction of $101.1 million at December 31, 2017. As of December 31, 2017, $44.9 million of deferred revenue related to the Pfizer Transaction was classified in Accrued expenses and $56.2 million was classified in Other long-term liabilities in our Consolidated Balance Sheet. During the year ended December 31, 2017, we incurred $47.7 million in research and development expenses related to hGH-CTP, respectively.

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 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 we received $30.0 million of milestone payments from TESARO upon achievement of certain regulatory and commercial sale milestones and we are eligible to receive 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, 2017, 2016 and 2015, $10.0 million, $0.0 million and $15.0 million of revenue, respectively, was 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 NK-1 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.

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 9%). We also granted rights to certain technologies in the Russian Federation, Ukraine, Belarus, Azerbaijan and Kazakhstan (the "Pharmsynthez 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 Pharmsynthez Territories, as well as a percentage of any sublicense income from third parties for the technologies in the Pharmsynthez Territories.

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 $18.9 million, $18.8 million, and $7.8 million for the years ended December 31, 2017, 2016, and 2015, respectively.

As of December 31, 2017, 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)
2018	$ 19,059
2019	15,166
2020	9,360
2021	6,079
2022	3,148
Thereafter	3,542
Total minimum operating lease commitments	$ 56,354

Capital leases

We acquired various assets under capital leases in connection with our acquisition of BioReference 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, 2017
Automobiles	$ 11,137
Less: Accumulated Depreciation	(4,366)
Net capital leases in Property, plant and equipment	$ 6,771

As of December 31, 2017, 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)
2018	$ 3,521
2019	3,029
2020	2,440
2021	1,586
2022	410
Thereafter	441
Total minimum capital lease commitments	11,427
Less: Amounts representing interest	242
Net capital liability	$ 11,185

Current	$ 3,399
Long-term	$ 7,786

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 BioReference 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, 2017	2016	2015
Revenue from services:			
Pharmaceutical	$ —	$ —	$ —
Diagnostics	889,076	1,012,129	329,599
Corporate	—	—	140
	$ 889,076	$ 1,012,129	$ 329,739
Revenue from products:			
Pharmaceutical	$ 107,759	$ 83,467	$ 80,146
Diagnostics	—	—	—
Corporate	—	—	—
	$ 107,759	$ 83,467	$ 80,146
Revenue from transfer of intellectual property:			
Pharmaceutical	$ 70,668	$ 126,065	$ 81,853
Diagnostics	—	—	—
Corporate	—	—	—
	$ 70,668	$ 126,065	$ 81,853
Operating loss:			
Pharmaceutical	$ (87,907)	$ (9,841)	$ (40,395)
Diagnostics	(136,540)	(3,393)	(10,294)
Corporate	(55,615)	(60,041)	(46,512)
Less: Operating loss attributable to noncontrolling interests	—	—	(1,280)
	$ (280,062)	$ (73,275)	$ (98,481)
Depreciation and amortization:			
Pharmaceutical	$ 27,513	$ 18,254	$ 10,245
Diagnostics	74,442	78,233	31,918
Corporate	138	89	85
	$ 102,093	$ 96,576	$ 42,248
Income (loss) from investment in investees:			
Pharmaceutical	$ (12,646)	$ (7,665)	$ (7,105)
Diagnostics	(1,825)	13	—
Corporate	—	—	—
	$ (14,471)	$ (7,652)	$ (7,105)
Revenues:			
United States	$ 908,971	$ 1,014,389	$ 344,464
Ireland	77,285	137,785	78,989
Chile	44,286	35,364	29,885
Spain	18,285	15,812	16,622
Israel	13,951	15,317	18,107
Mexico	4,605	2,988	3,671
Other	120	6	—
	$ 1,067,503	$ 1,221,661	$ 491,738

(In thousands)	December 31, 2017	December 31, 2016
Assets:		
Pharmaceutical	$ 1,282,564	$ 1,294,916
Diagnostics	1,241,388	1,408,522
Corporate	60,604	63,181
	$ 2,584,556	$ 2,766,619
Goodwill:		
Pharmaceutical	$ 264,313	$ 251,817
Diagnostics	452,786	452,786
Corporate	—	—
	$ 717,099	$ 704,603

During the year ended December 31, 2017, two customers represented more than 10% of our total consolidated revenue. 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. As of December 31, 2017, no customer represented more than 10% of our accounts receivable balance. As of December 31, 2016, 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, 2017	December 31, 2016
PP&E:		
U.S.	$ 89,114	$ 100,716
Foreign	57,443	22,115
Total	$ 146,557	$ 122,831

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, 2017			
(In thousands)	Amortized Cost	Gross unrealized gains in Accumulated OCI	Gross unrealized losses in Accumulated OCI	Fair value
Common stock investments, available for sale	$ 7,585	$ 5,075	$ (199)	$ 12,461

	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

Any future fluctuation in fair value related to our available for sale investments that is judged to be temporary, and any recoveries of previous temporary 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, 2017, 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 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 agreement with BioCardia, we record the related BioCardia options at fair value as well as the warrants from COCP, InCellDx, Inc., Xenetic, RXi and Neovasc.

Our financial assets and liabilities measured at fair value on a recurring basis are as follows:

	Fair value measurements as of December 31, 2017			
(In thousands)	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	$ 107	$ —	$ —	$ 107
Common stock investments, available for sale	12,461	—	—	12,461
Common stock options/warrants	—	3,333	—	3,333
Total assets	$ 12,568	$ 3,333	$ —	$ 15,901
Liabilities:				
Forward Contracts	—	317	—	317
Contingent consideration:	$ —	$ —	$ 41,353	41,353
Total liabilities	$ —	$ 317	$ 41,353	$ 41,670

	Fair value measurements as of December 31, 2016			
(In thousands)	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

The carrying amount and estimated fair value of our 2033 Senior Notes with 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, 2017				
(In thousands)	Carrying Value	Total Fair Value	Level 1	Level 2	Level 3
2033 Senior Notes	$ 29,160	$ 32,968	$ —	$ —	$ 32,968

(In thousands)	December 31, 2016				
	Carrying Value	Total Fair Value	Level 1	Level 2	Level 3
2033 Senior Notes	$ 26,965	$ 45,205	$ —	$ —	$ 45,205

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, 2017 and 2016, the carrying value of our other financial instrument assets and liabilities approximates their fair value due to their short-term nature or variable rate of interest.

The following tables reconcile the beginning and ending balances of our Level 3 assets and liabilities as of December 31, 2017 and 2016:

(In thousands)	December 31, 2017	
	Contingent consideration	Embedded conversion option
Balance at December 31, 2016	$ 45,076	$ 16,736
Total losses (gains) for the period:		
Included in results of operations	(3,423)	(3,185)
Foreign currency impact	3	—
Payments	(303)	—
Reclassification of embedded derivatives to equity	—	(13,551)
Balance at December 31, 2017	$ 41,353	$ —

(In thousands)	December 31, 2016	
	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)	—
Balance at December 31, 2016	$ 45,076	$ 16,736

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 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 $2.1 million. As of December 31, 2017, of the $41.4 million of contingent consideration, $11.8 million is recorded in Accrued expenses and $29.6 million is recorded in Other long-term liabilities. 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.

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, 2017	December 31, 2016
Derivative financial instruments:			
Common stock options/warrants	Investments, net	$ 3,333	$ 4,017
Embedded conversion option	2033 Senior Notes, net of discount	$ —	$ 16,736
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.	$ (317)	$ 39

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, 2017 and 2016, 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, 2017, 2016 and 2015:

	For the years ended December 31,		
(In thousands)	2017	2016	2015
Derivative gain (loss):			
Common stock options/warrants	$ (2,533)	$ (4,262)	$ (2,854)
2033 Senior Notes	3,185	7,001	(36,588)
Forward contracts	$ (600)	$ 39	$ 359
Total	$ 52	$ 2,778	$ (39,083)

Note 19 Selected Quarterly Financial Data (Unaudited)

	For the 2017 Quarters Ended			
(In thousands, except per share data)	March 31	June 30	September 30	December 31
Total revenues	$ 296,096	$ 314,213	$ 263,495	$ 193,699
Total costs and expenses	337,803	340,656	321,785	347,321
Net income (loss)	(30,995)	(17,528)	(46,442)	(213,905)
Net income (loss) attributable to common shareholders	(30,995)	(17,528)	(46,442)	(213,905)
Earnings (loss) per share, basic	$ (0.06)	$ (0.03)	$ (0.08)	$ (0.38)
Earnings (loss) per share, diluted	$ (0.06)	$ (0.04)	$ (0.08)	$ (0.38)

	For the 2016 Quarters Ended			
(In thousands, except per share data)	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)

Note 20 Subsequent Events

On February 28, 2018, BioReference and certain of its subsidiaries entered into Amendment No. 7 to the Credit Agreement with JPMorgan Chase Bank, N.A. (“CB”), which amended the Credit Agreement to permit BioReference and its subsidiaries to use cash on hand, up to a maximum amount set forth in the amendment, to meet the availability requirements that otherwise would trigger (i) covenants that would require BioReference to maintain a minimum fixed charge coverage ratio and provide certain increased reporting under the Credit Agreement and (ii) CB’s right, as agent for the lenders under the Credit Agreement, to exercise sole dominion over funds held in certain accounts of BioReference. The other terms of the Credit Agreement remain unchanged.

On February 27, 2018, we agreed to issue a series of 5% Convertible Promissory Notes (the “Notes”) in the aggregate principal amount of $55.0 million. The Notes mature five (5) years from the date of issuance. Each holder of a Note has the option, from time to time, to convert all or any portion of the outstanding principal balance of such Note, together with accrued and unpaid interest thereon, into shares of our common stock, par value $0.01 per share (“Common Stock”), at a conversion price of $5.00 per share of Common Stock (the “Shares”). We may redeem all or any part of the then issued and outstanding Notes, together with accrued and unpaid interest thereon, pro ratably among the holders, upon no fewer than 30 days, and no more than 60 days, notice to the holders. The Notes contain customary events of default and representations and warranties of OPKO. We intend to use the proceeds of the Notes for general corporate purposes.

The issuance of the Notes and the issuance of the Shares, if any, upon conversion thereof was not, and will not be, respectively, registered under the Securities Act of 1933, as amended, pursuant to the exemption provided by Section 4(a)(2) thereof, and we have not agreed to register the Shares if or when such Shares are issued.

Purchasers of the Notes include an affiliate of Dr. Phillip Frost, M.D., our Chairman and Chief Executive Officer, and Dr. Jane H. Hsiao, Ph.D., MBA, our Vice-Chairman and Chief Technical Officer.

We have reviewed all subsequent events and transactions that occurred after the date of our December 31, 2017 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 our 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, 2017. 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, 2017.

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, 2017, 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, 2017.

The effectiveness of the Company's internal control over financial reporting as of December 31, 2017 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 acquisition of Transition Therapeutics in August 2016, we began implementing standards and procedures at 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 Transition Therapeutics. We are continuing to integrate the acquired operations of Transition Therapeutics into our overall internal control over financial reporting process.

We are implementing new controls as part of our effort to adopt Accounting Standards Update ("ASU") No. 2014-09, "Revenue from Contracts with Customers." The adoption of the ASU is requiring the implementation of new accounting processes which necessitates changes to our internal controls over financial reporting.

We are in the process of implementing a new comprehensive enterprise resource planning ("ERP") system on a company-wide basis, which is one of the systems used for financial reporting. The implementation of the ERP system 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, 2017 have materially affected, or are reasonably likely to materially affect, the Company's internal control over financial reporting.

ITEM 9B. OTHER INFORMATION

On February 28, 2018, BioReference and certain of its subsidiaries entered into Amendment No. 7 to the Credit Agreement with JPMorgan Chase Bank, N.A. ("CB"), which amended the Credit Agreement to permit BioReference and its subsidiaries to use cash on hand, up to a maximum amount set forth in the amendment, to meet the availability requirements that otherwise would trigger (i) covenants that would require BioReference to maintain a minimum fixed charge coverage ratio and provide certain increased reporting under the Credit Agreement and (ii) CB's right, as agent for the lenders under the Credit Agreement, to exercise sole dominion over funds held in certain accounts of BioReference. The other terms of the Credit Agreement remain unchanged.

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 2018 Annual Meeting of Stockholders to be filed with the Securities and Exchange Commission within 120 days of December 31, 2017.

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[31]	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[32]	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[33]	OPKO Health, Inc. 2016 Equity Incentive Plan.
10.22[34]	Development and License Agreement between OPKO Health, Inc. and Vifor Fresenius Medical Care Renal Pharma Ltd., dated May 8, 2016.
10.23[35]	Amendment No. 3 to Credit Agreement, dated as of March 17, 2017, among Bio-Reference Laboratories, Inc. and certain of its subsidiaries and JPMorgan Chase Bank, N.A.
10.24[36]	Amendment No. 4 to Credit Agreement, dated as of August 7, 2017, among Bio-Reference Laboratories, Inc. and certain of its subsidiaries and JPMorgan Chase Bank, N.A.
10.25[36]	Commitment Letter by and between OPKO Health, Inc. and Veterans Accountable Care Group, LLC, dated August 15, 2017
10.26+**	Development and License Agreement by and between EirGen Pharma Limited, a subsidiary of OPKO Health, Inc., and Japan Tobacco Inc., dated October 12, 2017.
10.27**	Amendment No. 5 to Credit Agreement, dated as of November 8, 2017, among Bio-Reference Laboratories, Inc. and certain of its subsidiaries and JPMorgan Chase Bank, N.A.
10.28**	Amendment No. 6 to Credit Agreement, dated as of December 22, 2017, among Bio-Reference Laboratories, Inc. and certain of its subsidiaries and JPMorgan Chase Bank, N.A.
10.29**	Form of 5% Convertible Promissory Note dated February 27, 2018.
21	Subsidiaries of the Company.

23.1	Consent of Ernst & Young LLP.
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, 2017.
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, 2017.
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, 2017.
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, 2017.
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.

** Filed herewith.

\+ 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 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.

(32) 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.

(33) 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.

(34) 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.

(35) Filed with the Company's Current Report on Form 8-K filed with the Securities and Exchange Commission on March 23, 2017 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 November 8, 2017 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,	
	2017	2016
ASSETS		
Current assets:		
Cash and cash equivalents	$ 21,385	$ 15,744
Other current assets and prepaid expenses	4,586	12,446
Total current assets	25,971	28,190
Property, plant and equipment, net	150	503
Investments	1,893,371	2,114,473
Other assets	146	176
Total assets	$ 1,919,638	$ 2,143,342
LIABILITIES AND EQUITY		
Current liabilities:		
Accounts payable	$ 1,077	$ 1,070
Accrued expenses	3,023	5,769
Current portion of notes payable	521	522
Total current liabilities	4,621	7,361
2033 Senior Notes, net of discount	29,160	43,701
Deferred tax liabilities, net	479	472
Total long-term liabilities	29,639	44,173
Total liabilities	34,260	51,534
Equity:		
Common Stock - $0.01 par value, 750,000,000 shares authorized; 560,023,745 and 558,576,051 shares issued at December 31, 2017 and 2016, respectively	5,600	5,586
Treasury Stock, at cost - 549,907 and 586,760 shares at December 31, 2017 and 2016, respectively	(1,791)	(1,911)
Additional paid-in capital	2,889,256	2,845,096
Accumulated other comprehensive income (loss)	(528)	(27,009)
Accumulated deficit	(1,007,159)	(729,954)
Total shareholders' equity	1,885,378	2,091,808
Total liabilities and equity	$ 1,919,638	$ 2,143,342

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,		
	2017	2016	2015
Revenues:			
Revenue from products	$ —	$ —	$ 140
Revenue from transfer of intellectual property and other	1,069	—	154
Total revenues	1,069	—	294
Costs and expenses:			
Costs of revenue	1,438	875	798
Selling, general and administrative	57,410	60,819	47,708
Research and development	4,426	3,791	8,496
Total costs and expenses	63,274	65,485	57,002
Operating loss	(62,205)	(65,485)	(56,708)
Other income and (expense), net:			
Interest income	260	440	5
Interest expense	(4,426)	(3,585)	(5,347)
Fair value changes of derivative instruments, net	652	2,738	(39,442)
Other income (expense), net	5,177	(2,387)	2,141
Other income and (expense), net	1,663	(2,794)	(42,643)
Loss before income taxes and investment losses	(60,542)	(68,279)	(99,351)
Income tax benefit (provision)	(247)	(686)	—
Net loss before investment losses	(60,789)	(68,965)	(99,351)
Loss from investments in investees	(12,646)	(7,665)	(7,105)
Net income (loss) from subsidiaries, net of taxes	(235,435)	51,547	76,428
Net loss attributable to common shareholders	$ (308,870)	$ (25,083)	$ (30,028)

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,		
	2017	2016	2015
Net loss	$ (308,870)	$ (25,083)	$ (30,028)
Other comprehensive income (loss), net of tax:			
Change in foreign currency translation and other comprehensive income (loss)	22,724	(4,955)	(15,074)
Available for sale investments:			
Change in unrealized gain (loss), net of tax	3,790	(3,810)	(2,378)
Less: reclassification adjustments for losses included in net loss, net of tax	(33)	4,293	7,307
Comprehensive loss attributable to common shareholders	$ (282,389)	$ (29,555)	$ (40,173)

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,		
	2017	2016	2015
Cash flows from operating activities:			
Net loss	$ (308,870)	$ (25,083)	$ (30,028)
Adjustments to reconcile net loss to net cash used in operating activities:			
Depreciation and amortization	138	89	85
Non-cash interest	2,049	1,866	2,612
Amortization of deferred financing costs	574	149	1,212
Losses from investments in investees	12,646	7,665	7,105
(Income) loss from subsidiaries	235,435	(51,546)	(76,428)
Equity-based compensation – employees and non-employees	28,308	42,693	26,074
Realized loss (gain) on equity securities and disposal of fixed assets	(652)	(2,738)	7,091
Loss (gain) on conversion of 3.00% convertible senior notes	—	284	(943)
Change in fair value of derivative instruments	(4,953)	2,347	39,442
Gain on deconsolidation of SciVac	—	—	(15,940)
Changes in other assets and liabilities	4,258	(6,844)	(15,640)
Net cash used in operating activities	(31,067)	(31,118)	(55,358)
Cash flows from investing activities:			
Investments in investees	(9,625)	(14,424)	(4,375)
Subsidiary financing	41,990	(44,569)	62,471
Proceeds from sale of equity securities	2,211	—	—
Acquisition of businesses, net of cash acquired	—	—	(138)
Capital expenditures	—	(368)	(92)
Net cash provided by (used in) investing activities	34,576	(59,361)	57,866
Cash flows from financing activities:			
Proceeds from the exercise of Common Stock options and warrants	2,132	8,576	25,921
Net cash provided by financing activities	2,132	8,576	25,921
Net increase (decrease) in cash and cash equivalents	5,641	(81,903)	28,429
Cash and cash equivalents at beginning of period	15,744	97,647	69,218
Cash and cash equivalents at end of period	$ 21,385	$ 15,744	$ 97,647
SUPPLEMENTAL INFORMATION:			
Interest paid	$ 956	$ 966	$ 2,175
Income taxes paid, net of refunds	$ 327	$ —	$ —
Non-cash financing:			
Shares issued upon the conversion of:			
2033 Senior Notes	$ —	$ 583	$ 120,299
Common Stock options and warrants, surrendered in net exercise	$ 1,546	$ 350	$ 14,369
Issuance of capital stock to acquire or contingent consideration settlement:			
Transition Therapeutics, Inc.	$ —	$ 58,530	$ —
BioReference Laboratories, Inc.	$ —	$ —	$ 950,148
EirGen Pharma Limited	$ —	$ —	$ 33,569
OPKO Renal	$ —	$ 25,986	$ 20,113
OPKO Health Europe	$ 303	$ 313	$ 1,813
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, 2017 and 2016, approximately $1.9 billion and $2.1 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 BioReference, 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. BioReference and its subsidiaries' net assets as of December 31, 2017 were approximately $0.9 billion, which includes goodwill of $401.8 million and intangible assets of $446.5 million. BioReference's restricted net assets exceeds 25% of OPKO's consolidated net assets of $2.6 billion as of December 31, 2017.

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, as amended (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 Condensed Balance Sheets as of December 31, 2017:

(In thousands)	Embedded conversion option	2033 Senior Notes	Discount	Debt Issuance Cost	Total
Balance at December 31, 2016	$ 16,736	$ 31,850	$ (4,612)	$ (273)	$ 43,701
Amortization of debt discount and debt issuance costs	—	—	2,047	148	2,195
Change in fair value of embedded derivative	(3,185)	—	—	—	(3,185)
Reclassification of embedded derivatives to equity	(13,551)	—	—	—	(13,551)
Balance at December 31, 2017	$ —	$ 31,850	$ (2,565)	$ (125)	$ 29,160

The following table sets forth information related to the 2033 Senior Notes which is included our Condensed Balance Sheets 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 and debt issuance costs	—	—	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 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.

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 determined that these specific terms were 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 concluded that the embedded derivatives within the 2033 Senior Notes meet these criteria for periods prior to February 1, 2017 and, as such, were valued separate and apart from the 2033 Senior Notes and recorded at fair value each reporting period.

For accounting and financial reporting purposes, prior to 2017 we combined these embedded derivatives and valued them together as one unit of accounting.

On February 1, 2017, certain terms of the embedded derivatives expired pursuant to the original agreement and we determined that the embedded derivatives no longer met the criteria to be separated from the host contract and, as a result, the embedded derivatives are no longer required to be valued separate and apart from the 2033 Senior Notes and are not required to be measured at fair value subsequent to February 1, 2017.

The change in derivative income for the period from January 1, 2017 to February 1, 2017 related to the embedded derivatives was $3.2 million and the fair value at that date was $13.6 million. As the embedded derivatives are no longer required to be accounted for separately each period, the embedded derivative fair value of $13.6 million as of February 1, 2017 was reclassified to additional paid in capital.

From 2013 to 2016, holders of the 2033 Senior Notes converted 143.2 million in aggregate principal amount into an aggregate of 21,539,873 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, 2016 and the first quarter of 2017. They may become convertible again 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 November 2015, BioReference 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 BioReference and its domestic subsidiaries, as well as a non-recourse pledge by us of our equity interest in BioReference.

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, 2017, 2016 and 2015.

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, 2018

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, 2018
/s/ Jane H. Hsiao, Ph.D., MBA Jane H. Hsiao, Ph.D., MBA	Vice Chairman and Chief Technical Officer	March 1, 2018
/s/ Steven D. Rubin Steven D. Rubin	Director and Executive Vice President – Administration	March 1, 2018
/s/ Adam Logal Adam Logal	Senior Vice President, Chief Financial Officer, Chief Accounting Officer and Treasurer (Principal Financial Officer)	March 1, 2018
/s/ Richard Krasno, Ph.D. Richard Krasno, Ph.D.	Director	March 1, 2018
/s/ Richard A. Lerner, M.D. Richard A. Lerner, M.D.	Director	March 1, 2018
/s/ John A. Paganelli John A. Paganelli	Director	March 1, 2018
/s/ Richard C. Pfenniger, Jr. Richard C. Pfenniger, Jr.	Director	March 1, 2018
/s/ Alice Lin-Tsing Yu, M.D., Ph.D. Alice Lin-Tsing Yu, M.D., Ph.D.	Director	March 1, 2018

Exhibit Number	Description
21	Subsidiaries of the Company.
23.1	Consent of Ernst & Young LLP.
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, 2017.
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, 2017.
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, 2017.
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, 2017.
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

Execution Copy

CONFIDENTIAL

[***] Indicates portions of this exhibit that have been omitted and filed separately with the Securities and Exchange Commission pursuant to a request for confidential treatment.

DEVELOPMENT AND LICENSE AGREEMENT

BETWEEN

EIRGEN PHARMA LIMITED

AND

JAPAN TOBACCO INC.

October 12, 2017

[***] Indicates portions of this exhibit that have been omitted and filed separately with the Securities and Exchange Commission pursuant to a request for confidential treatment.

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DEVELOPMENT AND LICENSE AGREEMENT

This Development and License Agreement (this "**Agreement**") is entered into and effective as of the 12th day of October, 2017 (the "**Effective Date**"), by and between EirGen Pharma Limited, an entity formed under the laws of Ireland with registered seat at Westside Business, Old Kilmeaden, Waterford, Ireland ("**OPKO**"), which is an indirect wholly-owned subsidiary of OPKO Health, Inc., a Delaware corporation, on the one hand, and Japan Tobacco Inc., a corporation formed under the laws of Japan with registered seat at JT Building, 2-1, Toranomon 2-chome, Minato-ku, Tokyo 105-8422, Japan ("**Licensee**"), on the other hand. OPKO and Licensee are each referred to herein by name or as a "**Party**" or, collectively, as "**Parties**."

Recitals

A. OPKO is a diversified healthcare company that, through its pharmaceutical division and Affiliates (as hereinafter defined), commercializes the Product (as hereinafter defined), directly or through licensees in several jurisdictions throughout the world.

B. Licensee, through its pharmaceutical division and Affiliates, including Torii Pharmaceutical Co., Ltd. ("**Torii**"), is engaged in the research, development and commercialization of pharmaceutical products in Japan.

C. OPKO and its Affiliates desire to license its rights to the Product to Licensee in the Field (as hereinafter defined) in Japan, all on the terms and subject to the conditions set forth in this Agreement.

D. Licensee desires to Research (as hereinafter defined), develop, commercialize, distribute, sell, market and promote the Product in the Field in Japan, and OPKO is willing to grant Licensee the right to conduct such activities, all on the terms and subject to the conditions of this Agreement.

Agreement

1. Definitions; Interpretation

1.1 Defined Terms. When used in this Agreement, the following terms shall have the meanings set forth in this Section 1.1.

"**Accounting Standards**" means the then-current generally accepted accounting standards in the United States or Japan, in each case as applicable and consistently applied by the relevant Person.

"**Act on Drugs and Medical Devices**" means the Act on Assurance of Quality, Efficacy and Safety of Drugs and Medical Devices, etc. (Act No. 145 of 1960) of Japan, as amended from time to time.

"**Additional Indication**" means any therapeutic or preventative use for the Product other than the Initial Indications.

"**Adjusted Yakka Price**" means the price (in JPY) for the Product per patient per day calculated on the basis of (a) the standard daily dosage per patient, and (b) the most commonly used dosage unit (and dosage form), the price of which (dosage unit) is established by the National Health Insurance System in the License Territory, less the then-current consumption tax portion.

"**Adverse Event(s)**" means those events as defined by the FDA and published in the U. S. Code of Federal Regulations, as amended from time to time and published in the Federal Register, or by the PMDA or any similar definitions under laws within the License Territory relating to adverse drug experiences relating to the use of the Product in the License Territory.

"**Affiliate**" means any Person that, on the Effective Date or at any time during the Term, directly or indirectly through one (1) or more intermediaries controls, is controlled by or is under common control with a Party, but only while that Person directly or indirectly through one (1) or more intermediaries controls, is controlled by or is under common control with a Party. For purposes of this definition, a Person shall be deemed to "control" another Person if it (a) owns, directly or indirectly, beneficially or legally, at least fifty percent (50%) of the outstanding voting securities or capital stock (or such lesser percentage which is the maximum allowed to be owned by a Person in a particular jurisdiction) of such other Person, or has other comparable ownership interest with respect to any Person other than a corporation, or (b) has the power, whether pursuant to contract, ownership of securities or otherwise, to direct the management and policies of the Person.

"**Agreement Year**" means each twelve (12) month period commencing on January 1 and ending on December 31 during the Term; provided, that the first Agreement Year during the Term shall commence on the Effective Date and end on December 31, and the last Agreement Year during the Term shall commence on January 1 and end on the effective date of expiration or termination of the Term.

"**Applicable Law**" means any law, statute, rule, regulation, order, judgment, or ordinance of any Governmental Authority, including those concerning environmental, health, and safety matters. For clarity, Applicable Law shall include regulations applicable to a Party's activities related to this Agreement, such as Good Clinical Practices.

"**Business Day**" means a day on which commercial banks are open for business in New York City with respect to OPKO obligations and Tokyo, Japan with respect to Licensee obligations. References in this Agreement to "days" other than Business Days shall mean calendar days.

"**Calendar Quarter**" means the respective periods of three (3) consecutive calendar months ending on March 31, June 30, September 30 and December 31.

"**Change of Control**" shall occur if: (a) any Third Party acquires directly or indirectly the beneficial ownership of any voting security of a Party, or if the percentage ownership of such Person or entity in the voting securities of a Party is increased through stock redemption, cancellation or other recapitalization, and immediately after such acquisition or increase such Third Party is, directly or indirectly, the beneficial owner of voting securities representing more than fifty percent (50%) of the total voting power of all of the then outstanding voting securities of a Party; (b) a merger, consolidation, recapitalization or reorganization of a Party is consummated, other than any such

transaction which would result in stockholders or equity holders of such Party immediately prior to such transaction, owning, directly or indirectly, at least fifty percent (50%) of the outstanding securities of the surviving entity (or its parent entity) immediately following such transaction; (c) the stockholders or equity holders of a Party approve a plan of complete liquidation of such Party, or an agreement for the sale or disposition by such Party of all or substantially all of such Party's assets or business pertaining to this Agreement, other than pursuant to a transaction described above or to an Affiliate; (d) individuals who, as of the date hereof, constitute the Board of Directors of a Party (the "**Incumbent Board**") cease for any reason to constitute at least a majority of the Board of Directors of such Party (provided, however, that any individual becoming a director subsequent to the date hereof whose election, or nomination for election by such Party's shareholders, was recommended or approved by a vote of at least a majority of the directors then comprising the Incumbent Board shall be considered as though such individual were a member of the Incumbent Board); or (e) the sale or transfer to a Third Party of all or substantially all of such Party's assets is effected.

"**Commercially Reasonable Efforts**" means, with respect to the efforts to be expended by a Party with respect to any objective, those reasonable and good faith efforts and resources to accomplish such objective as [***] would normally use to accomplish a similar objective under similar circumstances, in each case taking into account all Relevant Factors in effect at the time such efforts are to be expended. With respect to any efforts relating to the development, Regulatory Approval and/or commercialization of a Product, generally in the License Territory, such Party will be deemed to have exercised Commercially Reasonable Efforts if such Party has exercised those efforts normally used by [***], in the [***], with respect to a compound, product or product candidate which is of [***], in each case taking into account all Relevant Factors in effect at the time such efforts are to be expended. With respect to any efforts to commercialize a Product, the Parties acknowledge and agree that Licensee would not have made Commercially Reasonable Efforts to commercialize a Product [***].

"**Competitive Product**" means any pharmaceutical product that: (a) is marketed in the License Territory by a Third Party; (b) [***]; and (c) [***].

"**Compound**" means calcifediol (25-hydroxyvitamin D_3) and any salt thereof, as well as any solvates of calcifediol or any of its salts (including, but not limited to, calcifediol monohydrate).

"**Control**" means, with respect to any Patent or other intellectual property right (including know-how, trade secrets and data), ownership thereof and/or possession of the ability to grant the licenses or sublicenses as provided herein without violating the terms of any agreement or other arrangement with any Third Party or being obligated to pay any royalties or other consideration therefor, but with respect to each Party excluding any Patent or other intellectual property right (including know-how, trade secrets and data) that comes into the Control of each Party pursuant to a Change of Control of such Party.

"**Cover(ed)**" means, with respect to any issued patent and the subject matter at issue, that, but for a license granted under such patent, the manufacture, development, use, sale, offer for sale or importation of the subject matter at issue would infringe such patent, or in the case of a patent application, would infringe such patent application if it were to issue as a patent.

"**Drug Approval Application** " means an application for marketing authorization or clearance required to be approved before commercial sale or use of a Product as a drug in a regulatory jurisdiction (i.e., New Drug Application or equivalent).

"**FDA**" means the United States Food and Drug Administration and any successor agency thereto.

"**Field**" means the use of the Product for the treatment or prevention of (a) the Initial Indications, and (b) any Additional Indication that is added to the scope of the license granted to Licensee under Section 2.1 in accordance with Article 4.

"**First Commercial Sale**" means, with respect to each Product, after all necessary Regulatory Approvals by the appropriate Regulatory Authority(ies), the first sale of a Product Covered by a Valid Claim of OPKO Patents and Other Licensee Patents in the License Territory by Licensee, any of its Affiliates or any permitted Sublicensee to a Third Party for end use or consumption of such Product. For clarity, a First Commercial Sale shall not be deemed to have occurred if the first sale of a Product is a sale or other distribution for clinical and pre-clinical or non-clinical or research and trials permitted under this Agreement, distribution of a promotional sample, a compassionate use sale, a sale under an indigent patient program or a named patient sale.

"**Good Clinical Practices**" means all applicable good clinical practice standards for the design, conduct, performance, monitoring, auditing, recording, analyses and reporting of clinical trials, including, as applicable, (a) the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Harmonized Tripartite Guideline for Good Clinical Practice (CPMP/ICH/135/95) and any other applicable guidelines for good clinical practice for clinical trials on medicinal products, (b) the Declaration of Helsinki (2004), as last amended at the 52nd World Medical Association General Assembly in October 2000, and any further amendments or clarifications thereto, and (c) the equivalent Applicable Laws in any relevant country, each as may be amended and applicable from time to time and, in each case, that provide for, among other things, assurance that the clinical data and reported results are credible and accurate and protect the rights, integrity, and confidentiality of trial subjects.

"**Government Official**" means (a) any elected or appointed government official (e.g., a member of a ministry of health), (b) any employee or Person acting for or on behalf of a government official, Governmental Authority, or other enterprise performing a governmental function, (c) any political party, candidate for public office, officer, employee, or Person acting for or on behalf of a political party or candidate for public office, and (d) any employee or Person acting for or on behalf of a public international organization (e.g., the United Nations). For clarity, healthcare providers employed by government-owned hospitals will also be considered Government Officials.

"**Governmental Authority**" means any court, agency, department, authority or other instrumentality of any national, state, county, city or other political subdivision.

"**Initial Indications**" means the treatment or prevention of (a) secondary hyperparathyroidism (" **SHPT**") in non-dialysis and dialysis chronic kidney disease patients,

(b) rickets, and (c) osteomalacia, including the use of the Product in combination with any other active ingredient or product, but in any event, solely for the foregoing indications.

"**Initiation**" or "**Initiated**" means, with respect to a clinical trial, the first dosing in the first patient in such clinical trial.

"**Insolvency Event**" means, means in respect of a Party:

(a) other than for the purposes of a bona fide reconstruction or amalgamation, such Party passing a resolution for its winding up, or a court of competent jurisdiction making an order for it to be wound up or dissolved, or that Party being otherwise dissolved;

(b) the appointment of an examiner, receiver or liquidator of, or a creditor taking possession of or selling, the whole or any material part of the entity's undertaking, assets, rights or revenue;

(c) that Party entering into an arrangement, compromise or composition in satisfaction (or with a view to satisfaction) of its debts with its creditors or any class of them, or taking steps to obtain a moratorium, or making an application to a court of competent jurisdiction for protection from its creditors;

(d) that Party being unable to pay its debts, or being capable of being deemed unable to pay its debts, within the meaning of Section 570 of the Irish Companies Act 2014 or similar legislation in the Applicable Law applicable to the relevant Party;

(e) any event occurs, or proceeding is taken, with respect to the other Party in any jurisdiction to which it is subject that has an effect equivalent or similar to any of the events mentioned in clause (a) to clause (d) (inclusive); or

(f) that Party suspending or ceasing to carry on its business.

"**Joint Patent**" means any Patent that Covers a Joint Invention. For the avoidance of doubt, Joint Patents do not include OPKO Patents, Other Licensee Patents or Licensee Patents.

"**JPY**" means Japanese Yen.

"**License Territory**" means Japan.

"**Licensee Patents**" means all Patents that Cover a Licensee Invention. Upon the request of OPKO, Licensee shall provide to OPKO a list of the then-current Licensee Patents. For the avoidance of doubt, Licensee Patents do not include OPKO Patents or Joint Patents.

"**Licensee Technology**" means all Technology that is developed or generated or otherwise becomes Controlled by Licensee or its Affiliates or Sublicensees during the Term. For the avoidance of doubt, Licensee Technology does not include OPKO Technology.

"**Manufacturing Cost**" means, with respect to the Product supplied hereunder, the direct and indirect costs incurred by OPKO or its Affiliates determined in accordance with the Accounting Standards and consistent with OPKO's internal accounting practices, consistently applied, for the manufacture and supply of Product (provided that any such indirect costs are reasonably allocable to the manufacture and supply of Product in accordance with the Accounting Standards and consistent with OPKO's internal accounting practices, consistently applied), which costs may include:

(a) the cost of active pharmaceutical ingredients, materials, components, supplies and other resources directly or indirectly consumed for the manufacture, testing, and supply of Product, in each case including freight, insurance, shipping, packaging (and including the cost of packaging) and other similar costs associated with acquiring such items;

(b) labor (including salaries, wages and current period employee benefits, but specifically excluding expenses associated with stock options or other equity-based or deferred compensation), including management salary and benefits reasonably allocable to the manufacture, testing, packaging (as applicable) and supply of Product;

(c) out-of-pocket expenses paid to a Third Party for the manufacture, testing and supply of Product, including transportation costs, customs, duty and transit insurance costs;

(d) scraps and batches that do not conform to the applicable specifications resulting from the manufacture and supply of the Product to the extent such failure to meet the specifications and non-conformities are not caused [***]; provided that [***];

(e) costs for quality control/assurance (including the costs of quantities destroyed in quality control testing) of the Product, including the costs of inspection, rejection and return of components, materials or services;

(f) costs reasonably allocable to ensuring manufacture and supply operations for Product comply with Applicable Laws, including costs for obtaining and maintaining permits, registrations, and authorizations required by Governmental Authorities;

(g) other costs reasonably allocable to the manufacture and supply of Product, including allocable occupancy, depreciation and amortization of facilities, allocable facilities costs, general and administrative costs; and

(h) the amount of any royalty payable by OPKO to Catalent Pharma Solutions, LLC (" **Catalent**") with respect to the use of Catalent Optishell technology.

"**Manufacturing/Research Territory**" means the [***]; provided, however, that, [***].

"**Marketing Material**" means the written, printed, electronic or graphic materials related to strategy, communications and programs associated with the marketing or promotion of the Product, including such strategy, communications, programs and any promotional and marketing

materials that (a) specifically identify or describe the Product, or (b) otherwise support the Product or raise awareness of the Product.

"**Net Sales**" means the gross amounts invoiced by Licensee and its Affiliates and Sublicensees for sales of Product to Third Parties in the License Territory during the Royalty Term, less the following deductions to the extent actually taken:

(a) bad debts and uncollectable invoiced amounts relating to sales of the Product that are [***] in accordance with the Accounting Standards, consistently applied; provided, that any [***] will be included in the current Net Sales calculation; provided further that Licensee shall act in good faith to ensure that any write-offs for bad debt and uncollectable amounts for Licensee customers [***];

(b) sales returns and allowances actually paid, granted or accrued, including trade, quantity and cash discounts and other adjustments, including those granted on account of price adjustments, returns, rebates, chargebacks or similar payments granted or given to wholesalers or other institutions;

(c) adjustments arising from consumer discount programs or other similar programs;

(d) clawback taxes, customs or excise duties, valued-added taxes, sales taxes, consumption taxes and other taxes (except income taxes) or duties relating to sales, any payment in respect of sales to any Governmental Authority, or with respect to any government subsidized program or managed care organization, each to the extent applicable and not already reflected in the amount invoiced; and

(e) freight, insurance and transportation costs for the Product to the extent included in the amount invoiced.

Net Sales shall be determined from books and records maintained in accordance with the Accounting Standards, as consistently applied, with respect to sales of any Product.

The sale of Products to Licensee's Affiliates and its Sublicensees shall not be deemed as a "sale" within the meaning of this definition except to the extent that such Affiliates and Sublicensees are end users of Products.

Net Sales will not include Products transferred for use in connection with clinical trials or other development activities, pre-clinical or non-clinical research and trials permitted under this Agreement, promotional use (including samples), compassionate sales or use or indigent programs.

If a Product is sold (i) as a single pharmaceutical product that includes, in combination with the Compound, one or more therapeutically-active ingredients other than the Compound (i.e., a "fixed-dose" combination), or (ii) as a combination therapy comprised of a Product and one or more products containing therapeutically-active ingredients (other than Compound) sold under a single Regulatory Approval and priced as a unit at a single price (either (i) or (ii), a "**Combination**

Product"), then "**Net Sales**," for purposes of determining Royalty Payments on the Combination Product, shall be calculated as follows:

(1) when the components of the Combination Product are sold separately in the License Territory, by multiplying the Net Sales of the Combination Product (calculated before application of this formula) by the fraction A/(A+B), where A is the Adjusted Yakka Price at the time of first publication of the Adjusted Yakka Price of the Product, and B is the Adjusted Yakka Price at the time of first publication of the Adjusted Yakka Price of the component of the Combination Product other than the Product (the "**Supplemental Component**") in the License Territory of the Supplemental Component(s); provided, however, that the [***].

(2) when either the Product or the Supplemental Component are not sold separately in the License Territory, the Parties shall negotiate in good faith to determine an appropriate allocation of Net Sales for the Product and the Supplemental Component.

"**New Drug Approval**" means an approval by a Regulatory Authority of a Drug Approval Application.

"**OPKO Patents**" means all Patents in the License Territory (including any PCT applications except those that are not transferred to the License Territory) that (a) are Controlled by OPKO or its Affiliates as of the Effective Date or become Controlled by OPKO or its Affiliates during the Term, and (b) claim an invention that Cover the Compound or Product or OPKO Inventions. The list of OPKO Patents as of the Effective Date is set forth in Appendix B attached hereto and, upon request of Licensee, OPKO shall provide to Licensee a list of the then-current OPKO Patents. For the purposes of this Agreement, OPKO Patents shall not include Other Licensee Patents, Licensee Patents or Joint Patents.

"**OPKO Technology**" means all Technology that (a) is Controlled by OPKO or its Affiliates as of the Effective Date, or (b) is developed or generated, or otherwise becomes Controlled by OPKO or its Affiliates during the Term. For the purposes of this Agreement, OPKO Technology shall not include Other Licensee Technology or Licensee Technology.

"**OPKO Territory**" means the entire world other than the License Territory.

"**OPKO Trademark(s)**" means Rayaldee™, a trademark Controlled by OPKO in the License Territory, and any other trademark, service mark or logo developed, applied for, registered, or to be applied for or registered by OPKO or its Affiliates for use in connection with the sale of the Product in the License Territory.

"**Other Licensee(s)**" means any Third Party licensee of OPKO or its Affiliates (a) to which OPKO or its Affiliates have granted rights to the Compound and/or Product under OPKO Patents and/or OPKO Technology in the OPKO Territory and/or outside the Field, and/or (b) from which OPKO or its Affiliates have received a grant of rights to the Compound and/or Product under Other Licensee Patents and Other Licensee Technology. For clarity, Catalent is not regarded as an Other Licensee.

"**Other Licensee Patents**" means all Patents of an Other Licensee to the extent related to the Compound or Product to which OPKO or its Affiliates have obtained rights, solely to the extent OPKO or its Affiliates has the right to grant a license to Licensee under the terms of such rights.

"**Other Licensee Technology**" means all material Technology of an Other Licensee to the extent related to the Compound or Product to which OPKO or its Affiliates have obtained rights, solely to the extent OPKO or its Affiliates has the right to grant a license to Licensee under the terms of such rights.

"**Patents**" means (a) all patents and patent applications in any country or jurisdiction in the relevant territory, and (b) any substitutions, divisions, continuations, continued prosecution applications, continuations-in-part, provisional applications, priority applications (including rights of priority), reissues, renewals, registrations, additions, confirmations, re-examinations, extensions, validations, supplementary protection certificates and the like of any such patents or patent applications.

"**Person**" means an individual, sole proprietorship, partnership, limited partnership, limited liability partnership, corporation, limited liability company, business trust, joint stock company, trust, incorporated association, joint venture or similar entity or organization, including a government or political subdivision or department or agency of a government.

"**Phase II Clinical Trial**" means a human clinical trial of a compound or product for an indication, the principal purpose of which is a determination of safety and efficacy for such indication in a target patient population over a range of doses, as more fully defined in 21 C.F.R. § 312.21(b), or its successor regulation, or the equivalent in any foreign country.

"**Phase III Clinical Trial**" means a human clinical trial of a compound or product for an indication on a sufficient number of subjects that is designed to establish that the compound or product is safe and efficacious for its intended use, and to determine warnings, precautions and adverse reactions that are associated with the compound or product in the dosage range to be prescribed, and to support Regulatory Approval of the compound or product for such indication, as more fully defined in 21 C.F.R. § 312.21(c), or its successor regulation, or the equivalent in any foreign country.

"**PMDA**" means the Pharmaceutical and Medical Devices Agency of Japan and any successor agency thereto.

"**Product**" means a modified, extended, sustained release, or any release other than immediate release, pharmaceutical product that contains Compound, either alone or in combination with one or more therapeutically active substances, in all dosage forms and formulations, contained in or Covered by the OPKO Patents and/or OPKO Technology.

"**Regulatory Approval**" means any approvals, product and/or establishment licenses, registrations, permits, or authorizations of any federal, state or local regulatory agency, department, bureau or other governmental entity or Regulatory Authority, necessary for the manufacture,

distribution, use, storage, importation, export, transport, marketing and sale of the Product in a regulatory jurisdiction.

"**Regulatory Authority**" means any national (e.g., the FDA or PMDA), supra-national, regional, state or local regulatory agency, department, bureau or other governmental entity responsible for issuing any technical, medical and scientific licenses, registrations, authorizations and/or approvals of the Product that are necessary for the manufacture, distribution, use, storage, importation, export, transport and sale of the Product in a regulatory jurisdiction.

"**Relevant Factors**" means all relevant factors that may affect the development, Regulatory Approval or commercialization of a Product, including (as applicable): actual and potential issues of safety, efficacy or stability; product profile (including product modality, category and mechanism of action); stage of development or life cycle status; actual and projected development, Regulatory Approval, manufacturing, and commercialization costs; any issues regarding the ability to manufacture or have manufactured any Product; the likelihood of obtaining Regulatory Approval; the timing of such Regulatory Approval; the current guidance and requirements for Regulatory Approval for the Product and similar products and the current and projected regulatory status; labeling or anticipated labeling; the then-current competitive environment and the likely competitive environment at the time of projected entry into the market and thereafter; past performance of the Product or similar products; present and future market potential; existing or projected pricing, sales, reimbursement and profitability; pricing or reimbursement changes; and proprietary position, strength and duration of patent protection and anticipated exclusivity.

"**Research**" means to conduct general research activities that are pre-clinical or non-clinical in nature, and that are [***]. For clarity, [***] or New Drug Approval (i.e., [***]), except that pre-clinical and non-clinical activities specifically related to the development and potential development of Product for the Initial Indications and Additional Indications in accordance with Section 6.6(d) shall be permitted and deemed to be Research.

"**Stand-alone Product**" means a Product is sold only as a single pharmaceutical product which does not include, in combination with the Compound, one or more therapeutically-active ingredients other than the Compound (i.e., a "fixed-dose" combination) and which is not sold as a combination therapy comprised of a Product and one or more products containing therapeutically-active ingredients (other than Compound) under a single Regulatory Approval and priced as a unit at a single price.

"**Sublicensee**" means an Affiliate or Third Party that has been granted a sublicense by a Party as permitted under Section 2.1 or 2.2 of this Agreement.

"**Technology**" means all information, in any form (including electronic form), that is not in the public domain and that is necessary or useful for the development, regulatory approval or commercialization of the Compound or the Product in the License Territory. Examples of Technology are, to the extent relating to the Compound or Product, biological, chemical, pharmacological, toxicological, medical or clinical, analytical, quality, manufacturing, research, regulatory and sales and marketing information. As used in this Agreement, the term "material Technology" refers to written (including electronic) information that is necessary or useful for the

development, regulatory approval or commercialization (but not including sales and marketing information) of the Compound or the Product in the License Territory.

"**Third Party(ies)**" means any Person other than OPKO and Licensee or their Affiliates.

"**Valid Claim**" means a claim of (a) an issued and unexpired patent included in the OPKO Patents, Licensee Patents or Other Licensee Patents that has not been (i) held unpatentable or unenforceable by a final decision of a court or other governmental body of competent jurisdiction, unappealable or unappealed within the time allowed for appeal, or (ii) abandoned or admitted to be invalid or unenforceable through reissue or disclaimer or otherwise, or (b) a pending patent application that continues to be prosecuted in good faith and has not been pending for longer than [***].

"**VAT**" means any value added, use or sales or similar tax imposed by applicable Governmental Authorities.

In addition to the defined terms set forth above, the following capitalized terms shall have the meaning ascribed to such terms in the Sections of this Agreement identified below:

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1.2 Interpretation.

(a) The words “hereof,” “herein” and “hereunder” and words of similar import when used in this Agreement shall refer to this Agreement as a whole and not to any particular provision of this Agreement, and section, schedule, exhibit and appendix references are to this Agreement unless otherwise specified. The words “will” and

“shall” shall have the same meaning. The meaning of defined terms shall be equally applicable to the singular and plural forms of the defined terms. Masculine, feminine and neuter pronouns and expressions shall be interchangeable.

The words "include," "includes" and "including" are not limiting and shall be deemed to be followed by the phrase "without limitation" or "without limiting," whether or not expressly stated.

(b) Whenever this Agreement refers to a number of days, unless otherwise specified, such number refers to calendar days. In the computation of periods of time from a specified date to a later specified date, the word "from" means "from and including"; the words "to" and "until" each mean "to but excluding," and the word "through" means "to and including."

(c) References to agreements and other contractual instruments shall be deemed to include all subsequent amendments and other modifications thereto, but only to the extent such amendments and other modifications are not expressly prohibited by the terms of this Agreement. References to this Agreement are to this Agreement as in effect as of the relevant time, and mean this Agreement as a whole, including all schedules, exhibits, or appendices hereto, which form part of the operative provisions of this Agreement, in each case, as amended or otherwise modified in accordance with the terms hereof.

(d) Unless otherwise specified, references to statutes or regulations are to be construed as including all statutory and regulatory provisions consolidating, amending or replacing the statute or regulation, and references to a particular Applicable Law include all rules and regulations promulgated by Governmental Authorities thereunder, whether or not expressly stated.

(e) The captions and headings of this Agreement are for convenience of reference only and shall not affect the construction of this Agreement.

(f) References in this Agreement to "Product-by-Product," mean that each of the following shall be deemed to be a single Product: (i) all Products marketed or sold [***]; and (ii) each Combination Product; provided, that [***] Products with the same active ingredients shall be regarded as [***], as long as they contain the [***] with [***].

(g) This Agreement has been prepared jointly by the Parties, and the provisions contained herein shall not be construed or interpreted for or against any Party because such Party drafted or caused such Party's legal representatives to draft any provision contained herein.

2. Grant of Rights

2.1 License to Licensee.

(a) Subject to the terms and conditions of this Agreement, OPKO hereby grants to Licensee and, to the extent any such rights are Controlled by an Affiliate of OPKO, OPKO shall cause such Affiliate to grant to Licensee:

(i) an exclusive, sublicenseable (subject to Section 2.1(c)), royalty-bearing license under the OPKO Patents and OPKO Technology to develop, use, import, export, offer to sell, sell and have sold Compounds and Product in the Field in the License Territory;

(ii) an exclusive, sublicensable (subject to Section 2.1(c)), fully paid-up, royalty-bearing license under OPKO's rights under the Joint Patents to develop, use, import, export, offer to sell, sell and have sold Compounds and Product in the Field in the License Territory;

(iii) a non-exclusive, sublicensable (subject to Section 2.1(c)), royalty-bearing license under the OPKO Patents and OPKO Technology to make and have made in the [***] solely for development and sale in the Field in the License Territory; and

(iv) a non-exclusive, sublicensable (subject to Section 2.1(c)), fully paid-up license under the OPKO Patents and OPKO Technology to [***] Compounds and Product solely in the [***].

(b) To the extent permitted by an agreement with Other Licensees, OPKO hereby grants to Licensee, and, to the extent any such rights are Controlled by an Affiliate of OPKO, OPKO shall cause such Affiliate to grant to Licensee, the same licenses set forth in Section 2.1(a) under Other Licensee Patents and Other Licensee Technology.

(c) Licensee may sublicense its rights under Section 2.1(a) and Section 2.1(b) to (i) its Affiliates without OPKO's prior written consent, or (ii) any Third Party with OPKO's prior written consent, which shall not be unreasonably withheld, delayed or conditioned ([***]). With respect to each sublicense that Licensee proposes to grant to a Third Party, Licensee shall notify OPKO in writing at least [***] Business Days in advance of the grant, including a description of the rights to be granted and the identity of the proposed Third Party sublicensee (which identity shall be deemed to be Confidential Information of Licensee). If OPKO does not respond to such notice granting or withholding its consent within [***] Business Days, OPKO will be deemed to have granted its consent to the proposed sublicense. Licensee shall ensure that: (A) each Sublicensee accepts all applicable material terms and conditions of this Agreement and shall use Commercially Reasonable Efforts to ensure that each Sublicensee complies with all applicable material terms and conditions of this Agreement; (B) each sublicense shall (1) be subject to an appropriate written agreement imposing on each Sublicensee the terms and conditions of this Agreement, including all restrictive covenants set forth in this Agreement, (2) contain a provision prohibiting such Sublicensee from further sublicensing its rights, and (3) not in any way diminish, reduce or eliminate any of Licensee's obligations under this Agreement; and (C) upon OPKO's request, Licensee shall provide to OPKO within [***] Business Days of such request, a copy of each sublicense agreement with a Third Party (after redacting any financial information and other provisions that are not necessary to understand the scope of the sublicense granted to such Sublicensee or to confirm that such sublicense is in compliance with the terms of this Agreement, including this Section 2.1(c)). In order to enable OPKO to exercise its rights under clause (C) above, Licensee shall notify OPKO promptly of sublicensing any of the licensed rights to a Third Party. For the avoidance of doubt, Licensee will remain directly responsible for all amounts owed to OPKO and the performance of all obligations under this Agreement. Licensee hereby expressly waives any requirement that OPKO exhaust any right, power or remedy, or proceed against a Sublicensee for any obligation or performance hereunder prior to proceeding directly against Licensee.

2.2 Grant Back Licensee to OPKO .

(a) Subject to the terms and conditions of this Agreement, Licensee hereby grants to OPKO and, to the extent any such rights are Controlled by an Affiliate of Licensee, Licensee shall cause such Affiliate to grant to OPKO:

(i) a non-exclusive, sublicenseable (subject to Section 2.2(b)), fully paid-up, royalty-free (subject to Section 16.4(a)(ii)), non-terminable (subject to Section 16.4(a)(ii)), perpetual license under the Licensee Patents and Licensee Technology to [***], develop, make, have made, use, import, export, offer to sell, sell and have sold Compounds and Product (A) in all fields of use in the OPKO Territory, and (B) outside the Field in the License Territory;

(ii) an exclusive, sublicensable (subject to Section 2.2(b)), fully paid-up, royalty-free (subject to Section 16.4(a)(ii)), non-terminable (subject to Section 16.4(a)(ii)), perpetual license under Licensee's rights under the Joint Patents in the Field in the OPKO Territory; and

(iii) an [***] to the Licensee Patents and Licensee Technology set forth in Section 2.2(a)(i), [***] (the "**Exclusive Grant-back License Option**"), on [***] to Licensee; provided, however, that Licensee shall retain the rights to such Licensee Patents and Licensee Technology to make, have made and [***] the Compound and Product in the [***].

OPKO shall be entitled to exercise the Exclusive Grant-back License Option during the OPKO Consideration Period and in accordance with the terms of Schedule 2.2(a).

(b) OPKO may sublicense its rights under Section 2.2(a) to its Affiliates and an Other Licensee; provided, that such [***] Other Licensee Patents and Other Licensee Technology to Licensee; provided, further, that (i) if such [***] OPKO to sublicense its rights to Other Licensee Patents and Other Licensee Technology to Licensee, OPKO may sublicense its rights under Section 2.2(a) to such [***] Licensee agrees to [***] for a similar grant of rights to Licensee Patents and Licensee Technology (taking into account the scope and materiality of the rights granted), which [***]; and (ii) if such Other Licensee [***] its Other Licensee Patents and Other Licensee Technology, [***] Licensee Patents and Licensee Technology to such Other Licensee. Notwithstanding the grant by OPKO of a sublicense to Licensee Patents and Licensee Technology, OPKO will remain directly responsible to Licensee for any actions by the Sublicensee that violate the scope of the license and, in connection therewith, OPKO hereby expressly waives any requirement that Licensee exhaust any right, power or remedy, or proceed against a Sublicensee for any obligation or performance hereunder prior to proceeding directly against OPKO.

2.3 Retained Rights.

Neither Party grants to the other Party any rights or licenses in or to any intellectual property, whether by implication, estoppel or otherwise, other than the license rights that are expressly granted under this Agreement. For the avoidance of doubt, OPKO retains all of its rights with respect to Compounds, Product, the OPKO Patents, the OPKO Technology and the OPKO Trademarks in order to (a) make and have made Compounds and Product in the License Territory, (b) conduct [***] and pre-clinical or non-clinical development of Compounds and Product in the Field in the License Territory, and (c) develop, use, import, export, offer to sell, sell and have sold Compounds and Product (i) in the OPKO Territory in all fields of use, and (ii) in the License Territory in all fields of use other than the Field, subject to Licensee's right to obtain an Expanded License for Additional Indications pursuant to Article 4.

2.4 Subcontracting.

Subject to the limitations on sublicenses set forth in Section 2.1(c), [***]. Licensee shall be responsible for the performance of all actions, agreements and obligations to be performed by any of its subcontractors under the terms and conditions of this Agreement, and shall use Commercially Reasonable Efforts to cause its subcontractors to comply with the provisions of this Agreement in connection with such performance. Any breach by Licensee's subcontractors of any of Licensee's obligations under this Agreement shall be deemed to be a breach by Licensee, and OPKO may proceed directly against Licensee without any obligation to first proceed against Licensee's subcontractors.

2.5 Ex-Territory and Ex-Field Activities.

(a) Licensee hereby covenants and agrees that, during the Term, Licensee shall not (and shall cause its Affiliates, Sublicensees and subcontractors not to), either itself or through a Third Party, market, promote or actively offer for sale the Product (i) outside the Field in the License Territory, or (ii) in any field of use in the OPKO Territory. Without limiting the generality of the foregoing, with respect to the OPKO Territory, Licensee shall not (A) engage in any promotional activities relating to the Product directed solely to customers in the OPKO Territory, or (B) solicit orders from any purchaser that intends to, or Licensee has a reasonable basis for believing may intend to, distribute the Product in the OPKO Territory. To the extent permitted by Applicable Law, including applicable antitrust laws, if Licensee receives any order for the Product under the preceding clause (B), then Licensee shall immediately refer that order to OPKO and shall not accept any such order or deliver or tender (or cause to be delivered or tendered) the Product under such order. If Licensee should reasonably know that a customer or distributor is engaged itself or through a Third Party in the sale or distribution of the Product in the OPKO Territory or outside the Field within the License Territory, then Licensee shall (1) within [***] Business Days of gaining knowledge of such activities, notify OPKO regarding such activities and provide all information available to Licensee that OPKO may reasonably request concerning such activities, and (2) take Commercially Reasonable Efforts (including cessation of sales to such customer) necessary to limit such sale or distribution, unless otherwise agreed in writing by the Parties.

(b) OPKO hereby covenants and agrees that, during the Term, OPKO shall not (shall cause its Affiliates not to, and shall use reasonable efforts to cause its Other Licensees, sublicensees and subcontractors not to), either itself or through a Third Party, market, promote or actively offer for sale the Product for use in the Field in the License Territory. Without limiting the generality of the foregoing, with respect to the License Territory, OPKO shall not (i) engage in any promotional activities relating to the Product for use in the Field directed solely to customers in the License Territory, or (ii) solicit orders from any purchaser that intends to, or OPKO has a reasonable basis for believing may intend to, distribute the Product in the License Territory for use in the Field. To the extent permitted by Applicable Law, including applicable antitrust laws, if OPKO receives any order for the Product under the preceding clause (ii), then OPKO shall immediately refer that order to Licensee and shall not accept any such order or deliver or tender (or cause to be delivered or tendered) the Product under such order. If OPKO should reasonably know that a customer or distributor is engaged itself or through a Third Party in the sale or distribution of the Product for

use in the Field in the License Territory, then OPKO shall (A) within [***] Business Days of gaining knowledge of such activities, notify Licensee regarding such activities and provide all information available to OPKO that Licensee may reasonably request concerning such activities, and (B) take Commercially Reasonable Efforts (including cessation of sales to such customer) necessary to limit such sale or distribution, unless otherwise agreed in writing by the Parties.

2.6 Licensee Right of First Refusal for [***] Products .

OPKO hereby grants to Licensee a right of first refusal (the " **ROFR**") to obtain an [***] to develop and commercialize in the License Territory any pharmaceutical product (other than a Product) containing [***] (including, but not limited to, [***]) [***]. If at any time during the Term OPKO or its Affiliates intend to enter into discussions or negotiations with a Third Party with respect to any license to develop or commercialize the [***] in the License Territory or plans to develop or commercialize the [***] by itself or through its Affiliate in the License Territory, OPKO shall provide written notice of its intention to Licensee (the "**ROFR Notice**"). Licensee shall have the right to exercise the ROFR by delivery to OPKO of a written notice of exercise (the "**ROFR Exercise Notice**") within [***] days after the date it receives the ROFR Notice. If Licensee exercises the ROFR by delivery to OPKO of the ROFR Exercise Notice, then the Parties and, if applicable, OPKO's Affiliates shall have [***] days from the date of the ROFR Exercise Notice (the "**ROFR Negotiation Period**") to negotiate in good faith the terms of such exclusive license, which terms shall be commercially reasonable for an exclusive license of such type. If (a) Licensee has not delivered an ROFR Exercise Notice to OPKO within the [***] day period set forth above, (b) Licensee notifies OPKO prior to the expiration of the [***] day period set forth above that it does not intend to exercise the ROFR, or (c) the Parties and, if applicable, OPKO's Affiliates are unable to reach agreement on the economic or other terms for such exclusive license prior to the expiration of the ROFR Negotiation Period, then OPKO, or its Affiliates, shall have the right to license to a Third Party the right to develop and commercialize in the License Territory [***] or to develop and commercialize them by themselves in the License Territory; provided, that OPKO or its Affiliates shall not, within [***] days of the applicable date described in clause (a), (b) or (c) of the foregoing sentence, offer to grant a license to a Third Party for the development and commercialization of the [***] in the License Territory on more favorable terms, taken as whole, than those last offered to Licensee without reoffering those terms to Licensee, which Licensee shall have [***] days to accept or reject. If OPKO or an Affiliate intend to conduct such development or commercialization of [***] directly or if OPKO (or its Affiliate) and Licensee do not reach an agreement pursuant to the foregoing, and such development or commercialization [***] by Licensee or its Affiliates in the Field in the License Territory, OPKO and Licensee shall [***].

3. Term

3.1 Term.

The term of this Agreement shall commence on the Effective Date and shall continue on a Product-by-Product basis until the expiration of all Royalty Terms and Extended Payment Terms under this Agreement, unless earlier terminated pursuant to Section 16.1 (the "**Term**").

3.2 Expiration.

Upon the expiration of the Royalty Term (and not including any early termination of this Agreement under Section 16.1) with respect to a Product, the licenses granted to Licensee under Section 2.1 shall become fully-paid, royalty-free, perpetual and non-exclusive. If Licensee or its Affiliates or Sublicensees use the OPKO Trademarks in the License Territory after the expiration of the Royalty Term for a Product, then Licensee's license to use the OPKO Trademarks shall remain exclusive so long as Licensee pays OPKO a royalty of [***] of any Net Sales in the License Territory with respect to such Product; provided, however, that Licensee shall not be required to make such royalty payment for any Calendar Quarter in which Net Sales does not reach [***] (the "**Extended Payment Term**"); provided further, that if the Net Sales do not reach [***] for [***] consecutive Calendar Quarters after expiration of the Royalty Term, then Licensee [***] in the future.

4. Additional Indications

4.1 OPKO Additional Indications.

OPKO hereby grants Licensee an exclusive option (the " **Licensee Option**") to acquire the right to develop and commercialize the Product in the License Territory for certain Additional Indications (the "**Expanded License**"), as further described in this Section 4.1.

(a) If OPKO and/or its Affiliates plan to develop and commercialize the Product in the License Territory for an Additional Indication (each such Additional Indication, an " **OPKO Additional Indication**"), OPKO shall provide Licensee written notice thereof (an "**OPKO Additional Indication Notice**") including (i) a proposal of the material terms and conditions for expansion of the Field to include the OPKO Additional Indication, (ii) the pre-clinical or nonclinical and/or clinical data, if any, generated by or on behalf of OPKO and/or its Affiliates to support the development and commercialization of the Product for the OPKO Additional Indication and, if available, and (iii) the then-applicable development plan of the Product in OPKO Territory.

(b) Licensee shall have the right to exercise the Licensee Option with respect to such OPKO Additional Indication by delivery to OPKO of a written notice of exercise (the "**Licensee Notice of Exercise**") within [***] days after the date it receives the OPKO Additional Indication Notice.

(c) If Licensee exercises the Licensee Option by delivery to OPKO of the Licensee Notice of Exercise, then the Parties shall have [***] days from the date it receives the Licensee Notice of Exercise (the "**OPKO Additional Indication Negotiation Period**") to negotiate in good faith to enter into an amendment to this Agreement to (i) [***], and (ii) revise and clarify any other provisions of this Agreement as are deemed necessary or appropriate in view of the grant of the Expanded License, as may be mutually agreed to.

(d) If (i) Licensee has not delivered a Licensee Notice of Exercise to OPKO within the [***] day period set forth in Section 4.1(b), (ii) Licensee notifies OPKO prior to the expiration of the [***] day period set forth in Section 4.1(b) that it does not intend to exercise the Licensee Option with respect to the relevant OPKO Additional Indication, or (iii) the Parties, and, if applicable, OPKO's Affiliates are unable to reach agreement on the economic or other terms for the Expanded License prior to the expiration of the OPKO Additional Indication Negotiation Period,

then OPKO shall have the right to develop or commercialize, by itself or through an Affiliate or Third Party licensee, the Product for such OPKO Additional Indication in the License Territory; provided, that OPKO and its Affiliates shall not, within [***] days of the applicable date described in clause (i), (ii) or (iii) of the foregoing sentence, offer to grant a license to a Third Party for the development and commercializaton of the Product in the License Territory for the OPKO Additional Indication on more favorable terms, taken as a whole, than those last offered to Licensee without reoffering those terms to Licensee, which Licensee shall have [***] days to accept or reject. If OPKO or an Affiliate intend to conduct such development or commercialization of the Products directly for OPKO Additional Indication or if OPKO and Licensee do not reach an agreement pursuant to the foregoing, and such development or commercialization [***] development or commercialization of the Product [***] by Licensee or its Affiliates in the [***], OPKO and Licensee shall [***].

4.2 Licensee Additional Indications.

Licensee shall have the right to propose to OPKO the development and commercialization of the Product in the License Territory for Additional Indications, and if such proposal is approved by OPKO, Licensee shall have the right to obtain an Expanded License with respect thereto, as further described in this Section 4.2.

(a) If Licensee desires to develop and commercialize the Product in the License Territory for an Additional Indication (each such Additional Indication, a "**Licensee Additional Indication**"), Licensee shall provide OPKO written notice thereof (a "**Licensee Additional Indication Notice**") including (i) a proposal of the material terms and conditions for expansion of the Field to include the Licensee Additional Indication, and (ii) the nonclinical and/or clinical data, if any, generated by or on behalf of Licensee to support the development and commercialization of the Product for the Licensee Additional Indication.

(b) OPKO shall, by delivery of a written notice to Licensee within [***] days after the date it receives the Licensee Additional Indication Notice (the "**OPKO Response Notice**"), either (i) approve the development and commercialization of the Product in the License Territory for the Licensee Additional Indication, or (ii) reject such development and commercialization if OPKO [***].

(c) If OPKO rejects Licensee's proposal to develop and commercialize the Product in the License Territory for the Licensee Additional Indication, then at the request of Licensee, OPKO shall in [***] with Licensee the [***] with respect thereto.

(d) If OPKO has accepted Licensee's proposal to develop and commercialize the Product in the License Territory for the Licensee Additional Indication, then the Parties shall have [***] days from Licensee's receipt of the OPKO Response Notice (the "**Licensee Additional Indication Negotiation Period**") to negotiate in good faith to enter into an amendment to this Agreement to (i) provide for the grant by OPKO to Licensee of the Expanded License in exchange for commercially reasonable consideration (which consideration shall be based on the commercial value of such Licensee Additional Indication and each Party's contribution to develop the Product for such Licensee Additional Indication), and (ii) revise and clarify any other provisions of this

Agreement as are deemed necessary or appropriate in view of the grant of the Expanded License, as may be mutually agreed to.

(e) If OPKO has rejected Licensee's proposal to develop and commercialize the Product in the License Territory for the Licensee Additional Indication other than in good faith in accordance with Section 4.2(b)(ii), OPKO shall not [***] with Licensee in accordance with the Section 4.2(d).

(f) If OPKO has rejected Licensee's proposal to develop and commercialize the Product in the License Territory for the Licensee Additional Indication (whether in good faith or otherwise) and OPKO desires to develop or commercialize, have developed or have commercialized the Product for the Licensee Additional Indication anywhere in the OPKO Territory, [***]. Notwithstanding the foregoing, in no event shall OPKO be [***] and commercialization of Product in the OPKO Territory [***] therefor by Licensee (as evidenced by OPKO's written records).

(g) If the Parties are unable to reach agreement on the economic or other terms for the Expanded License prior to the expiration of the Licensee Additional Indication Negotiation Period and OPKO desires to enter into a license agreement with respect to the Licensee Additional Indication with a Third Party in the License Territory, OPKO shall give Licensee written notice of such desire including the proposed terms thereof, and Licensee will have a right of first refusal to enter into an agreement with OPKO on terms no less favorable in any material respect than those on which OPKO had offered to enter into an agreement with the Third Party for the License Territory. If Licensee desires to enter into such an agreement with OPKO, Licensee shall provide notice of its desire to negotiate with OPKO within [***] days after it receives OPKO's notice, and thereafter the Parties shall negotiate the final terms of the agreement during the [***] day period commencing upon receipt of the notice from Licensee. If Licensee does not provide notice of its desire to enter into such an agreement within [***] days after it receives OPKO's notice or the Parties cannot reach an agreement during such [***] day negotiation period, OPKO shall be free for a period of [***] days from the end of such [***] day period to enter into an agreement with a Third Party containing terms no more favorable to the Third Party in any material respect than those that were presented to Licensee for the Licensee Additional Indication in the License Territory and Licensee shall have no further rights with respect to such Licensee Additional Indication. If at the end of the [***] day period, OPKO has not entered into such an agreement with the Third Party or if the agreement with the Third Party is terminated, the right of OPKO in the future to enter into a licensing or other arrangement with a Third Party with respect to the Licensee Additional Indication in the License Territory shall again be subject to the right of first refusal set forth in this Section 4.2(g). If OPKO or an Affiliate intend to conduct such development or commercialization of the Products [***] Additional Indication or if [***] an agreement pursuant to the foregoing, and such development or commercialization [***] of the Product in the Field by Licensee or its Affiliates in the License Territory, OPKO and Licensee shall [***].

(h) Notwithstanding anything contrary herein, if OPKO develops and commercializes the Product, by itself or through its Affiliates or Other Licensee, in the License Territory for the Licensee Additional Indication pursuant to this Section 4.2, OPKO shall not have the right to use or have used Licensee Trademarks or OPKO Trademarks (unless Licensee has

determined not to use OPKO Trademarks), to develop and commercialize the Product in such Licensee Additional Indication in the License Territory.

5. Fees and Payments

5.1 Upfront Payment.

In consideration for the rights under the OPKO Patents, Other Licensee Patents, Joint Patents, OPKO Technology, Other Licensee Technology (subject to Section 2.2(b)) and OPKO Trademarks granted to Licensee in this Agreement, Licensee shall pay to OPKO a non-refundable and non-creditable payment of Six Million United States Dollars ($6,000,000) within [***] days after the later of (a) the Effective Date, and (b) receipt from OPKO of all completed tax documents to file with tax authorities in Japan in order to reduce OPKO's liability ("**Tax Documents**") for the amount payable to OPKO under this Section 5.1.

5.2 Payment upon Commencement of OPKO Phase II Study .

In consideration for the rights under the OPKO Patents, Other Licensee Patents, Joint Patents, OPKO Technology, Other Licensee Technology (subject to Section 2.2(b)) and OPKO Trademarks granted to Licensee in this Agreement, Licensee shall pay to OPKO a non-refundable and non-creditable payment of Six Million United States Dollars ($6,000,000) within [***] days after the later of (a) notification by OPKO to Licensee of Initiation of the OPKO Phase II Study, and (b) receipt from OPKO of the Tax Documents for the amount payable to OPKO under this Section 5.2.

5.3 Milestone Payments.

As additional consideration for the rights under the OPKO Patents, Other Licensee Patents, Joint Patents, OPKO Technology, Other Licensee Technology and OPKO Trademarks granted to Licensee in this Agreement, Licensee shall pay to OPKO the non-refundable and non-creditable milestone payments in the amounts and upon the occurrence of the milestone events for the Product set forth below.

Milestone Event	Milestone Payment (in United States Dollars)
1. Initiation of the [***] in the License Territory	$[***]
2. [***] in the License Territory for the prevention or treatment of [***]	$[***]
3. [***] in the License Territory (a) for the prevention or treatment of [***] patients, or (b) for any other Initial Indication	$[***]
4. [***] in the License Territory for the prevention or treatment of [***]	$[***]
5. [***] in the License Territory (a) for the prevention or treatment of [***] patients, or (b) for any other Initial Indication	$[***]
6. First time aggregate Net Sales of Products in the License Territory exceed [***] in an Agreement Year	$[***]
7. First time aggregate Net Sales of Products in the License Territory exceed [***] in an Agreement Year	$[***]

Each such milestone payment shall be made within [***] days of the later of (a) the achievement or occurrence of the relevant milestone event, and (b) receipt from OPKO of the Tax Documents for the amount of such milestone payment. Each milestone payment will be payable only one (1) time and, for the avoidance of doubt, no more than One Hundred and Six Million United States Dollars ($106,000,000) in milestone payments shall be payable under this Section 5.3. For purposes of clarity, (i) if the PMDA accepts a Drug Approval Application for a Product in the License Territory but, at the time that such milestone was achieved, Licensee had not Initiated the first Phase III Clinical Trial for a Product in the License Territory, then the milestone payment with respect to Initiation of the first Phase III Clinical Trial for a Product in the License Territory shall become due and payable at the same time, and (ii) if Net Sales of the Product in the License Territory during a particular Agreement Year exceed [***], and it was the first Agreement Year in which Net Sales of the Product in the License Territory exceeded [***], then Licensee would owe both the [***] and [***] milestone payments and no other milestone payments would be due in any following Agreement Year with respect to such milestone events.

5.4 Royalty Payments.

Subject to the terms and conditions of this Agreement, during the Royalty Term, Licensee shall pay to OPKO royalty payments (the "**Royalty Payments**") on a Calendar Quarter basis in an amount equal to the aggregate annual Net Sales of Products within the License Territory multiplied by the Applicable Percentage, as may be adjusted as set forth in this Agreement. The "**Applicable Percentage**" shall be as follows:

Aggregate Net Sales in an Agreement Year	**Applicable Percentage**
For the portion up to and including [***]	[***]
For the portion in excess of [***] up to and including [***]	[***]
For the portion in excess of [***] up to and including [***]	[***]
For the portion in excess of [***]	[***]

By way of example and without limitation of the foregoing, if the aggregate Net Sales of Product are [***] in any Agreement Year, the calculation of Royalty Payments shall be as follows: [***] for the first [***] in Net Sales; [***] for the Net Sales in excess of [***] through [***]; and [***] for the Net Sales in excess of [***], totaling [***].

5.5 Royalty Term.

The Royalty Payments due under Section 5.4 will be payable on a Product-by-Product basis beginning from the First Commercial Sale and continuing until the last of the following (the "**Royalty Term**"):

(a) expiration of the last to expire Valid Claim (but, notwithstanding the definition thereof, only to the extent of OPKO Patents and Other Licensee Patents) Covering the Product in the License Territory;

(b) expiration of all regulatory and data exclusivity applicable to the Product in the License Territory; and

(c) if the indication first approved for the first Product is SHPT, (i) ten (10) years from the First Commercial Sale for such Product (the "**Initial Term**"), and (ii) four (4) years from the First Commercial Sale for any subsequent Product in the License Territory; provided that if a subsequent Product is launched during the Initial Term, the Royalty Payments for the subsequent Product shall continue for the longer of the duration of the Initial Term or four (4) years from the First Commercial Sale of the subsequent Product.

If the indication first approved for the first Product will not be SHPT, then the Parties shall promptly meet and discuss in good faith a commercially reasonable number of years to replace the number of years set forth in Section 5.5(c).

5.6 Royalty Reductions and Credits.

(a) If any Competitive Product is launched by a Third Party in the License Territory and thereafter (i) such Competitive Product during [***] consecutive Calendar Quarters achieves a market share (calculated on a unit basis) in the aggregate equal to or higher than [***] of the total unit sales of all Competitive Products and Products sold in the License Territory, or (ii) the [***] for the relevant Product is more than [***] below the [***] at the time of the relevant First Commercial Sale, then the Royalty Payments with respect to the relevant Product shall be

reduced by [***] starting with such [***] Calendar Quarter for so long as such Competitive Product is being sold in the License Territory.

(b) If Licensee, its Affiliates or permitted Sublicensees are required to pay royalties directly to a Third Party in consideration for a license under Relevant Patents, Licensee shall [***] any Royalty Payments due hereunder; provided, that Licensee, its Affiliates and permitted Sublicensees shall [***] to the Relevant Patents is required (i) due to a [***] or the [***] by Licensee, its Affiliates or permitted Sublicensees, or (ii) as a result of Licensee [***] its [***] from a Third Party. Notwithstanding the foregoing, in no event shall any Royalty Payments be reduced below [***] of the Royalty Payments that would otherwise be due to OPKO not including any such reductions.

(c) For clarification, as an example only, after applying the reductions in Section 5.6(a) and 5.6(b), in no event shall the Royalty Payments be reduced below [***], [***], [***] and [***], respectively, based on the Applicable Percentages set forth in Section 5.4.

5.7 Late Payments.

Any amount required to be paid by a Party hereunder which is not paid on the date due shall bear interest at a rate equal to the [***] day U.S. dollar LIBOR rate effective for the date that payment was first due as reported by The Wall Street Journal (Internet Edition) plus [***]. Such interest shall be computed on the basis of a year of three hundred sixty (360) days for the actual number of days payment is delinquent.

5.8 Reports, Timing and Method of Payments.

(a) Within [***] days following the end of each Calendar Quarter, commencing with the end of the first Calendar Quarter during which the First Commercial Sale occurs, Licensee shall provide OPKO with a report including (i) gross sales of Products in the License Territory during the prior Calendar Quarter in local currency, (ii) Net Sales of Products in the License Territory during the prior Calendar Quarter in local currency, and all calculations used to determine such Net Sales from gross sales, and (iii) a calculation of the amount (including applicable exchange rate) of the Royalty Payment due to OPKO under Section 5.4 with respect to the prior Calendar Quarter, including calculation of any reductions or credits against Royalty Payments taken in accordance with Section 5.6. Not later than [***] days following the end of each Calendar Quarter, Licensee shall pay to OPKO the Royalty Payment to which OPKO is entitled under Section 5.4 by wire transfer to a bank account designated in writing by OPKO.

(b) In the event that a Party disputes an invoice or other payment obligation under this Agreement, such Party shall timely pay the undisputed amount of the invoice or other payment obligation, and the Parties shall resolve such dispute in accordance with Article 21.

5.9 Taxes.

(a) Each Party shall be responsible for any income taxes payable by such Party on incomes made to it under this Agreement. Licensee shall have the right to deduct any withholding

tax required to pay or withhold on behalf of OPKO from the payments pursuant to this Article 5 and other payments as long as Licensee shall provide OPKO with certified receipts of the payments of such withholding taxes duly issued by the Governmental Authorities in the License Territory and shall give OPKO such assistance as may be reasonably necessary for Licensee to claim exemption from income tax in Ireland. The Parties acknowledge and agree that it is their mutual objective and intent to minimize, to the extent feasible, taxes payable with respect to this Agreement and that they shall use their Commercially Reasonable Efforts to cooperate and coordinate with each other to achieve such objective as allowed under Applicable Laws. To the extent that the Party making the payment under this Agreement ("**Paying Party**") is required to deduct and withhold taxes on any payment to the other Party (" **Receiving Party**"), Paying Party shall pay the amounts of such taxes to the proper Governmental Authority in a timely manner and promptly transmit to the other Party an official tax certificate or other evidence of such withholding sufficient to enable Receiving Party to claim credit or deduction of such payment of taxes. Receiving Party shall provide Paying Party with any completed tax forms that may be reasonably necessary in order for Paying Party not to withhold tax or to withhold tax at a reduced rate under an applicable bilateral income tax treaty. The Parties acknowledges that said tax forms have to be filed with the Governmental Authority periodically. Paying Party will file any Tax Documents with the relevant Governmental Authorities prior to the relevant payment and promptly after receipt thereof from Receiving Party. Each Party shall cooperate with the other to the extent reasonably requested for the purpose of filing any tax returns relating to sales, use, transfer, stamp, VAT, withholding, or similar taxes, if any, levied on amounts payable hereunder.

(b) For purposes of clarity, all sums payable under this Agreement shall be exclusive of VAT. In the event that any VAT is owing in Paying Party's jurisdiction in respect of any such payment, Paying Party shall pay such VAT and the payment in respect of which such VAT is owing shall be made by Paying Party without deduction for or on account of such VAT to ensure that Receiving Party receives a sum equal to the sum which it would have received had such VAT not been due.

5.10 Currency Exchange.

If any Product sold by Licensee under this Agreement is invoiced in a currency other than U.S. dollars, all Royalty Payments by Licensee to OPKO shall be converted into U.S. dollars at the average of exchange rates on the last days of all months in the applicable Calendar Quarter based on the middle market spot rate therefor published in The Wall Street Journal (Internet Edition).

5.11 Adjustments.

If there is any major change in the pharmaceutical regulatory environment relating to the Product in the License Territory (including, but not limited to, the drug pricing system and bundled payments), then upon the request of either Party, the Parties shall meet and discuss in good faith to determine whether an adjustment to the terms and conditions of this Agreement, including the financial provisions set forth in this Article 5, is appropriate.

6. Development

6.1 Development Responsibilities.

Licensee shall be responsible, at its sole cost and expense, for performing, or causing to be performed, all development activities necessary to obtain Regulatory Approval for the Product in the Field in the License Territory. Without limitation of the foregoing, Licensee agrees that Licensee and its Affiliates will use Commercially Reasonable Efforts to (a) develop the Product in the Field in the License Territory, and (b) obtain and maintain Regulatory Approval for the Product in the Field in the License Territory, in each case in accordance with the Development Plan (including the projected timelines set forth in the Development Plan). Licensee and its Affiliates shall conduct all such development activities in accordance with Applicable Laws.

6.2 Development Plan.

(a) The initial version of the plan setting forth the proposed overall program of development, including projected timelines for the completion of significant development activities (as such plan may be amended from time to time in accordance with this Agreement, the "**Development Plan**") is attached hereto as Appendix C. Except as set forth in this Section 6.2, Licensee shall have the right to modify the Development Plan [***] and consistent at all times with Article 9 and its obligations to use Commercially Reasonable Efforts to carry out its obligations under this Agreement, as applicable. Without limiting the foregoing or any provision of Article 9, if and when there is a [***] to be conducted by Licensee, Licensee shall [***] or JDC, and Licensee will otherwise provide OPKO with [***] to the Development Plan (including all changes thereto). To the extent any terms or conditions of the Development Plan expressly conflict with the terms or conditions of this Agreement, the terms and conditions of this Agreement shall control.

(b) Any change to the Development Plan that could reasonably be expected to have the [***] shall be approved by the mutual agreement of the Parties in accordance with Section 9.1(c)(ii).

6.3 OPKO Phase II Study.

OPKO or its Affiliates shall use Commercially Reasonable Efforts to Commence a Phase II Clinical Trial in the United States, the synopsis of which is attached hereto as Schedule 6.3 (the "**OPKO Phase II Study**"), by [***]. For the purposes of this Section 6.3, the term "**Commence**" shall mean that a potential study subject [***] in the OPKO Phase II Study.

6.4 Publications.

Neither Party nor its Affiliates or future Sublicensees may publish or otherwise disseminate peer reviewed manuscripts or give other forms of public disclosure such as abstracts and media presentations regarding the Compound or Product (such disclosure collectively, for purposes of this Section 6.4, "**Publication**"), without the opportunity for prior review by the other Party. A Party seeking Publication shall provide the other Party the opportunity to review and comment on any proposed Publication at least [***] days (or at least [***] days in the case of abstracts and media presentations) prior to its intended submission for Publication. The other Party shall provide the Party seeking Publication with its initial comments in writing, if any, within [***] days (or within

[***] days in the case of abstracts and media presentations) after receipt of such proposed Publication. The Party seeking Publication shall consider in good faith any comments thereto provided by the other Party and shall comply with the other Party's reasonable request to remove any and all of such other Party's Confidential Information from the proposed Publication. In addition, the Party seeking Publication shall delay the submission for a period of up to [***] days in the event that the other Party can demonstrate reasonable need for such delay in order to accommodate the preparation and filing of a patent application. If the other Party fails to provide its comments to the Party seeking Publication within such [***]-day period (or [***] period, as the case may be), such other Party shall be deemed not to have any comments, and the Party seeking Publication shall be free to publish in accordance with this Section 6.4. Notwithstanding the foregoing, the Parties acknowledge and agree that from time to time on a case by case basis, a Party may request to expedite the timelines set forth above for review and comment by the other Party of a manuscript, abstract or presentation. In such event, the Parties will work together in good faith to accommodate the requesting Party's timeline. The Party seeking Publication shall provide the other Party with a copy of the Publication at the time of the submission. Each Party agrees to acknowledge the contributions of the other Party and/or its Affiliates, Sublicensees or Other Licensees and their employees in all Publications as scientifically appropriate. In addition, the Parties shall discuss in good faith an appropriate procedure to coordinate comments on the publications regarding the Compound and Product by the Parties, its Affiliates, existing and future Sublicensees, and Other Licensees.

6.5 Development Records.

(a) Licensee and its Affiliates shall maintain complete and accurate records of all work conducted by or on behalf of Licensee in furtherance of the development of the Product in the Field in the License Territory and all material results, data and developments made in conducting such activities. Such records shall be maintained in sufficient detail and in good scientific manner appropriate for patent and regulatory purposes and in accordance with Applicable Laws.

(b) OPKO and its Affiliates shall maintain, and OPKO shall use reasoanble efforts to cause any Other Licensee to maintain, complete and accurate records of (i) all work conducted by OPKO in furtherance of the development of the Product (A) outside the Field in the License Territory, and (B) in the OPKO Territory, and (ii) all material results, data and developments made in conducting such activities, in each case to the extent reasonably necessary or useful to support Licensee's development of the Product in the Field in the License Territory. Such records shall be maintained in sufficient detail and in good scientific manner appropriate for patent and regulatory purposes and in accordance with Applicable Laws.

6.6 Data Sharing.

(a) Within [***] days after the Effective Date, OPKO shall, [***], transfer to Licensee, all material data, results and reports included within the OPKO Technology and the Other Licensee Technology, that is necessary [***] to develop the Compound and the Product in the Field in the License Territory.

(b) From time to time during the Term, OPKO shall transfer to Licensee in a timely manner any new material data, results and reports included within the OPKO Technology and the Other Licensee Technology, that is necessary [***] to develop the Compound and the Product in the Field in the License Territory that was not previously transferred to Licensee; provided, that any such material data, results and reports included within the OPKO Technology and Other Licensee Technology that is provided by OPKO to Licensee under this Section 6.6(b) (i) [***] Technology, and (ii) subject to Section 17.3, will be provided to Licensee with Licensee [***]. For clarity, OPKO shall ensure that (A) all data, results and reports related to safety included within [***] will be shared to Licensee [***]; and that (B) any data, results and reports generated from clinical studies conducted [***] for the treatment of SHPT in dialysis patients (including Phase II Clinical Trials and Phase III Clinical Trials) [***].

(c) From time to time during the Term, Licensee shall transfer to OPKO in a timely manner all material data, results and reports included within the Licensee Technology that is necessary or useful to develop the Compound and the Product (i) in all fields of use in the OPKO Territory, and (ii) outside the Field in the License Territory.

(d) Licensee shall share with OPKO, through the JSC or JDC, a written plan describing any and all [***] relating to the Compound and the Product intended to be conducted by or on behalf of Licensee, its Affiliates and permitted Sublicensees in the [***], as well as all material data, results and reports of [***] relating to the Compound and Product conducted by or on behalf of Licensee, its Affiliates and permitted Sublicensees in the [***]. OPKO shall have the right to share all material data, results and reports included within the Licensee Technology to an Other Licensee [***] included within such Other Licensee Technology. If such [***] and reports to Licensee, OPKO shall ensure that such [***] shall [***] consideration to be granted to rights to access similar data, results and reports included within Licensee Technology, [***] over by OPKO to Licensee.

6.7 Reimbursement of Certain Costs for Pre-Clinical or Non-Clinical Studies .

[***] of the costs and expenses incurred by Licensee for [***] relating to the Compound or Product that are required by the PMDA or which Licensee reasonably believes is necessary to obtain Regulatory Approval for the Product for treatment of SHPT in the License Territory; provided that such [***] in the aggregate [***] ("**Reimbursable Expenses**"). Upon OPKO's request, Licensee shall deliver to OPKO at [***] a copy (in English) of the final study reports for the studies whose cost has been reimbursed by [***] (or are to be reimbursed by [***], in accordance with this Section 6.7), including all underlying raw data, and OPKO shall have the right to use the data and reports of such studies in accordance with Section 6.6. [***] shall deliver to [***] an invoice within [***] after the end of each Calendar Quarter during which any [***] were incurred by [***] setting forth an itemized breakdown of [***]. Upon request by [***], [***] shall promptly provide to [***] relevant supporting documentation relating to such [***]. [***] shall pay any such invoice within [***] after receipt thereof. If Reimbursable Expenses were paid by [***] to a Third Party vendor in local currency, the foreign exchange rate set forth in Section 5.10 shall apply with respect to the conversion of such amounts to U.S. Dollars.

6.8 Cooperation on Development.

Upon Licensee's request, OPKO and its Affiliates shall reasonably cooperate with Licensee for Licensee's development, including manufacturing development and toxicological or pharmacokinetic studies, necessary or useful to develop and commercialize the Product in the Field in the License Territory. The [***] and any [***] of OPKO for such activities shall be promptly [***]; provided, however, that such [***] prior to commencement of the related activities. Such cooperation shall include:

(a) supplying sample materials to be used for toxicological or pharmacokinetic studies (e.g. radio labeled standards and metabolite reference standards);

(b) supplying reference standard materials and other sample materials to be used for the analysis of the Compound and Product, in case OPKO or its Affiliate supply the Product pursuant to Section 10.2 (e.g. reference standard of API and impurities); and

(c) conducting development works (e.g. analytical method development, analytical method transfer, and modification to the dosage or formulation (e.g. colors) of the Product).

7. Regulatory Matters

7.1 Regulatory Filings and Regulatory Approvals.

(a) Licensee shall be responsible for preparing and filing Drug Approval Applications and seeking and maintaining Regulatory Approval for the Product in the Field in the License Territory, including preparing all documentation and reports necessary in connection therewith, as well as securing data and market exclusivity where applicable in compliance with the Act on Drugs and Medical Devices and other Applicable Laws in the License Territory. All such Drug Approval Applications and Regulatory Approvals shall be owned by Licensee and Licensee shall promptly provide to OPKO a copy of each such Drug Approval Application, Regulatory Approval and material submission to and communication with a Regulatory Authority regarding the same. Upon OPKO's request, Licensee shall, [***], provide an English translation thereof. Except as expressly set forth in this Agreement, [***] incurred by Licensee in connection with the preparation, filing and maintenance of Drug Approval Applications and Regulatory Approvals for the Product in the Field in the License Territory shall be borne solely by [***]. Notwithstanding the foregoing to the contrary, any costs and expenses related to the translation to English of the Drug Approval Applications, Regulatory Approvals or material communications with a Regulatory Authority in the License Territory to be provided to OPKO by Licensee shall be borne by [***], while any costs and expenses related to the translation to Japanese of the Drug Approval Applications, Regulatory Approvals or material communications with a Regulatory Authority in OPKO Territory to be provided to Licensee shall be borne by [***].

(b) OPKO shall (i) make available to Licensee all information, data, and reports Controlled by OPKO or its Affiliates that Licensee reasonably indicates to OPKO is required to file Drug Approval Applications or obtain Regulatory Approval for the Product in the Field in the License Territory, (ii) make its personnel with relevant subject matter expertise available on a

reasonable basis to consult with Licensee with respect thereto. Licensee shall reimburse the out-of-pocket expenses incurred by OPKO.

(c) If OPKO, its Affiliates or its contract manuracturers desire to protect their respective trade secrets, OPKO shall, or shall use reasonable efforts to cause its contract manufacturers to, submit and maintain an appropriate drug master files application(s) in accordance with the Applicable Law in the License Territory at the cost of OPKO or the contract manufacturers.

(d) If OPKO does not have the rights to provide the information of the nature described in Section 7.1(b)(i) to Licensee for its use in the Field and the License Territory, then OPKO shall use [***] to [***].

7.2 Right of Reference to Regulatory Filings; Third Party Clinical Data .

(a) Each Party shall have the right of cross-reference to the other Party's regulatory filings to the extent necessary to obtain Regulatory Approval for the Product in such Party's respective territory.

(b) OPKO shall use reasonable efforts to ensure that Licensee has the right of cross-reference to an Other Licensee's regulatory filings for the purposes described in the foregoing sentence. OPKO may grant the right to cross-reference to Licensee's regulatory filings only to an Other Licensee that has agreed to grant Licensee the reciprocal right of cross-reference.

(c) If [***] is required to [***] in order to obtain the right to cross-reference an Other Licensee's regulatory filings (including, clinical data), then prior to providing Licensee with any, or a right of reference thereto, other than as required by Applicable Law, the Parties shall mutually agree on an [***] or other [***] by Licensee; provided, however, that (i) OPKO shall ensure that such Other Licensee shall agree to [***]; and (ii) if such Other Licensee does not permit Licensee the right to cross-reference to an Other Licensee's regulatory filings, [***] to Licensee's regulatory filings.

7.3 Cooperation.

Each Party shall keep the other Party informed of any material regulatory developments relating to the Product in its own territory through reports at the JSC meetings, or more frequently if the circumstances reasonably require. The Parties shall consult and cooperate in (a) the preparation of each Drug Approval Application for the Product in the Field in the License Territory, and (b) the maintenance of Regulatory Approvals for the Product in the Field in the License Territory; provided that Licensee shall be primarily responsible for interactions with Regulatory Authorities throughout the License Territory. Licensee shall provide OPKO with reasonable advance notice of any material scheduled meeting with the PMDA or any other Regulatory Authority in the License Territory relating to any Drug Approval Application or Regulatory Approval for the Product. Licensee shall duly take OPKO's input into consideration and, if OPKO desires and permitted by Applicable Law, permit OPKO to participate in any such meeting, as long as the interpreters for OPKO's benefit are paid for by OPKO. Licensee shall (i) provide OPKO with copies of any minutes or other records,

in English, relating to such meetings with Regulatory Authorities in a timely manner, and (ii) promptly inform OPKO about any significant Regulatory Approval milestones achieved.

7.4 Threatened Regulatory Action.

Each Party shall promptly notify the other Party of any information it receives regarding any threatened or pending action, inspection or communication by any Regulatory Authority against itself, its Affiliates, Other Licensees, Sublicensees or any of its subcontractors (including those in the supply and distribution chain of the Product), which may materially and adversely affect development, commercialization or regulatory status of the Product in the other Party's territory (a "**Regulatory Action**"). The Parties shall reasonably and in good faith consult with each other in an effort to determine a mutually acceptable procedure for addressing this Regulatory Action.

7.5 Recalls.

In the event that any Governmental Authority threatens or initiates any action to remove the Product from the market or there is any recall, withdrawal, market notification or equivalent action to remove the Product from the market (whether voluntary or involuntary) (a "**Recall**"), each Party shall notify the other Party thereof as soon as practicable. The Parties shall assist each other in gathering and evaluating the relevant information as is necessary of conducting a Recall. Each Party shall, and shall cause its Affiliates, and use reasonable commercial efforts to cause its Other Licensees, Sublicensees and subcontractors to, maintain adequate records to permit the Parties to trace the distribution and use of the Products in their respective territories. Unless otherwise agreed by the Parties in a subsequent written agreement, Licensee shall have the right to decide whether any Recall with respect to Products in the Field and in the License Territory should be commenced and Licensee shall have the obligation, at its expense to control and coordinate all efforts necessary to conduct such Recall for the Field and in the License Territory. Notwithstanding the foregoing, if a "Quality Agreement" or "Pharmacovigilance Agreement" has been executed and is applicable with respect to any recall, withdrawal or market notification of the Product in the License Territory, then any such recall, withdrawal or market notification shall be conducted as set forth in that agreement.

7.6 Clinical Trial Registries.

From and after the Effective Date, Licensee will be responsible, in consultation with the JDC, for registering, maintaining and updating any registries pertaining to any clinical trial for the Product conducted in the License Territory pursuant to this Agreement to the extent required by Applicable Laws (collectively, the " **Clinical Trial Registries**"). For clarity, Licensee will use reasonable efforts to ensure that the information on all Clinical Trial Registries is correct, consistent and compliant with Applicable Laws.

8. Commercialization

8.1 Licensee Efforts.

Subject to the terms and conditions of this Agreement, Licensee agrees that Licensee and its Affiliates will use Commercially Reasonable Efforts to (a) launch the Product in the License Territory as soon as commercially practicable after receipt of Regulatory Approval, and (b) continue diligently thereafter to commercialize, market, promote and sell the Product in the License Territory, in each case for each Initial Indication or Additional Indication for which the Product has received Regulatory Approval in the License Territory.

8.2 Promotional Activities.

(a) Upon request of Licensee, OPKO shall deliver to Licensee, [***], a copy of the then existing Marketing Material developed or used by OPKO or its Affiliates in connection with the promotion or marketing of the Product in the OPKO Territory. OPKO makes no representation as to the appropriateness or applicability of the Marketing Material in the License Territory. Licensee and its Affiliates shall, subject to Applicable Laws, have the right to use and modify all such Marketing Material in connection with its marketing of the Product in the License Territory [***]. Licensee and its Affiliates also shall have the right to create, develop and use other Marketing Material in the License Territory at [***]. Licensee shall ensure that any Marketing Material developed or used by Licensee or its Affiliates complies with all Applicable Laws in the License Territory. OPKO shall not have any liability with respect to use by or on behalf of Licensee of any Marketing Material provided by OPKO to Licensee under this Section 8.2(a).

(b) Upon request of OPKO, Licensee shall provide to OPKO a copy of any Marketing Material developed by Licensee or its Affiliates, including, if requested by OPKO, an English translation thereof, which translation will be provided at [***]. Subject to the terms and conditions of this Agreement, OPKO (and any of its Affiliates and Other Licensees) shall have the right to use in the OPKO Territory and modify such Marketing Material created and developed by Licensee for the License Territory [***]; provided, that OPKO shall be solely responsible for ensuring that such Marketing Material complies with any Applicable Laws in the OPKO Territory, and Licensee shall not have any liability with respect to use by or on behalf of OPKO of any Marketing Material provided by Licensee to OPKO under this Section 8.2(b).

(c) While Licensee and its Affiliates shall use Commercially Reasonable Efforts to [***] for branding the Product (including reasonably considering the use of a trademark consistent with OPKO Trademark for the Product), [***] using the trademarks that [***] from the viewpoint of maximizing the value of the Product in the License Territory. Licensee and its Affiliates shall allow the JSC to review the candidate trademarks and [***]. Any trademark selected by Licensee or its Affiliates (other than those originally owned by OPKO) shall be owned by [***] or its Affiliates ("**Licensee Trademark**") and will be assigned by [***] or its Affiliates to [***] upon early termination of this Agreement for any reason other than by Licensee in accordance with Section 16.1(b)(ii) or (iii).

(d) In addition, upon Licensee's request, OPKO shall assign or grant an exclusive license to Licensee to the OPKO Trademark Controlled by OPKO in the License Territory, which license will continue in perpetuity after the expiration or termination of the Royalty Term, subject to payment and other obligations set forth under Section 3.2 of this Agreement.

9. Governance

9.1 Joint Development Committee and Joint Steering Committee .

(a) Within [***] days following the date of this Agreement, the Parties shall form: (i) a joint steering committee (the "**JSC**") with responsibility for the overall coordination and oversight of activities under this Agreement and the Supply Agreement, and (ii) a specialized joint committee focusing on development and Regulatory Approval of Products in the Field in the License Territory (the "**JDC**"). The JSC and JDC shall have the responsibilities and authority allocated to it in this Article 9 and elsewhere in this Agreement, and as otherwise agreed by the Parties. The JSC and JDC may be referred to separately as a "**Committee**" and jointly as the " **Committees**".

(b) The Committees shall have representatives from each of OPKO and Licensee and their Affiliates. Each Party may replace its Committee representatives at any time upon written notice to the other Party. Each Committee shall have a chairperson. The chairperson of the JDC and JSC shall be designated by Licensee for the first Agreement Year, shall be designated by OPKO for the second Agreement Year, and shall alternate between the Parties on an annual basis thereafter. The chairperson shall be responsible for calling meetings, and preparing and circulating an agenda in advance of each meeting of such Committee. An OPKO designee shall be responsible for preparing and issuing minutes of each meeting within [***] thereafter. The minutes of each meeting shall, among other things, record all matters acted upon and approved or disapproved by the Committee, actions to be taken, and any matters the Committee failed to resolve. Such minutes will not be finalized until both Alliance Managers review and confirm in writing the accuracy of such minutes.

(c) Each Party's designees on a Committee shall, collectively, have [***] vote (the " **Party Vote**") on all matters brought before the Committee, which Party Vote shall be determined by consensus of such Party's designees present (in person or otherwise) at the meeting. Except as expressly provided in this Section 9.1(c), each Committee shall operate as to matters within its jurisdiction by [***] Party Vote. Any disagreement between the representatives of the Parties on the JDC as to matters within the JDC's jurisdiction shall be submitted for discussion and resolution by the JSC. If following such submission, the disagreement is still not resolved, then the disagreement shall be resolved by the Parties as follows:

(i) any disagreement regarding an amendment to the Development Plan that relates to whether [***];

(ii) any disagreement regarding an amendment to the Development Plan that relates to whether a [***];

(iii) any disagreement regarding modifications to the Development Plan other than items (i) and (ii) above, shall be resolved by [***]; and

(iv) any disagreement regarding any matters solely related to the OPKO Territory or matters outside the Field in the License Territory, shall be resolved by OPKO.

(d) Each Party will disclose to the other proposed agenda items along with appropriate information at least [***] Business Days in advance of each meeting of each Committee, as applicable; provided, that under exigent circumstances requiring a Committee's input, a Party may provide its agenda items to the other Party within a lesser period of time in advance of the meeting, or may propose that there not be a specific agenda for a particular meeting, and such items shall be included in such agenda if such other Party consents to such later addition of such agenda items or the absence of a specific agenda for such Committee meeting.

(e) Notwithstanding the Committee structure established under Section 9.1(a), each Party shall retain the rights, powers and discretion granted to it under this Agreement, and no such rights, powers, or discretion shall be delegated to or vested in a Committee unless such delegation or vesting of rights is expressly provided for in this Agreement or the Parties expressly so agree in writing. Without limiting the generality of the foregoing, no Committee shall have any authority or jurisdiction to amend, modify, or waive compliance with this Agreement, any of which shall require mutual written agreement of the Parties.

9.2 Joint Steering Committee.

Each Party shall appoint an equal number of up to [***] of its or its Affiliates' senior employees to serve on the JSC. The JSC shall: (a) oversee and coordinate the development of, and the preparation and filing of Drug Approval Applications and other regulatory submissions for, the Products in the License Territory in the Field; (b) oversee the supply of Products for the License Territory in the Field; (c) review material activities to be conducted in connection with commercialization of the Products in the License Territory in the Field; (d) review any [***] relating to the Compounds and Products in the [***] by Licensee, its Affiliates and permitted Sublicensees; and (e) oversee such other matters as are agreed by the Parties.

9.3 Joint Development Committee.

Each Party shall appoint [***] of its or its Affiliates' employees to serve on the JDC. The JDC shall coordinate as between the Parties communication and operations regarding the development of, and preparation and filing of, Drug Approval Applications and other regulatory submissions for, the Products in the License Territory in the Field. The JDC will also facilitate the exchange of data arising in clinical trials of Products relevant to the License Territory, whether conducted in or outside the License Territory or the Field.

9.4 Committee Meetings.

(a) The JSC shall meet at least semi-annually and the JDC shall meet at least quarterly, unless no later than [***] days in advance of any meeting there is a determination, by agreement of both Parties, that no new business or other activity has transpired since the previous meeting, and that there is no need for a meeting. In such instance, the next meeting will be scheduled. Each Party may also call a special meeting of the Committees in the event such Party reasonably believes that a significant matter must be addressed prior to the next regularly scheduled meeting. Committees may establish subcommittees; provided that such subcomittees are comprised of equal representation from both Parties and may dissolve them.

(b) The Committee meetings may, upon the agreement of both Parties, be via teleconference and/or videoconference; provided, however, that at least one (1) of the Committee meeting per Agreement Year shall be in person, such meetings to be held on an alternating basis between the United States and Japan, unless the Parties mutually agree otherwise in writing to waive such requirement.

(c) Each Party shall bear their own expenses in connection with attending meetings of the Committees.

9.5 Alliance Managers.

(a) Each of the Parties shall appoint a single individual to act as that Party's point of contact for day to day communications between the Parties relating to the activities conducted under this Agreement (each, an "**Alliance Manager**"). Each Party may change its designated Alliance Manager from time to time upon written notice to the other Party. Any Alliance Manager may designate a substitute to temporarily perform the functions of that Alliance Manager by written notice to the other Party.

(b) Each Alliance Manager shall be charged with creating and maintaining a collaborative work environment within the JSC and JDC. Each Alliance Manager will also: (i) be the point of first referral in all matters of conflict resolution; (ii) coordinate the relevant functional representatives of the Parties and their Affiliates in developing and executing strategies and the Development Plan for the Products in the License Territory in the Field; (iii) provide a single point of communication for seeking consensus both internally within the respective Parties' organizations and between the Parties regarding key strategy and Development Plan issues; (iv) identify and bring disputes to the attention of the JSC and JDC in a timely manner; (v) plan and coordinate cooperative efforts and internal and external communications; and (vi) coordinate governance activities, such as the conduct of JSC and JDC meetings and production of meeting minutes so that they occur as set forth in this Agreement, and take actions necessary to facilitate performance of relevant action items resulting from such meetings.

(c) The Alliance Managers shall attend all Committee meetings and support the chairperson of the JSC and JDC in the discharge of their responsibilities. The Alliance Managers shall be nonvoting participants in Committee meetings, unless they are also appointed members of a Committee; provided, however, that an Alliance Manager may bring any matter to the attention of any Committee if such Alliance Manager reasonably believes that such matter warrants such attention.

9.6 Global Development Meetings.

Subject to the agreement of the Other Licensees, OPKO and Licensee shall consider holding a meeting among OPKO, Licensee and the Other Licensees and their Affiliates to discuss the development status of the Product and, if agreed by all attendees at such meeting, to coordinate with respect to the global development strategy for the Product.

10. Manufacturing, Distribution and Supply

10.1 Manufacturing and Supply by Licensee.

Consistent with the license granted to Licensee in Section 2.1(a), Licensee shall have the right to manufacture and have manufactured Compound and Product in the License Territory and the [***] solely for its clinical, pre-clinical or non-clinical and commercial use in the Field in the License Territory. If Licensee elects to manufacture Compound and Product, then within [***] days of Licensee's election, OPKO shall transfer and deliver to Licensee, [***], copies of tangible embodiments of the OPKO Technology and, to the extent avaialable subject to Section 17.3, Other Licensee Technology, necessary to enable Licensee or its designee to manufacture Compound and/or Products for use in the Field in the License Territory. Additionally, upon Licensee's election, OPKO shall use Commercially Reasonable Efforts to provide to Licensee, to the extent that such information may be disclosed, information retained by any Third Party contract manufacturers engaged by OPKO to manufacture the Compound or Products so that Licensee may consider directly engaging such Third Party contract manufacturers. For clarity, an election by Licensee to manufacture Compound and/or Product would not preclude OPKO, under its retained rights, to make, and have made, Compounds and Product in the License Territory or conduct Research of Compounds and Product in the License Territory consistent with Section 2.3.

10.2 Manufacture and Supply by OPKO.

Upon Licensee's request, OPKO and Licensee shall negotiate in good faith the terms of a supply agreement (the "**Supply Agreement**") and related quality agreement (the "**Quality Agreement**") pursuant to which OPKO shall supply to Licensee, directly or through a Third Party, Product in bulk capsule form ("**Bulk Product**") to support the development, sale and commercialization of the Product in the Field in the License Territory. For clarity, Licensee shall be responsible for packaging the Product to meet any requirements under Applicable Law in the License Territory. In addition, OPKO shall supply reasonable quantities of Compound required by Licensee for [***] and pre-clinical or non-clinical development of the Product permitted under this Agreement. Notwithstanding the foregoing to the contrary, OPKO shall have no obligation to enter into a Supply Agreement with Licensee with respect to the supply of Product in a dosage form or formulation that is different than the dosage form or formulation that OPKO is manufacturing or has manufactured for the use of OPKO, its Affiliates and Sublicensees in the OPKO Territory; provided, however that, upon Licensee's request, OPKO and Licensee shall discuss in good faith OPKO or its Affiliates providing the Product with modifications necessary or useful for the development and commercialization of the Product in the Field in the License Territory. The clinical supply of Bulk Product and Compound for Research, pre-clinical or non-clinical work will be supplied to Licensee at [***] and the commercial supply of Bulk Product will be supplied to Licensee at [***]. Certain terms to be included in the Supply Agreement are set forth in Schedule 10.2 attached hereto and the Supply Agreement shall contain such other terms customary and reasonable for an agreement of such type.

10.3 ICH-M7 Compliance.

If requested by a Regulatory Authority in the License Territory, [***] shall complete ICH-M7 validation to assess and control DNA reactive (mutagenic) impurities that may exist in the Bulk Product and Compound supplied by OPKO to Licensee under the Supply Agreement. The cost for

such ICH-M7 validation shall be (a) borne solely by [***] for the License Territory, and (b) borne [***] if it is required for the License Territory [***] the License Territory.

10.4 Manufacturing Specific Provisions.

If OPKO supplies Bulk Product and/or Compound to Licensee, the following terms shall apply:

(a) Accreditation. OPKO and the Licensee acknowledge that, pursuant to Applicable Law, the manufacturing sites for the Compound and Product, including any test or storage facilities, are required to be accredited as of the time when the Licensee files for Regulatory Approval for the Product in the License Territory. In order to assist Licensee in obtaining Regulatory Approval for the Product in the License Territory, OPKO shall (i) cooperate reasonably with Licensee to apply for, or use diligent efforts to cause its contract manufacturers to apply for, or (ii) permit Licensee to apply on OPKO's behalf for, or use diligent efforts to cause its contract manufacturers to permit Licensee to apply for, on their behalf, accreditation to the Regulatory Authorities in the License Territory, prior to Licensee's anticipated date for the filing of a New Drug Approval for the Product in the License Territory. In the case of application by the Licensee on behalf of OPKO and/or its contract manufacturers, OPKO shall provide, or shall use diligent efforts to cause its contract manufacuturer to provide, Licensee with all documents and information available to OPKO or its contract manufacturer and reasonably necessary to support accreditation requested by the Licensee in a timely manner. In the event that OPKO or its contract manufacturer makes changes with respect to the following matters after the accreditation, OPKO shall notify, or shall use diligent efforts to cause its contract manufacturer to notify, Licensee within seven (7) days:

(i) corporate name or address of the manufacturer

(ii) name or address of the Person responsible for the manufacturing establishment;

(iii) name of the executives responsible for the services;

(iv) name of the manufacturing establishment;

(v) major part of buildings and facilities of the manufacturing establishment; and

(vi) category and (deemed) accreditation number, when a foreign manufacturer obtains additional accreditations for another category, or discontinues operation of their accredited manufacturing establishment.

(b) Audits of Manufacturing Facilities by Regulatory Authority. If a Regulatory Authority in the License Territory requests an inspection or audit of OPKO's facilities and/or a contract manufacturer's facilities manufacturing a Compound or Product (including any test or storage facilities), OPKO shall, and shall use diligent efforts to cause its contract manufacturer to, cooperate with the Licensee and the Regulatory Authority in fulfilling such request. Following

receipt of the inspection or audit observations of the Regulatory Authority (a copy of which OPKO shall provide as soon as reasonably possible to the Licensee; provided, that there shall be no obligation to provide information to the extent such information is not related to nor negatively affect a Compound or Product), OPKO shall, and shall cause its contract manufacturers, to use good faith and reasonable efforts to consult with Licensee and prepare the response to any such observations, in English. OPKO shall [***] associated with such an inspection or audit. Nothing contained within this Section 10.4 shall restrict either Party from making a timely report to a Regulatory Authority or take other action that it deems to be appropriate or required by Applicable Law.

(c) Audits of Manufacturing Facilities by Licensee. OPKO shall permit the Licensee to perform a standard GMP compliance audit at its manufacturing sites (including any test or storage facilities) relating to the Compound or Product [***] per year without cause upon reasonable notice during regular business hours. For clarity, OPKO shall permit the Licensee to perform a GMP compliance audit at its manufacturing site at any time for cause. An audit "for cause" shall mean an audit in response to a regulatory authority audit notice setting forth significant observations regarding quality system issues or failures.

11. Safety and Surveillance

11.1 Reporting.

Licensee shall be responsible for any reporting of matters regarding the safety of the Product, including Adverse Events, to the appropriate Regulatory Authority in the License Territory, in accordance with Applicable Laws. Licensee shall promptly notify OPKO of any such matter and furnish complete copies of such reports to OPKO in accordance with the Pharmacovigilance Agreement. In the event Licensee or OPKO should become aware of information that may require a Product recall, field alert, withdrawal or field correction arising from any defect in the Product, it shall immediately notify the other Party in writing.

11.2 Adverse Events.

Promptly after the Effective Date or as otherwise agreed by the Parties, the Parties shall agree upon the terms of a pharmacovigilance agreement (the "**Pharmacovigilance Agreement**"). The Parties shall implement the Pharmacovigilance Agreement and shall provide each other on a regular basis with any appropriate information that enables the other Party to meet its regulatory obligations with respect to the Product or that is relevant to the safe use of the Product, whether inside or outside the License Territory. The Pharmacovigilance Agreement will be reviewed jointly on an annual basis or when there is a material change in Applicable Laws governing Adverse Event reporting, whether inside or outside the License Territory. OPKO shall maintain the global safety database for the Product, to be set forth in greater detail in the Pharmacovigilance Agreement.

11.3 Medical Inquiries.

Following the Effective Date, Licensee shall be responsible for handling all medical questions or inquiries in the License Territory, including all Product complaints, with regard to any

Product sold by or on behalf of Licensee (or any of its Affiliates or Sublicensees) (including having a call center in connection therewith), in each case in accordance with Applicable Laws and this Agreement. OPKO shall immediately forward any and all medical questions or inquiries which it receives with respect to any Product sold by or on behalf of Licensee (or any of its Affiliates or Sublicensees) in the License Territory to Licensee in accordance with all Applicable Laws and Licensee shall immediately forward to OPKO any and all medical questions or inquiries that it receives with respect to Product sold by or on behalf of OPKO in the OPKO Territory or in the License Territory outside the Field, in each case in accordance with all Applicable Laws. OPKO shall be primarily responsible for handling any Product complaints related to quality of the Product if such Product was manufactured by or on behalf of OPKO, and Licensee shall (a) promptly refer all such Product complaints to OPKO, and (b) provide all assistance reasonably requested by OPKO in order to address such Product complaints in the License Territory. Licensee shall be primarily responsible for handling any Product complaints related to quality of the Product if such Product was manufactured by or on behalf of Licensee, and OPKO shall promptly refer all such Product complaints to Licensee.

12. Audit Rights

12.1 Audit Rights.

Licensee shall keep complete and accurate records which are relevant to Product revenues in the License Territory (including gross revenues and Net Sales) and payments under this Agreement (including milestone payments and Royalty Payments) and such records shall be maintained by Licensee for at least [***] years following their creation. OPKO shall have the right, at OPKO's expense, through an independent certified public accounting firm selected by OPKO that is internationally recognized as one of the four largest accounting firms in the world or like Person reasonably acceptable to Licensee, to examine such records during regular business hours upon reasonable notice during the Term and for [***] years after its expiration or termination to verify the amounts payable to OPKO under Article 5; provided, however, that such examination shall not take place more often than [***] per Agreement Year and shall not cover such records for more than the preceding [***]. OPKO shall bear the full cost of the audit unless such audit discloses that the deficiency as between the payments made to OPKO during the audited period differs by more than [***] from the amount the accountant determines is correct, and in such case Licensee shall pay to OPKO any outstanding amounts due to OPKO along with the reasonable fees and expenses charged by the accountant within [***] of such determination. If the audit reveals that Licensee made an overpayment, Licensee may offset the amount of such overpayment against its next scheduled future payment obligations.

13. Intellectual Property

13.1 Ownership of Intellectual Property.

(a) OPKO or its Affiliates, as the case may be, shall own all right, title and interest in and to all OPKO Patents, OPKO Technology, OPKO Trademarks and all other intangible property rights, including, without limitation, any and all inventions, discoveries, writings, trade secrets, methods, practices, procedures, engineering information, designs, devices, improvements,

manufacturing information and other technology, including any derivatives of any of the foregoing, whether or not patentable or copyrightable, and any patent applications, patents, or copyrights based therein, thereon and therefrom ("**Inventions**") that are made, discovered, conceived, reduced to practice or generated during the Term by OPKO or its Affiliates (or its or their employees or representatives), solely or with a Third Party, in connection with any activity that is related to the Compound or the Product ("**OPKO Inventions**").

(b) The Parties shall jointly own all right, title and interest in and to all Inventions made, discovered, conceived, reduced to practice or generated during the Term jointly by a Party or its Affiliates, on the one hand, and the other Party or its Affiliates, on the other hand (or its or their respective employees or representatives), with or without a Third Party, in connection with any activity that is related to the Compound or the Product ("**Joint Inventions**").

(c) Licensee or its Affiliates, as the case may be, shall own all right, title and interest in and to all Inventions made, discovered, conceived, reduced to practice or generated during the Term solely by Licensee, or its Affiliates (or its or their respective employees or representatives), with or without a Third Party, in connection with any activity that is related to the Compound or the Product ("**Licensee Inventions**").

(d) The determination of inventorship for Inventions under this Section 13.1 shall be in accordance with U.S. inventorship laws as if such Inventions were conceived or reduced to practice in the U.S.

(e) On a periodic basis during the Term, but no less frequently than [***] per Calendar Quarter, each Party shall disclose to the other Party all OPKO Inventions, Joint Inventions and Licensee Inventions.

(f) Subject to Sections 2.1(a)(ii) and 2.2(a)(ii), each Party shall have the right to practice its rights under Joint Patents and to license such rights to its Affiliates or a Third Party without the permission of or accounting or payment to the other Party.

13.2 Patent Prosecution.

(a) OPKO, at its expense, shall have [***] responsibility for [***] (the Patents referenced in clauses (i) through (iii), the "**OPKO Prosecution Patents**").

(b) Licensee, at its expense, shall have [***] responsibility for filing, prosecuting and maintaining all of the (i) [***] in the License Territory (the Patents referenced in clause (i) through (iii), the "**Licensee Prosecution Patents**"); provided, however, that [***] of the reasonable costs and expenses for filing, prosecuting and maintaining all of the Licensee Patents in the OPKO Territory that specifically Cover the Product and to which OPKO [***] shall be reimbursed by [***] to [***].

(c) [***], as the case may be. Each Party agrees to comply with all requirements of the applicable patent office in the relevant territory to secure the validity and enforceability of Patents (e.g., filing working statements), keep the other Party promptly and fully informed of the

course of patent prosecution or other related proceedings, provide the other Party with copies of all material communications from or responses to any patent office or similar patent authority regarding such Patent, and consider any comments of the other Party in good faith. For clarity, OPKO Patents shall be prosecuted in the name of OPKO or its Affiliates, Licensee Patents shall be prosecuted in the name of Licensee or its Affiliates, and Joint Patents shall be prosecuted in the name of both of OPKO and Licensee or their respective Affiliates.

(d) OPKO shall also have responsibility for filing for any applicable supplementary protection certificates, patent term extensions, pediatric extensions, or their equivalent, if available, in the License Territory with respect to the OPKO Prosecution Patents. Licensee agrees to cooperate with OPKO to secure any such supplementary protection certificates, patent term extensions or their equivalents.

(e) If OPKO wishes to abandon any OPKO Prosecution Patent in anywhere in the world, then, prior to abandonment, OPKO shall notify in writing Licensee at least [***] days in advance of any statutory bar or other deadline that would result in loss of such OPKO Prosecution Patent. Following such notification, Licensee may, at its option, notify OPKO in writing that it is electing to undertake the filing, prosecution, defense and maintenance of such to-be-abandoned OPKO Prosecution Patent. If Licensee elects to undertake the filing, prosecution, defense and maintenance of such OPKO Prosecution Patent by providing written notice thereof to OPKO, Licensee will be responsible for any direct, out-of-pocket costs relating thereto. For clarity, if Licensee has undertaken prosecution of an OPKO Patent under this Section 13.2(e), it shall no longer be considered an OPKO Patent under this Agreement for the purpose of the Royalty Term or otherwise.

(f) If Licensee wishes to abandon any Licensee Prosecution Patent anywhere in the world, then, prior to abandonment, Licensee shall notify in writing OPKO at least [***] days in advance of any statutory bar or other deadline that would result in loss of such Licensee Prosecution Patent. Following such notification, OPKO may, at its option, notify Licensee in writing that it is electing to undertake the filing, prosecution, defense and maintenance of such to-be-abandoned Licensee Prosecution Patent. If OPKO elects to undertake the filing, prosecution, defense and maintenance of such Licensee Prosecution Patent by providing written notice thereto to Licensee, OPKO will be responsible for any direct, out-of-pocket costs relating thereto. For clarity, if OPKO has undertaken prosecution of a Licensee Patent under this Section 13.2(f), it shall no longer be considered a Licensee Patent under this Agreement for the purpose of any royalty obligation contemplated hereunder.

(g) Without limiting the foregoing, OPKO shall keep Licensee reasonably informed of any challenge to the Patents owned or Controlled by OPKO that Cover the Product that is reasonably likely to materially and adversely affect the Product in the License Territory.

13.3 Patent Infringement of a Third Party Patent .

(a) In the event of the institution of any suit by a Third Party against either Party or their respective Affiliates, licensees or sublicensees in respect of patent infringement involving the manufacture, use, sale, license or marketing of the Product in anywhere in the world, such Party

sued or to whom notice or knowledge of such proceeding shall arise, shall promptly notify the other Party in writing.

(b) If an action, claim, demand, suit, or proceeding (a " **Claim**") alleging infringement involving the manufacture, use, sale, license or marketing of the Product anywhere in the License Territory is commenced against either Party or their Affiliates, licensees or sublicensees, then the Parties [***]. [***] Business Days after receiving notice of such Claim. [***] Business Days or if OPKO [***] to continue such defense [***], except for the expenses for which [***] is to indemnify [***] pursuant this Agreement. In that case, OPKO shall cooperate with Licensee and provide any documentation or other assistance reasonably requested by Licensee at [***] expense. In any case, the Party controlling the defense of such Claim shall keep the other Party promptly and fully informed of the course of patent litigation or other related proceedings, provide the other Party with copies of all material communications from or responses to any patent office or similar patent authority regarding such Patent, and consider any comments of the other Party in good faith.

13.4 Patent Enforcement.

(a) In the event that OPKO or Licensee or their Affiliates becomes aware of actual or threatened infringement of an OPKO Prosecution Patent or a Licensee Prosecution Patent anywhere in the world, that Party shall promptly notify the other Party in writing.

(i) OPKO shall have the first right to investigate and/or bring an infringement action against any Third Party relating to the OPKO Prosecution Patents. If OPKO elects to bring such action, then OPKO shall have full control over the conduct of such action, including the settlement thereof; provided that such settlement does not materially adversely affect Licensee's rights under this Agreement. Licensee may join the proceeding [***] with the counsel of its choice. Licensee shall reasonably assist OPKO and cooperate in any such action at OPKO's request, including being joined as a party in such action upon OPKO's written request. The cost of such action shall be borne by [***].

(ii) Licensee shall have the first right to investigate and/or bring an infringement action against any Third Party relating to the Licensee Prosecution Patents. If Licensee elects to bring such action, then Licensee shall have full control over the conduct of such action, including the settlement thereof; provided that such settlement does not materially adversely affect OPKO's rights under this Agreement. OPKO may join the proceeding [***] with the counsel of its choice, except in case that only Licensee's Patent within the License Territory is at issue. OPKO shall reasonably assist Licensee and cooperate in any such action at Licensee's request, including being joined as a party in such action upon Licensee's written request. The cost of such action shall be borne by [***].

(b) The Party having the first right to investigate and/or bring an infringement action in accordance with Section 13.4(a) shall provide information about its preliminary intention within [***] days after it first learns of any actual or alleged infringement of the relevant Patents. If the Party having the first right to investigate and/or bring an infringement action fails to notify the allegedly infringing party with respect to the relevant Patents and its infringement allegation

within [***] days after receiving such information or, thereafter, fails to initiate an enforcement action with respect to such actual infringement within [***] days [***] thereafter and the [***] this [***] day period, the other Party shall have the right to enforce the relevant Patents against such infringers to the extent such infringement relates to the manufacture, use, or sale of products Covered by the related Patents; provided, however, that (i) Licensee's investigation or infrigement action relating to OPKO Patents shall be limited to the Field in the License Territory and (ii) OPKO's investigation or infringement action relating to Licensee Patents shall be limited to the scope that OPKO is granted an exclusive license outside the License Territory. The cost of such action shall be borne by such other Party.

(c) Any [***] as follows:

(i) In case of infringement of the OPKO Patents in the Field in the License Territory, [***]; provided, however, that such received [***] in accordance with Article 5.

(ii) In case of infringement of the Licensee Patents that are exclusively licensed to OPKO, [***], (A) [***]; provided, however, that such received [***]; (B) to the extent such infringement does not fall within the scope of the exclusive license, [***].

(iii) In case of infringement of the Licensee Patents that are not exclusively licensed to OPKO, [***].

(iv) In case of infringement of the Joint Patents, [***].

(v) If the [***].

(d) In the event that entry of a product to a market segment in which the Product is sold in the License Territory appears imminent and the [***], OPKO shall take all reasonable actions to determine, within [***] days from the date on which OPKO has legally sufficient basis to believe that such product entry would infringe the OPKO Patents or any longer time period agreed by the Parties, whether OPKO intends to apply promptly and diligently for an interim injunction with regard to such possible product entry and shall promptly inform Licensee of such determination. If OPKO does not take such action within such [***] days, Licensee may take such action.

(e) In any case, the Parties shall reasonably assist each other and cooperate in any such investigation and litigation to ensure there is an aligned global litigation and enforcement strategy.

(f) Without limiting the foregoing, OPKO shall keep Licensee reasonably informed of the infringement or suspected infringement of Patents owned or Controlled by OPKO that Cover the Product that could reasonably be expected to adversely affect the Product in the License Territory.

13.5 Registration of Exclusive License (Senyo-Jisshiken)

(a) Subject to Section 13.5(b), OPKO shall, and shall cause its relevant Affiliates, to file at the Japan Patent Office a request to register as a registered exclusive license (a "*Senyo-*

Jisshiken" under Section 77 of the Japanese Patent Law) Licensee's exclusive license under the OPKO Patents to develop, use, import, export, offer to sell, sell and have sold Compounds and Product in the Field in the License Territory ("**JPO Registration Request**"), to the extent such license is granted to Licensee pursuant to Section 2.1(a)(i).

(b) The time by which OPKO shall comply with Section 13.5(a) shall depend on the type of OPKO Patent, as follows:

(i) in respect of OPKO Patents that are Controlled by OPKO or its Affiliates as of the Effective Date, OPKO shall comply by [***], to the extent such OPKO Patents remain Controlled by OPKO or its Affiliates at the date of filing the JPO Registration Request;

(ii) For any OPKO Patents not included in clause (i) above, OPKO shall use its reasonable endeavours to add such OPKO Patents within [***] days of such Patents becoming Controlled by OPKO or its Affiliates; provided, that [***].

(c) License shall not exercise its rights with respect to the Senyo Jisshiken if OPKO has initiated an enforcement action under Section 13.4(d), with respect to any OPKO Patent. Any breach of this Section 13.5(c) shall be deemed to be a material breach of this Agreement, but shall not be entitled to the cure periods therefor.

13.6 Other Licensee Patents

OPKO shall duly exercise its rights and comply with the obligations set forth under the terms of agreements with Other Licensees to file, prosecute, defend or maintain Other Licensee Patents. To the extent that OPKO has the right to file, prosecute, defend or maintain Other Licensee Patents pursuant to an agreement with that Other Licensee, such Other Licensee Patents shall be deemed to be OPKO Patents solely for the purposes of Sections 13.2 and 13.4, subject to the terms of the agreement with the Other Licensee.

13.7 Title to Trademarks.

The ownership and all goodwill from the use of OPKO Trademarks shall vest in and inure to the benefit of OPKO. The ownership and all goodwill from the use of Licensee Trademarks shall vest in and inure to the benefit of Licensee.

13.8 Trademark License of OPKO Trademark.

Upon Licensee's request, OPKO shall grant to Licensee a fully paid-up, exclusive license to use the OPKO Trademarks in the License Territory for the Term in connection with the marketing and promotion of the Product in the Field as contemplated in this Agreement, without limiting in any way OPKO's rights with respect to the OPKO Trademarks in the OPKO Territory; provided, however, that after expiration of this Agreement, Licensee's license may be exclusive and royalty-bearing pursuant to Section 3.2. OPKO shall use its Commercially Reasonable Efforts to obtain and secure the corresponding domain names in the License Territory that the Parties determine to

be appropriate and make such domain names available to Licensee under the conditions of this Section 13.8.

13.9 Maintenance of OPKO Trademarks.

(a) OPKO agrees to use Commercially Reasonable Efforts to register and maintain a registration for the OPKO Trademarks in the License Territory during the Term for use with the Product (including corresponding domain names). Such expenses incurred in connection with the OPKO Trademarks or domain names shall be paid [***]. In the event that any of the OPKO Trademarks are not available for use and registration in connection with the Product in the License Territory due to a rejection of the trademark by a government agency, actual or threatened opposition, cancellation or litigation as to use and/or registration of the OPKO Trademarks by a Third Party, and/or a decision by the JSC that use of the OPKO Trademarks is likely to cause confusion with another's trademark, OPKO shall use Commercially Reasonable Efforts to provide an alternate trademark and shall develop, search, file, register and maintain such alternate trademark at [***].

(b) OPKO shall maintain and monitor the OPKO Trademarks (including the corresponding domain names) and take all reasonable actions to protect the OPKO Trademarks (and the corresponding domain names) from similar Third Party trademarks filed in the License Territory.

(c) OPKO shall maintain and defend all the OPKO Trademarks (and corresponding domain names) as necessary to allow Licensee to fully exercise its rights under Sections 3.2 and 13.8.

(d) If OPKO wishes to abandon the OPKO Trademarks in anywhere in the License Territory, then, prior to abandonment, OPKO shall notify in writing Licensee at least [***] days in advance of any statutory bar or other deadline that would result in loss of such OPKO Trademark. Following such notification, Licensee may, at its option, notify OPKO in writing that it is electing to undertake the filing, prosecution, defense and maintenance of such to-be-abandoned OPKO Trademark. If Licensee elects to undertake the filing, prosecution, defense and maintenance of the OPKO Trademark by providing written notice thereof to OPKO, Licensee will be responsible for any direct, out-of-pocket costs relating thereto. For clarity, if Licensee has undertaken prosecution of an OPKO Trademark under this Section 13.9(d), it shall no longer be considered an OPKO Trademark under this Agreement for the purpose of Section 3.2 or otherwise.

13.10 Notification of Trademark Litigation.

(a) In the event of the institution of any suit by a Third Party against OPKO or Licensee for trademark infringement involving the marketing, promotion or sale of the Product in accordance with the annual marketing plan in the License Territory, the Party sued shall promptly notify the other Party in writing.

(b) In the event of any infringement of OPKO Trademark, OPKO shall defend such action [***], and [***] from any damages, judgment, costs and expenses (including, reasonable attorneys' fees) arising or resulting therefrom. Licensee shall assist and cooperate with OPKO, at

[***], to the extent necessary in the defense of such suit. In the event and, as a result of the suit, it becomes necessary to secure or file for a new trademark for the Product, OPKO shall be responsible for searching for and filing for such a mark pursuant to Section 13.9.

(c) In the event of any infringement of Licensee Trademark, Licensee shall defend such action [***], and [***] from any damages, judgment, costs and expenses (including, reasonable attorneys' fees) arising or resulting therefrom. OPKO shall assist and cooperate with Licensee, [***], to the extent necessary in the defense of such suit. In the event and, as a result of the suit, it becomes necessary to secure or file for a new trademark for the Product, Licensee shall be responsible for searching for and filing for such a mark pursuant to Section 13.9.

13.11 Trademark Infringement.

(a) In the event that OPKO or Licensee becomes aware of actual or threatened infringement of a OPKO Trademark anywhere in the License Territory, that Party shall promptly notify the other Party in writing. OPKO shall have the first right, but not the obligation, to investigate and/or bring an infringement and/or opposition or cancellation action against any Third Party. OPKO shall have full control over the conduct of such investigations and litigation. The cost of such investigation and litigation [***]. Any [***]; provided, however, that such received [***] in accordance with Article 5. Licensee shall reasonably assist OPKO and cooperate in any such investigation and litigation at OPKO's request, including being joined as a party in such action upon OPKO's written request.

(b) OPKO shall provide information about its preliminary intention with respect to any actual or threatened OPKO Trademark within [***] days after it first learns of such actual or alleged infringement. Licensee shall have the right to enforce such OPKO Trademark if OPKO does not initiate an enforcement action within [***] days after it first learns of such infringement. The cost of such litigation brought by Licensee shall be borne [***]. Any [***]; provided, however, that such received [***] in accordance with Article 5.

(c) In the event that OPKO or Licensee becomes aware of actual or threatened infringement of a Licensee Trademark anywhere in the License Territory, that Party shall promptly nofity the other Party in writing. Licensee shall have the sole right, but not the obligation, to investigate and/or bring an infringement and/or opposition or cancellation action against any Third Party. Licensee shall have full control over the conduct of such investigations and litigtion, including the settlement thereof [***]. [***] generated from such litigation.

13.12 Information and Settlements.

Each Party shall keep the other Party informed of the status of any patent or trademark infringement litigation or settlement thereof concerning the Product or the OPKO Trademarks, OPKO Patents, Licensee Patents and Joint Patents; provided, however that, except those only for Licensee Patents in the Field in the License Territory and Licensee Trademark in the License Territory, no settlement or consent judgment or other voluntary final disposition of any suit defended or action brought pursuant to this Article 13 shall be entered into without the consent of the other Party if such settlement shall require Licensee to be subject to an injunction or to make a monetary

payment or shall otherwise adversely affect the other Party's rights under this Agreement, such consent not to be unreasonably withheld.

13.13 Employees.

Each Party will require all of its and its Affiliates' employees to assign all Inventions that are developed, made or conceived by such employees to the Party according to the ownership principles described in this Article 13 free and clear of all liens, encumbrances, charges, security interests, mortgages or other similar restrictions. Each Party will also require any agents, independent contractors or sublicensees performing an activity pursuant to this Agreement to assign all Inventions that are developed, made or conceived by such agents, independent contractors or sublicensees to the Party according to the ownership principles described in this Article 13 free and clear of all liens, encumbrances, charges, security interests, mortgages or other similar restrictions. Each Party will be responsible for any payments required to be made to its or its Affiliates' employees, agents, independent contractors, or sublicensees in connection with any such assignment.

13.14 Third Party Licenses.

(a) If Third Party Patents are identified by either Party that Cover [***], and the Parties [***] under such identified Third Party patent applications or patents (for patent applications, assuming pending claims therein had issued) for the development, manufacture or commercialization of the Product in the Field in the License Territory to avoid infringement ("**Relevant Patents**"), [***] to obtain a license to such Relevant Patents, with the right to sublicense, in order to permit [***] to conduct their obligations and exercise their rights under this Agreement; provided, that if [***] declines to obtain such license, then [***] shall have the right to do so. The Parties will consult with each other with respect to the negotiation and the final form of such terms and conditions and discuss [***] upon which such Parties shall [***] to obtain the license; provided, however, that Licensee [***] in accordance with Section 5.6(b).

(b) If Third Party Patents are identified by either Party that [***] for the development, manufacture or commercialization of the Product in the Field in the License Territory, but the Parties [***] a license to such [***]; provided, that if [***].

14. Confidentiality

14.1 Disclosure of OPKO Technology.

To the extent that OPKO has disclosed or in the future discloses to Licensee any OPKO Technology, Licensee shall not acquire any ownership rights in such OPKO Technology by virtue of this Agreement or otherwise.

14.2 Confidential Information.

OPKO and Licensee shall not use or reveal or disclose to Third Parties (other than the Sublicensee) any confidential and proprietary information and materials, patentable or otherwise, in any form (written, oral, photographic, electronic, magnetic, or otherwise), including Technology,

which is disclosed to it by the other Party or otherwise received or accessed from the other Party in the course of performing its obligations or exercising its rights under this Agreement ("**Confidential Information**") without first obtaining the written consent of the disclosing Party, except as may be otherwise provided in, or required in order for a Party to fulfill its obligations under, this Agreement. This confidentiality obligation shall not apply to such information that (a) is or becomes a matter of public knowledge (other than by breach of this Agreement by the receiving Party), (b) is required by law to be disclosed, (c) the receiving Party can establish was already known to it or was in its possession at the time of disclosure without obligation of confidentiality, or (d) is disclosed to the receiving Party by a Third Party having the right to do so. The Parties shall take reasonable measures to assure that no unauthorized use or disclosure is made by others to whom access to such information is granted.

Nothing in this Agreement shall be construed as preventing either Party from disclosing any information received from the other Party to an Affiliate or Sublicensee of the receiving Party or agent who is necessary for the purposes of enabling the receiving Party to fulfill its obligations under this Agreement; provided, that the receiving Party shall be responsible for breaches of the confidentiality obligations by such Affiliate, Sublicensee or agent.

14.3 Public Announcements.

Upon execution of this Agreement, each Party may issue a press release in a form reasonably approved by the other Party in writing. After release of such press releases, no public announcement or other disclosure to Third Parties concerning the existence of or terms of this Agreement shall be made, either directly or indirectly, by either Party, except as may be legally required (including pursuant to stock exchange rules) or as may be required for financial reporting purposes, without first obtaining the written approval of the other Party and agreement upon the nature and text of such announcement or disclosure. A Party seeking public announcement shall, to the extent practicable and permitted under Applicable Laws, give reasonable prior advance notice of the proposed text of such announcement to the other Party for its prior review and approval. A Party commenting on such a proposed press release shall provide its comments, if any, within seven (7) Business Days after receiving the press release for review. A Party seeking public announcement shall consider in good faith any comments thereto provided by the other Party and shall comply with the other Party's reasonable request to remove any and all of such other Party's Confidential Information from the proposed publication to the extent that such Confidential Information may be removed under Applicable Laws, stock exchange rules or under financial reporting requirements.

14.4 Change of Control.

In the event that OPKO or any applicable Affiliate undergoes a Change of Control to a competitor of Licensee (as reasonably determined by Licensee), then the successor in interest to OPKO or any applicable Affiliate (a) shall prevent the disclosure of Confidential Information of Licensee beyond (i) personnel reasonably needing to have access to and knowledge of Confidential Information in support of the development and commercialization of the Compound and the Product, and (ii) personnel performing or immediately directing the day-to-day activities regarding the Compound and the Product, and (b) shall not disclose Confidential Information of Licensee to any personnel who are involved in the development or commercialization of any of the Competitive

Products. The purposes of such procedures shall be to prevent the use of Confidential Information for competitive reasons against Licensee.

15. Restrictive Covenants

15.1 Non-solicitation.

Without the prior written consent of the other Party, each of OPKO and Licensee agrees that during the term of this Agreement and for [***] following termination of this Agreement for any reason, neither it nor any of its Affiliates will directly or indirectly solicit for purposes of hiring any Person employed by the other Party or any of their Affiliates or who was employed by the other Party or any of their Affiliates within the then prior [***] months, or in any manner seek to induce any such Person to leave his or her employment; provided, however, that this restriction shall not apply to a general advertisement of employment. The foregoing covenant will only apply to persons employed by the other Party or any of their Affiliates who were actively involved in the activities with respect to the Product contemplated by this Agreement.

15.2 Non-competition.

[***] agrees, on a Product-by-Product basis commencing on [***] and continuing for a [***] period thereafter, that [***] shall promote, market or sell, or enter into any agreement to promote, market or sell, any [***], in the License Territory in the Field. The provisions of this Section 15.2 will not apply to any Product that Licensee has a right to develop and commercialize for an OPKO Additional Indication or Licensee Additional Indication in the License Territory in accordance with Article 4.

16. Termination; Rights And Duties Upon Termination

16.1 Early Termination.

(a) Licensee shall have the right to terminate this Agreement upon [***] days' prior written notice to OPKO for any reason.

(b) Each Party shall have the right to terminate this Agreement before the end of the Term:

(i) by mutual agreement of the Parties;

(ii) upon a material breach of this Agreement by the other Party where such breach is not cured within [***] days (or [***] days for any payment breach) following the breaching Party's receipt of written notice of such breach from the non-breaching Party; provided, however, that if any breach is not reasonably curable within [***] days and if the breaching Party is making a bona fide effort to cure such breach, such termination shall be delayed for a time period to be agreed by both Parties (but in no event more than [***] days) in order to permit the breaching Party a reasonable period of time to cure such breach; provided, that if Licensee has the right to terminate this Agreement under this Section 16.1(b)(ii), [***], as applicable, promptly following

resolution of such dispute pursuant to mutually agreed terms under Section 21.1 or a written instruction given by an arbitral tribunal under Section 21.2; or

(iii) upon the occurrence of an Insolvency Event with respect to the other Party or its Affiliates.

(c) If the breaching Party disputes in good faith that it has materially breached one of its obligations under this Agreement, termination shall not take effect pending resolution of such dispute pursuant to Article 21.

16.2 Continuing Obligations.

In addition to those specifically identified in the Agreement, the following provisions shall survive the termination or expiration of this Agreement for any reason: Sections 2.2 (except for termination by Licensee is pursuant to Section 16.1(b)(ii) or 16.1(b)(iii)), 2.3, 3.2 (expiration only), 6.5, 7.4, 7.5, 7.6, 8.2(d), 11.1, 13.1, 15.1, and 17.5 through 17.9 (inclusive), and Articles 14, 16, 19, 20, and 21 and associated definitions and interpretation provisions. In addition, any other provision required to interpret and enforce the Parties' rights and obligations under this Agreement shall also survive, but only to the extent required for the full observation and performance of this Agreement.

16.3 Remedies.

Termination of this Agreement in accordance with its provisions shall not limit the remedies that may be otherwise available to either Party in law or equity.

16.4 Effects of Termination.

(a) Following a termination of this Agreement by Licensee under this Article 16:

(i) subject to Section 16.4(a)(iv), all licenses granted to Licensee or its Affiliates under this Agreement shall terminate and all rights in and to the Products in the License Territory shall revert to OPKO;

(ii) the rights granted by Licensee to OPKO or its Affiliates under Section 2.2 shall continue in accordance with their terms, subject to the following:

(1) in case that [***] terminates this Agreement in accordance with [***] shall pay the following rate of royalties:

a. [***] of Net Sales all over the world, if such termination occurs prior to [***] in the License Territory; or

b. [***] of Net Sales all over the world, if such termination occurs after [***] in the License Territory;

(2) in case that Licensee terminates this Agreement for any reason other than the reason set forth in Section 16.4(a)(ii)(1) and a [***] at the rate of [***] of Net Sales in the License Territory; and

(3) [***] that this Agreement is terminated; provided that if the Minimum OPKO Consideration Period has not expired on or prior to such termination and unless termination by Licensee is pursuant to Section 16.1(b)(ii) or 16.1(b)(iii), the [***] for the period remaining in the Minimum OPKO Consideration Period.

For the purposes of this Section 16.4(a), Net Sales shall be calculated on sales of OPKO or its Affiliates and Sublicensees (rather than as set forth Section 1.1). The royalty period under this Section 16.4(a)(ii) shall continue, on a country-by-country basis, until the latest of: (i) [***]; (ii) expiration of the last-to-expire of the [***] of Licensee Patents; and (iii) (only applicable for the Net Sales in the License Territory) expiration of [***] in the License Territory.

(iii) Licensee shall transfer to OPKO, [***] (unless termination by Licensee was pursuant to Section 16.1(b)(ii) or 16.1(b)(iii), in which case [***]), all relevant and necessary materials, results, analyses, reports, Product data, the URL for Product-specific websites, technology, know-how, regulatory filings, Regulatory Approvals, Licensee Trademarks (in accorance with Section 8.2(c)), and other information in whatever form developed or generated as of the effective date of such termination by or on behalf of Licensee or its Affiliates or Sublicensees with respect to Products;

(iv) Licensee shall submit to any and all Regulatory Authorities in the License Territory in which any regulatory filings have been made or Regulatory Approvals have been granted with respect to the Products, within [***] days after the effective date of such termination, a letter (with a copy to OPKO) notifying such Regulatory Authorities of the transfer of any regulatory filings and Regulatory Approvals for Products in the License Territory from Licensee to OPKO; provided, that [***] associated with such transfer if such termination by Licensee is pursuant to Section 16.1(b)(ii) or 16.1(b)(iii);

(v) Licensee, its Affiliates and Sublicensees shall be permitted to sell, subject to the payment of applicable Royalty Payments due under Article 5 and Section 3.2, any Products in inventory (including completion for sale of any work in progress) over the [***] month period following termination; and

(vi) any sublicense granted to a Sublicensee that is not in breach under the applicable sublicense or the terms of this Agreement will continue in effect so long as the Sublicensee makes the payments required under Article 5.

(b) Following a termination of this Agreement by OPKO under this Article 16:

(i) all licenses granted to Licensee by OPKO shall terminate; provided, that, unless, at [***], [***] or [***], Licensee, its Affiliates and Sublicensees shall be permitted to sell, subject to the payment of applicable Royalty Payments due under Article 5 and Section 3.2,

any Products in inventory (including completion for sale of any work in progress) over the [***] month period following termination;

(ii) all rights in and to the Products in the License Territory shall revert to OPKO;

(iii) the license granted by Licensee to OPKO under Section 2.2 shall continue perpetually in accordance with its terms, except that the Exclusive Grant-back License Option [***] on or prior to such termination, the the Exclusive Grant-back License Option shall continue for the period remaining in the Minimum OPKO Consideration Period;

(iv) Licensee shall transfer to OPKO ([***]), all relevant and necessary intellectual property rights, materials, results, analyses, reports, Product data, technology, know-how, regulatory filings, Regulatory Approvals and other information in whatever form developed, controlled, or generated as of the effective date of such termination by or on behalf of Licensee or its Affiliates with respect to Products;

(v) Licensee shall submit to any and all Regulatory Authorities in the License Territory, within [***] days after the effective date of such termination, a letter (with a copy to OPKO) notifying such Regulatory Authorities of the transfer of any regulatory filings and Regulatory Approvals for Products in the License Territory from Licensee to OPKO; and

(vi) any sublicense granted to a Sublicensee that is not in breach under the applicable sublicense or the terms of this Agreement will, at the option of OPKO, continue in effect so long as the Sublicensee makes the payments required under Article 5.

(c) Nothing in this Article 16 shall limit the Parties' respective rights to damages or specific performance upon the occurrence of an event that constitutes grounds for termination of this Agreement pursuant to Section 16.1, as applicable.

17. Representations, Warranties, Covenants, and Indemnification

17.1 Mutual Representations and Warranties.

Each Party hereby represents and warrants (as applicable) to the other Party as of the Effective Date as follows:

(a) It is an entity duly organized, validly existing, and in good standing under the laws of the jurisdiction in which it is formed, and has full power and authority and the legal right to own and operate its property and assets and to carry on its business as it is now being conducted and as contemplated in this Agreement.

(b) It has the power and authority and the legal right to enter into this Agreement and perform its obligations hereunder; it has taken all necessary action on its part required to authorize the execution and delivery of this Agreement and the performance of its obligations hereunder, and this Agreement has been duly executed and delivered on behalf of such Party, and constitutes a legal, valid, and binding obligation of such Party that is enforceable against it in

accordance with its terms, except as enforcement may be affected by bankruptcy, insolvency or other similar laws and by general principles of equity.

(c) The execution, delivery and performance of this Agreement by it does not conflict with any agreement, instrument or understanding, oral or written, to which it is a party and by which it may be bound, or violate any Applicable Laws of any Governmental Authority having jurisdiction over it.

(d) Except with respect to Regulatory Approvals for the development, manufacturing or commercialization of the Product or as otherwise described in this Agreement, all necessary consents, approvals and authorizations of, and all notices to, and filings by such Party with, all Governmental Authorities and other Persons required to be obtained or provided by such Party as of the Effective Date in connection with the execution, delivery and performance of this Agreement have been obtained and provided, except for those approvals, if any, not required at the time of execution of this Agreement.

17.2 Representations and Warranties of OPKO.

Except as disclosed on Schedule 17.2, OPKO represents and warrants to Licensee that:

(a) it Controls as of the Effective Date the OPKO Patents, OPKO Trademarks and OPKO Technology;

(b) it has the right to grant Licensee the rights and licenses described in this Agreement;

(c) Appendix B includes a complete and accurate list of all existing OPKO Patents as of the Effective Date;

(d) the OPKO Patents listed on Appendix B that constitute issued patents are in full force and effect and all applicable filing, maintenance and other fees have been timely paid;

(e) the OPKO Patents listed on Appendix B are not the subject as of the Effective Date of any pending re-examination, opposition, interference, inter partes review, litigation or other proceeding;

(f) it has received no written notice of (i) any claim that a Patent or trade secret owned or controlled by a Third Party is or would be infringed or misappropriated by the manufacture, use, sale, offer or sale or import of Products in the Field, or (ii) any threatened claims or litigation seeking to invalidate or challenge the OPKO Patents or OPKO's rights thereto;

(g) to OPKO's knowledge, no Third Party is infringing the OPKO Patents listed on Appendix B;

(h) to OPKO's knowledge, there have been no inventorship or ownership challenges with respect to any of the OPKO Patents listed on Appendix B;

(i) to the extent that any of the OPKO Patents listed on Appendix B are pending patent applications as of the Effective Date, those applications are being diligently prosecuted at the relevant patent offices; and

(j) OPKO has prepared, maintained and retained records of the material activities conducted by OPKO and its Affiliates in furtherance of the development of the Compound and the Product and the data resulting therefrom in sufficient detail and in good scientific manner appropriate for patent and regulatory purposes and in accordance with Applicable Laws in the OPKO Territory.

17.3 OPKO Covenants.

(a) OPKO shall use reasonable efforts to obtain from an Other Licensee the rights to grant the license included under Section 2.1(b) to Licensee; provided, that in no event shall the exercise of reasonable efforts require OPKO to provide monetary or non-monetary consideration for such rights unless Licensee agrees to incur such consideration;

(b) If Licensee desires to conduct to [***] or manufacture of the Compound or Product [***]; provided, that in no event shall the exercise of reasonable efforts require [***] agrees to incur such consideration; and

(c) OPKO shall not take any action and shall cause its Affiliates not to take any action that would adversely affect the ability of OPKO or any of its Affiliates to grant the licenses granted to Licensee under Section 2.1 or perform any of its or their obligations under this Agreement and OPKO shall cause its Affiliates to grant such licenses and perform such obligations.

17.4 Compliance with Law and Ethical Business Practices .

In addition to the other representations, warranties and covenants made by each Party elsewhere in this Agreement, each Party represents and warrants or covenants and agrees, as applicable, with the other Party that during the Term:

(a) it is licensed, registered, or qualified under all Applicable Laws to do business, and has obtained such licenses, consents, authorizations or completed such registrations or made such notifications as may be necessary or required by Applicable Law to provide any products, goods or services encompassed within this Agreement, and providing such products, goods or services is not inconsistent with any other obligation of such Party;

(b) in conducting its activities and obligations hereunder, such Party will and will cause its Affiliates and, to the extent of its legal right to do so, use reasonable efforts to cause its other representatives to comply in all material respects with all Applicable Laws and accepted pharmaceutical industry business practices, including, to the extent applicable to such Party and each of its Affiliates and other representatives;

(c) to its knowledge with respect to any products, payments or services provided under this Agreement, it has not taken and will not during the Term take any action directly or

indirectly to offer, promise or pay, or authorize the offer or payment of, any money or anything of value in order to improperly or corruptly seek to influence any Government Official or any other Person in order to gain an improper advantage, and has not accepted, and will not accept in the future, such payment;

(d) it complies in all material respects with the laws and regulations of the countries where it operates, including anti-bribery and anti-corruption laws, accounting and record keeping laws, and laws relating to interactions with healthcare professionals or healthcare providers and Government Officials;

(e) to its knowledge, it and each of its Affiliates has been and will, for the Term, be in compliance in all material respects with all applicable global trade laws, including those related to import controls, export controls or economic sanctions, and such Party will cause each of its Affiliates to remain in compliance in all material respects with the same during the Term;

(f) to its knowledge, except to the extent permissible under United States law, neither it nor any of its Affiliates has, on its own behalf or acting on behalf of any other Person, directly or indirectly engaged with, and will not for the Term, directly or indirectly engage in any transactions with, or otherwise deal with, any country or Person targeted by United States, European Union, United Kingdom or other relevant economic sanctions laws in connection with any activities related to such Party's interaction with the other Party, including those contemplated under this Agreement; and

(g) it is, as between the Parties, solely responsible for ensuring the adherence by the Parties and its respective Affiliates in all material respects to all Applicable Laws, in each case with respect to the activities to be conducted under this Agreement.

17.5 Indemnification by OPKO.

OPKO shall defend, indemnify and hold harmless Licensee and its Affiliates and their officers, directors, shareholders, employees, agents, representatives, successors and assigns from and against all claims, complaints, or lawsuits for damages brought by Third Parties (collectively referred to as "**Losses**") arising out of (a) any negligent act or omission, or willful wrongdoing by OPKO, its Affiliates or representatives in the performance of this Agreement, (b) the failure by OPKO, its Affiliates or representatives to comply with any Applicable Law in the performance of this Agreement, (c) the infringement or misappropriation by OPKO of any patent, copyright, trademark or service mark, as a result of OPKO's marketing or promotion of the Product in the License Territory which is not pursuant to the terms of this Agreement, (d) any breach of any representation or warranty or covenant or other obligations of OPKO under this Agreement, and (e) the sale of the Product in the OPKO Territory or outside the Field in the License Territory by OPKO, its Affiliates or its licensees/sublicensees. OPKO shall not be obligated under this Section 17.5 to the extent that Licensee is responsible for indemnifying OPKO for such Losses under Section 17.6.

17.6 Indemnification by Licensee.

Licensee shall defend, indemnify and hold harmless OPKO and its Affiliates and their officers, directors, shareholders, employees, agents, representatives, successors and assigns from and against all Losses arising out of (a) any negligent act or omission, or willful wrongdoing by Licensee, its Affiliates or representatives in the performance of this Agreement, (b) the failure by Licensee, its Affiliates or representatives to comply with any Applicable Law in the performance of this Agreement, (c) the infringement or misappropriation by Licensee of any patent, copyright, trademark, or trade secret, as a result of Licensee's marketing or promotion of the Product which is not pursuant to the terms of this Agreement or in conformity with the direction of the JSC, (d) any breach of any representation or warranty or covenant or other obligations of Licensee under this Agreement, and (e) the sale of the Product in the License Territory in the Field by Licensee, its Affiliates or its licensees/sublicensees. Licensee shall not be obligated under this Section 17.6 to the extent that OPKO is responsible for indemnifying Licensee for such Losses under Section 17.5.

17.7 Limitations on Indemnification.

The obligations to indemnify, defend, and hold harmless set forth in Sections 17.5 and 17.6 shall be contingent upon the Party seeking indemnification (the "**Indemnitee**"): (a) notifying the indemnifying Party of a claim, demand or suit within [***] Business Days of receipt of same (provided, however, that Indemnitee's failure or delay in providing such notice shall not relieve the indemnifying Party of its indemnification obligation except to the extent the indemnifying Party is materially prejudiced thereby); (b) allowing the indemnifying Party and/or its insurers the right to assume direction and control of the defense of any such claim, demand or suit; (c) using its Commercially Reasonable Efforts to cooperate with the indemnifying Party and/or its insurers in the defense of such claim, demand or suit; and (d) agreeing not to settle or compromise any claim, demand or suit without prior written authorization of the indemnifying Party. The Indemnitee shall have the right to participate in the defense of any such claim, demand or suit referred to in this Section 17.7 utilizing attorneys of its choice, at its own expense, provided, however, that the indemnifying Party shall have full authority and control to handle any such claim, demand or suit.

17.8 Insurance.

During the Term and for a period of [***] years after the expiration or termination of this Agreement, each Party shall obtain and/or maintain, respectively, at its sole cost and expense, product liability insurance in amounts, respectively, which are reasonable and customary in the pharmaceutical industry for companies of comparable size and activities at the respective place of business of each Party. Such product liability insurance shall insure against physical injury, property damage or other damages arising out of the manufacture, sale, distribution, or promotion of the Product in each Party's respective territory. Each Party shall provide written proof of the existence of such insurance to the other Party upon request.

17.9 Limitation of Liability.

EXCEPT IN THE CASE OF A BREACH OF ARTICLES 13 AND 14, NEITHER PARTY SHALL BE LIABLE TO THE OTHER PARTY FOR SPECIAL, INDIRECT, INCIDENTAL, PUNITIVE, OR CONSEQUENTIAL DAMAGES (INCLUDING, WITHOUT LIMITATION, DAMAGES RESULTING FROM LOSS OF USE, LOSS OF PROFITS, INTERRUPTION OR

LOSS OF BUSINESS, OR OTHER ECONOMIC LOSS) ARISING OUT OF THIS AGREEMENT OR WITH RESPECT TO A PARTY'S PERFORMANCE OR NON-PERFORMANCE HEREUNDER.

18. Assignment

18.1 Assignment.

Neither Party shall assign or transfer its rights or obligations under this Agreement in whole or in part without the prior written consent of the other Party, except to (a) any of its respective Affiliates, or (b) to a Third Party successor or purchaser of all or substantially all of its business or assets to which this Agreement relates, whether in merger, sale of stock, sale of assets or similar transaction. Any such assignment or transfer is subject to the rights of the other Party under this Agreement. Any attempted assignment in contravention of this Section 18.1 shall be null and void.

19. Notices

19.1 Notices.

Any notice, request, approval or other document required or permitted to be given under this Agreement shall be in writing and shall be deemed to have been given when delivered in person, or sent by overnight courier service, postage prepaid, or sent by certified or registered mail, return receipt requested, to the following addresses of the Parties and to the attention of the persons identified below (or to such other address, addresses or persons as may be specified from time to time in a written notice). Any notices given pursuant to this Agreement shall be deemed to have been given and delivered upon the earlier of (a) if sent by overnight courier service, on the date when received at the address set forth below as proven by a written receipt from the delivery service verifying delivery, (b) if sent by certified or registered mail, three (3) Business Days after mailed by certified or registered mail postage prepaid and properly addressed, with return receipt requested, or (c) if delivered in person, on the date of delivery to the address set forth below as proven by written signature of the recipient.

EirGen Pharma Limited:

EirGen Pharma Limited
Westside Business Park, Old Kilmeaden Road
Waterford, Ireland
Attention: Patsy Carney, CEO

With a copy (which shall not constitute notice) to:

OPKO Health, Inc.
4400 Biscayne Boulevard
Miami, FL 33137, U.S.A.
Attention: Kate Inman, General Counsel

With a copy (which shall not constitute notice) to:

Hogan Lovells US LLP
100 International Drive
Suite 2000
Baltimore, MD 21202, U.S.A.
Attention: Asher M. Rubin, Esq.

Licensee:

Japan Tobacco Inc. (Pharmaceutical Division)
Torii Nihonbashi Building
4-1 Nihonbashi-Honcho, 3-chome, Chuo-ku
Tokyo 103-0023, Japan
Attention: Vice President, Business Planning & Development

With a copy (which shall not constitute notice) to:

Holland & Knight LLP
31 West 52nd Street
New York, New York 10019, U.S.A.
Attention: Neal N. Beaton

20. Miscellaneous

20.1 Force Majeure.

If the performance of any part of this Agreement by either Party, or of any obligation under this Agreement, is prevented, restricted, interfered with or delayed by reason of any cause beyond the reasonable control of the Party liable to perform, unless conclusive evidence to the contrary is provided, the Party so affected shall, upon giving written notice to the other Party, be excused from such performance to the extent of such prevention, restriction, interference or delay; provided that the affected Party shall use Commercially Reasonable Efforts to avoid or remove such causes of nonperformance and shall continue performance with the utmost dispatch whenever such causes are removed. When such circumstances arise, the Parties shall discuss what, if any modification of the terms of this Agreement may be required in order to arrive at an equitable solution.

20.2 No Partnership or Joint Venture.

It is expressly agreed that OPKO and Licensee shall be independent contractors and that the relationship between the two (2) Parties shall not constitute a partnership, joint venture or agency. Neither OPKO nor Licensee shall have the authority to make any statements, representations or commitments of any kind, or to take any action, which shall be binding on the other, without the prior written consent of the other Party to do so.

20.3 Execution in Counterparts.

This Agreement may be executed in any number of counterparts, each of which shall be deemed an original but all of which together shall constitute one (1) and the same instrument. Counterparts may be signed and delivered by facsimile or .PDF file, with the same effect as if delivered personally.

20.4 Governing Law.

This Agreement shall be deemed to have been made in the State of New York and its form, execution, validity, construction and effect shall be determined in accordance with the substantive laws of the State of New York, without regard to conflict of law principles thereof.

20.5 Waiver of Breach.

The failure of either Party at any time or times to require performance of any provision hereof shall in no manner affect its rights at a later time to enforce the same. No waiver by either Party of any condition or term in any one (1) or more instances shall be construed as a further or continuing waiver of such condition or term or of another condition or term.

20.6 Severability.

In the event any portion of this Agreement is held illegal, void or ineffective, the remaining portions of this Agreement shall remain in full force and effect. If any of the terms or provisions of this Agreement are in conflict with any applicable statute or rule of law, then such terms or provisions shall be deemed inoperative to the extent that they may conflict therewith and shall be deemed to be modified to conform with such statute or rule of law. In the event that the terms and conditions of this Agreement are materially altered as a result of this Section 20.6, the Parties shall renegotiate the terms and conditions of this Agreement to resolve any inequities.

20.7 Entire Agreement.

This Agreement, together with the appendices and schedules hereto and the undertaking and side letter from OPKO Affiliates being delivered contemporaneously, shall constitute the entire agreement between the Parties and their Affiliates relating to the subject matter thereof and shall supersede all previous writings and understandings, except that the relevant Parties shall continue to be bound by the confidentiality provisions of that certain Confidentiality Agreement dated September 3, 2014 as amended between OPKO Health, Inc. and Torii, as amended. No terms or provisions of this Agreement shall be varied or modified by any prior or subsequent statement, conduct or act of either of the Parties, except that the Parties may amend this Agreement by written instruments specifically referring to and executed in the same manner as this Agreement.

20.8 Currency.

Unless otherwise specified in this Agreement, all amounts set forth in this Agreement are in U.S. dollars.

20.9 Form of Payments.

All payments under this Agreement shall be in U.S. dollars in immediately available funds, and, unless instructed otherwise by the receiving Party, shall be made via wire transfer to the account designated from time to time by the receiving Party.

20.10 Good Faith.

Each Party agrees to act reasonably, and to cause its Affiliates to act reasonably, in giving effect to the provisions of this Agreement.

21. Dispute Resolution

21.1 Internal Resolution.

Any dispute, controversy or claim arising out of or relating to a breach or alleged breach of this Agreement, excluding termination (collectively referred to as "**Dispute**"), shall be attempted to be settled by the Parties, in good faith, by submitting each such Dispute to the designated senior management representatives of each Party, who shall meet within [***] Business Days as reasonably requested by either Party to review any Dispute. If the Dispute is not resolved by the designated representatives by mutual agreement within [***] Business Days after a meeting to discuss the Dispute, either Party may at any time thereafter provide the other Party written notice specifying the terms of such Dispute in reasonable detail. Within [***] Business Days of receipt of such notice, the chief executive officer (or other senior executive with authority to resolve the dispute) of each Party shall meet at a mutually agreed upon time and location for the purpose of resolving such Dispute. They will discuss the problems and/or negotiate for a period of up to [***] days in an effort to resolve the Dispute or negotiate an acceptable interpretation or revision of the applicable portion of this Agreement mutually agreeable to both Parties, without the necessity of formal procedures relating thereto.

21.2 Arbitration.

Any controversy or claim arising out of or relating to this Agreement (other than any matter subject to a Party's final decision-making authority as described in Section 9.1(c)) shall be settled by arbitration in accordance with the Commercial Arbitration Rules and supplementary rules for international commercial arbitrations of the American Arbitration Association ("**AAA**") then in effect. The arbitration shall be conducted in English. The seat of the arbitration shall be in the City of New York, Borough of Manhattan. In any arbitration pursuant to this Agreement, the award or decision shall be rendered by a majority of the members of an arbitration panel consisting of three (3) independent arbitrators. Each Party shall appoint one (1) arbitrator, and the third arbitrator shall be selected jointly by the two arbitrators appointed by the Parties, unless the Parties otherwise agree as to the identity of the third arbitrator. If the two arbitrators appointed by the Parties are unable to agree upon the third arbitrator within [***] days of any request for arbitration, such arbitrator shall be selected by the AAA. Persons selected to serve as an arbitrator need not be a professional arbitrator, and persons such as lawyers, accountants, brokers and bankers shall be acceptable. Before undertaking to resolve the dispute, the arbitrators shall be duly sworn faithfully and fairly to hear and examine the matters in controversy and to make a just award according to the best of his or her understanding. The written decision of the arbitrators shall be final, conclusive and binding on the

Parties. Each Party shall bear its own costs and expenses (including legal fees and expenses) relating to the arbitration proceeding, except that the fees of the arbitrators and other related costs of the arbitration shall be shared equally by the Parties. The arbitrators shall be required, in granting any relief, to comply with any express provisions of this Agreement relating to damages or the limitation thereof. Judgment upon the award may be entered by any court having jurisdiction thereof or having jurisdiction over the relevant Party or its assets. Either Party has the right to apply to the state courts of the State of New York located in the City of New York or the United States District Court for the Southern District of New York for interim relief necessary to preserve the Party's rights, including pre-arbitration attachments or injunctions, until the arbitral tribunal is constituted. After the constitution of the arbitral tribunal, the arbitrators shall have exclusive jurisdiction to consider applications for interim relief.

22. Performance

To the extent that the performance of a Party's obligations hereunder is adversely affected by the other Party's failure to perform its obligations hereunder, the impact of such performance failure will be taken into account in determining whether such Party has used its requisite efforts (which may be Commercially Reasonable Efforts) to perform any such affected obligations as required by this Agreement.

[Signatures on following page]

NOW THEREFORE, the Parties, through their authorized officers, have executed this Agreement as of the date first written above.

EIRGEN PHARMA LIMITED

By: /s/ Patsy Carny

Name: Patsy Carney

Title: CEO

[Signature Page to Development and License Agreement]

NOW THEREFORE, the Parties, through their authorized officers, have executed this Agreement as of the date first written above.

JAPAN TABACCO INC.

By: /s/ Muneaki Fujimoto

Muneaki Fujimoto

Name:

President, Pharmaceutical Business

Title:

[Signature Page to Development and License Agreement]

[***] Indicates portions of this exhibit that have been omitted and filed separately with the Securities and Exchange Commission pursuant to a request for confidential treatment.

APPENDIX A

PARENT GUARANTY

As an inducement to Torii Pharmaceutical Co., Ltd. and Japan Tobacco Inc. (" **Licensee**") to enter into the foregoing Agreement (this "**Agreement**") with EirGen Pharma Limited ("**OPKO**"), OPKO Health, Inc., a Delaware corporation ("**Guarantor**"), hereby irrevocably and unconditionally (i) guarantees [***] and (ii) [***].

Any assignee will assume all obligations of its assignor under this guaranty and [***]. Subject to the foregoing, this guaranty binds and inures to the benefit of the Parties and their heirs, successors and assigns.

No failure or delay by Licensee in exercising any right under this guaranty shall operate as a waiver thereof, nor shall any single or partial exercise of any such right preclude any other or further exercise thereof or the exercise of any other right under this guaranty.

OPKO HEALTH, INC.

By: _____

Name: Adam Logal

Title: Senior Vice President, Chief Financial Officer

[***] Indicates portions of this exhibit that have been omitted and filed separately with the Securities and Exchange Commission pursuant to a request for confidential treatment.

APPENDIX B

OPKO PATENTS

Ctry	App No.	Filed	Publication No.	Publication Date	Patent No.	Issue Date	Status
[***]	[***]	[***]	[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]	[***]	[***]	[***]

[***] Indicates portions of this exhibit that have been omitted and filed separately with the Securities and Exchange Commission pursuant to a request for confidential treatment.

APPENDIX C

INITIAL DEVELOPMENT PLAN

[***]

[***] Indicates portions of this exhibit that have been omitted and filed separately with the Securities and Exchange Commission pursuant to a request for confidential treatment.

SCHEDULE 2.2(a)

GRANT-BACK LICENSE OPTION

[***]

[***] Indicates portions of this exhibit that have been omitted and filed separately with the Securities and Exchange Commission pursuant to a request for confidential treatment.

SCHEDULE 6.3

[***]

SCHEDULE 10.2

TERMS FOR SUPPLY AGREEMENT

Parties	**[***]**
Definitions	**[***]**
Background	**[***]**
Forecasting	**[***]**
Ordering	**[***]**
Delivery; Risk of Loss	**[***]**
Acceptance or Rejection	**[***]**
Pricing	**[***]**
Payment	**[***]**
Term and Termination	**[***]**
Quality Agreement	**[***]**
Back-up Rights	**[***]**
Indemnification	**[***]**
Facility Inspection	**[***]**
Governing Law	**[***]**
Other Terms	**[***]**

SCHEDULE 17.2

[***]

AMENDMENT NO. 5 TO CREDIT AGREEMENT

AMENDMENT NO. 5 TO CREDIT AGREEMENT (this " Amendment"), dated as of November 8, 2017, is entered into among BIO-REFERENCE LABORATORIES, INC., a New Jersey corporation (" Company"), the Subsidiary Borrowers party hereto ("Subsidiary Borrowers," and together with Company, each a " Borrower" and, collectively, the "Borrowers"), the other Loan Parties party hereto, the Lenders party hereto, and JPMORGAN CHASE BANK, N.A., as the administrative agent for the Lenders (the "Administrative Agent").

W I T N E S S E T H :

WHEREAS, the Borrowers, the other Loan Parties party thereto, the Lenders party thereto, and the Administrative Agent have executed and delivered that certain Credit Agreement dated as of November 5, 2015, as amended by Amendment No. 1 to Credit Agreement dated as of February 29, 2016, as amended by Amendment No. 2 to Credit Agreement dated as of September 26, 2016, as amended by Amendment No. 3 to Credit Agreement dated as of March 17, 2017, and as amended by Amendment No. 4 to Credit Agreement dated as of August 7, 2017 (as further amended, restated, supplemented, or otherwise modified from time to time prior to the date hereof, the "Credit Agreement"); and

WHEREAS, the Borrowers have requested that the Lenders and the Administrative Agent make certain amendments to the Credit Agreement, and the Lenders party hereto, constituting all Lenders under the Credit Agreement, have agreed to such amendments, subject to the terms and conditions hereof.

NOW, THEREFORE, for and in consideration of the above premises and other good and valuable consideration, the receipt and sufficiency of which is hereby acknowledged by the parties hereto, each of the Borrowers, the other Loan Parties, the Lenders and the Administrative Agent hereby covenant and agree as follows:

SECTION 1. Definitions. Unless otherwise specifically defined herein, each term used herein (and in the recitals above) which is defined in the Credit Agreement shall have the meaning assigned to such term in the Credit Agreement. As of the date hereof, each reference in the Credit Agreement to "this Agreement," "hereunder," "hereof," "herein," or words of like import, and each reference in the other Loan Documents to the Credit Agreement (including, without limitation, by means of words like "thereunder," "thereof" and words of like import), shall mean and be a reference to the Credit Agreement, as amended hereby.

SECTION 2. Amendments to Credit Agreement . Effective as of the Amendment No. 5 Effective Date (as defined below), the Credit Agreement is hereby amended as follows:

(a) Amendments to Section 1.01 .

(i) Section 1.01 of the Credit Agreement is hereby amended by adding the following definitions in appropriate alphabetical order:

"Amendment No. 5 Effective Date" means November 8, 2017.

"Modified Availability" means, at any time, an amount equal to (a) the lesser of (i) the Aggregate Revolving Commitment and (ii) the Borrowing Base plus (b) Qualified Cash *minus* (c) the Aggregate Revolving Exposure (calculated, with respect to any Defaulting Lender, as if such Defaulting Lender had funded its Applicable Percentage of all outstanding Borrowings), all as determined by the Administrative Agent in its Permitted Discretion in accordance with this Agreement.

"Qualified Cash" means cash of any Loan Party on deposit in a Deposit Account (as defined in the Security Agreement) subject to a Deposit Account Control Agreement (as defined in the Security Agreement) but not to exceed $13,125,000 in the aggregate.

(ii) Section 1.01 of the Credit Agreement is amended by replacing the definitions of " Increased Reporting Period" and "Specified Post Closing Dividends " with the following:

"Increased Reporting Period" means any period (a) commencing on the date when Modified Availability is less than the greater of (i) $35,000,000 and (ii) 20% of the Aggregate Revolving Commitment, in each case for a period of five (5) consecutive Business Days, or an Event of Default occurs and is continuing, and (b) ending on the date when Modified Availability shall have been equal to or greater than the greater of (i) $35,000,000 and (ii) 20% of the Aggregate Revolving Commitment for a period of ten (10) consecutive days and no Event of Default is in existence.

"Specified Post Closing Dividends" means the following:

(a) a one-time cash dividend by the Company to Parent so long as (i) such dividend is made within fifteen (15) calendar days after the Effective Date, (ii) immediately before and after giving effect to such dividend no Default shall exist, (iii) after giving effect to such dividend the Company is Solvent, (iv) after giving effect to such dividend, Availability shall not be less than the greater of (A) $50,000,000 and (B) 25% of the Aggregate Revolving Commitment, and (v) prior to such dividend, the Borrower Representative shall have delivered to the Administrative Agent an officer's certificate from a Financial Officer of the Borrower Representative, in form and substance reasonably satisfactory to the Administrative Agent, certifying that all of the foregoing conditions are satisfied (such dividend, the "Initial Post Closing Dividend"); and

(b) other cash dividends by the Company to Parent (through Intermediate Holdco if Intermediate Holdco is in existence) made after the date that is fifteen (15) calendar days after the Effective Date so long as (i) immediately before and after giving effect to such dividend no Default shall exist, (ii) after giving effect to such dividend Availability shall not be less than the greater of (A) $26,250,000 and (B) 15% of the Aggregate Revolving Commitment, (iii) after giving pro forma effect to such dividend, the Company shall have a Fixed Charge Coverage

Ratio of not less than 1.15 to 1.00 as of the last day of the most recent fiscal quarter or year, as applicable, for which financial statements and a Compliance Certificate have been delivered to the Administrative Agent pursuant to Sections 5.01(a) or (b) and (d), and (iv) prior to such dividend, the Borrower Representative shall have delivered to the Administrative Agent an officer's certificate from a Financial Officer of the Borrower Representative, containing calculations with respect to clause (iii) and otherwise in form and substance reasonably satisfactory to the Administrative Agent, certifying that all of the foregoing conditions are satisfied.

(b) Section 5.01(f) of the Credit Agreement is amended and restated so that it reads, in its entirety, as follows:

(f) on or before each Borrowing Base Reporting Date, as of the period then ended, a Borrowing Base Certificate and supporting information in connection therewith, together with any additional reports with respect to the Borrowing Base as the Administrative Agent may reasonably request; provided, however, that during any Increased Reporting Period (i) if the Borrower does not have the information to calculate the actual amount of Additions, Deductions and Collateral Ineligibles (as such terms are used in the Borrowing Base Certificate) with respect to the gross Accounts set forth in a weekly Borrowing Base, the Borrower may submit a Borrowing Base Certificate utilizing amounts for such items which shall be based upon percentages of Additions, Deductions and Collateral Ineligibles (determined in relation to the gross Accounts) in each case reflected on the most recently delivered monthly Borrowing Base Certificate (whether delivered with respect to a period prior to such Increased Reporting Period or pursuant to clause (ii) below); provided further, that once the Borrower has determined the actual amounts of Additions, Deductions and Collateral Ineligibles (as such terms are used in the Borrowing Base Certificate) with respect to the gross Accounts, it shall update the most recently delivered Borrowing Base Certificate within five (5) Business Days thereof and (ii) for each fiscal month, the Borrower shall also be required to deliver a Borrowing Base Certificate within twenty (20) Business Days after the end of such fiscal month, which Borrowing Base Certificate shall use actual amounts of Additions, Deductions and Collateral Ineligibles;

(c) Exhibit B hereto (Borrowing Base Certificate) hereby replaces existing Exhibit B to the Credit Agreement in its entirety.

SECTION 3. Conditions Precedent. This Amendment shall become effective on the date (such date, the "Amendment No. 5 Effective Date") the following conditions precedent shall have been satisfied:

(a) receipt by the Administrative Agent of signatures to this Amendment from the parties listed on the signature pages hereto;

(b) the Administrative Agent shall have received from the Borrowers (or the Administrative Agent shall be satisfied with arrangements made for the payment thereof) all other costs, fees, and expenses owed by the Borrowers to the Administrative Agent in connection with

this Amendment, including, without limitation, reasonable attorneys' fees and expenses, in accordance with Section 9.03 of the Credit Agreement; and

(c) the Administrative Agent shall have received from the Borrowers each of the original notes evidencing the Special Intercompany Loans.

SECTION 4. Miscellaneous.

(a) Representations and Warranties. To induce the Administrative Agent and Lenders to enter into this Amendment, the Borrowers hereby represent and warrant to the Administrative Agent and the Lenders that all representations and warranties of the Borrowers contained in Article III of the Credit Agreement or any other Loan Document are true and correct in all material respects with the same effect as though made on and as of the Amendment No. 5 Effective Date (except with respect to representations and warranties made as of an expressed date, which representations and warranties are true and correct in all material respects as of such date).

(b) No Offset. To induce the Administrative Agent and Lenders to enter into this Amendment, the Borrowers hereby acknowledge and agree that, as of the date hereof, and after giving effect to the terms hereof, there exists no right of offset, defense, counterclaim, claim, or objection in favor of the Borrowers or arising out of or with respect to any of the loans or other obligations of the Borrowers owed by the Borrowers under the Credit Agreement or any other Loan Document.

(c) Loan Document. The parties hereto hereby acknowledge and agree that this Amendment is a Loan Document.

(d) Effect of Amendment. Except as set forth expressly hereinabove and in Section 4(m) below, all terms of the Credit Agreement and the other Loan Documents shall be and remain in full force and effect, and shall constitute the legal, valid, binding, and enforceable obligations of the Borrowers, enforceable in accordance with their terms, subject to applicable bankruptcy, insolvency, reorganization, moratorium or other laws affecting creditors' rights generally and subject to general principles of equity, regardless of whether considered in a proceeding in equity or at law.

(e) No Novation or Mutual Departure. The Borrowers expressly acknowledge and agree that (i) this Amendment does not constitute or establish, a novation with respect to the Credit Agreement or any of the other Loan Documents, or a mutual departure from the strict terms, provisions, and conditions thereof, other than with respect to the amendments set forth in Section 2 above and the limited waiver set forth in Section 4(m) below, and (ii) nothing in this Amendment shall affect or limit the Administrative Agent's or any Lender's right to (x) demand payment of the Obligations under, or demand strict performance of the terms, provisions and conditions of, the Credit Agreement and the other Loan Documents (in each case, as amended hereby and subject to

the limited waiver set forth in Section 4(m) below), as applicable, (y) exercise any and all rights, powers, and remedies under the Credit Agreement or the other Loan Documents (in each case, as amended hereby and subject to the limited waiver set forth in Section 4(m) below) or at law or in equity, or (z) do any and all of the foregoing, immediately at any time during the occurrence of an Event of Default and in each case, in accordance with the terms and provisions of the Credit Agreement and the other Loan Documents.

(f) Counterparts. This Amendment may be executed in any number of counterparts and by different parties hereto in separate counterparts, each of which when so executed and delivered shall be deemed to be an original and all of which counterparts, taken together, shall constitute but one and the same instrument. This Amendment may be executed by each party on separate copies, which copies, when combined so as to include the signatures of all parties, shall constitute a single counterpart of this Amendment.

(g) Fax or Other Transmission. Delivery by one or more parties hereto of an executed counterpart of this Amendment via facsimile, telecopy, or other electronic method of transmission pursuant to which the signature of such party can be seen (including, without limitation, Adobe Corporation's Portable Document Format) shall have the same force and effect as the delivery of an original executed counterpart of this Amendment. Any party delivering an executed counterpart of this Amendment by facsimile or other electronic method of transmission shall also deliver an original executed counterpart, but the failure to do so shall not affect the validity, enforceability, or binding effect of this Amendment.

(h) Recitals Incorporated Herein. The preamble and the recitals to this Amendment are hereby incorporated herein by this reference.

(i) Section References. Section titles and references used in this Amendment shall be without substantive meaning or content of any kind whatsoever and are not a part of the agreements among the parties hereto evidenced hereby.

(j) Governing Law. This Amendment shall be governed by and construed in accordance with the internal laws (and not the law of conflicts) of the State of New York, but giving effect to federal laws applicable to national banks.

(k) Severability. Any provision of this Amendment which is prohibited or unenforceable shall be ineffective to the extent of such prohibition or unenforceability without invalidating the remaining provisions hereof in that jurisdiction or affecting the validity or enforceability of such provision in any other jurisdiction.

(l) Reaffirmation of Loan Parties. Each Loan Party (i) consents to the execution and delivery of this Amendment, (ii) reaffirms all of its obligations and covenants under the Loan

Documents (including, without limitation, the Collateral Documents and the Loan Guaranty) to which it is a party, and (iii) agrees that, except to the extent amended hereby, none of its respective obligations and covenants under the Loan Documents shall be reduced or limited by the execution and delivery of this Amendment.

(m) Waiver by Lenders of Certain Items . Subject to the satisfaction of the conditions precedent set forth in Section 3 above, the Lenders hereby waive any Default or Event of Default that has occurred and is continuing as of the date hereof solely as a result of the Loan Parties' failure on or prior to the date hereof to (i) deliver a Borrowing Base Certificate to the Administrative Agent on a timely basis during any Increased Reporting Report and (ii) deliver the original notes evidencing the Special Intercompany Loans to the Administrative Agent as required by the Loan Documents. This waiver is an accommodation, and the Loan Parties acknowledge and agree that the Lenders shall require strict compliance with the Credit Agreement, as amended by this Amendment, hereafter.

[SIGNATURES ON FOLLOWING PAGES.]

IN WITNESS WHEREOF, the Borrowers, the other Loan Parties, the Administrative Agent and the Lenders have caused this Amendment to be duly executed by their respective duly authorized officers as of the day and year first above written.

BORROWERS:

BIO-REFERENCE LABORATORIES, INC.
GENEDX, INC.
FLORIDA CLINICAL LABORATORY, INC.
MERIDIAN CLINICAL LABORATORY CORP.

By: /s/ Adam Logal
Name: Adam Logal
Title: Director, Vice President

OTHER LOAN PARTIES:

CAREEVOLVE.COM, INC.
BRLI-GENPATH DIAGNOSTICS, INC.
GENEDX MENA LLC

By: /s/ Adam Logal
Name: Adam Logal
Title: Director, Vice President

Approved for Signature
OPKO Legal Department
By: /s/Kate Inman
Date: November 8, 2017

JPMORGAN CHASE BANK, N.A.,
Individually as a Lender and as Administrative Agent, Issuing Bank and Swingline Lender

By: /s/ Eric A. Anderson

Name: Eric A. Anderson
Title: Authorized Officer

EXHIBIT B

BORROWING BASE CERTIFICATE

[PLEASE SEE ATTACHED]

NAI-1503140770v6

AMENDMENT NO. 6 TO CREDIT AGREEMENT

AMENDMENT NO. 6 TO CREDIT AGREEMENT (this " Amendment"), dated as of December 22, 2017, is entered into among BIO-REFERENCE LABORATORIES, INC., a New Jersey corporation (" Company"), the Subsidiary Borrowers party hereto ("Subsidiary Borrowers," and together with Company, each a " Borrower" and, collectively, the "Borrowers"), the other Loan Parties party hereto, the Lenders party hereto, and JPMORGAN CHASE BANK, N.A., as the administrative agent for the Lenders (the "Administrative Agent").

W I T N E S S E T H :

WHEREAS, the Borrowers, the other Loan Parties party thereto, the Lenders party thereto, and the Administrative Agent have executed and delivered that certain Credit Agreement dated as of November 5, 2015, as amended by Amendment No. 1 to Credit Agreement dated as of February 29, 2016, as amended by Amendment No. 2 to Credit Agreement dated as of September 26, 2016, as amended by Amendment No. 3 to Credit Agreement dated as of March 17, 2017, as amended by Amendment No. 4 to Credit Agreement dated as of August 7, 2017, and as amended by Amendment No. 5 to Credit Agreement dated as of November 8, 2017 (as further amended, restated, supplemented, or otherwise modified from time to time prior to the date hereof, the "Credit Agreement"); and

WHEREAS, the Borrowers have requested that the Lenders and the Administrative Agent make certain amendments to the Credit Agreement, and the Lenders party hereto, constituting all Lenders under the Credit Agreement, have agreed to such amendments, subject to the terms and conditions hereof.

NOW, THEREFORE, for and in consideration of the above premises and other good and valuable consideration, the receipt and sufficiency of which is hereby acknowledged by the parties hereto, each of the Borrowers, the other Loan Parties, the Lenders and the Administrative Agent hereby covenant and agree as follows:

SECTION 1. Definitions. Unless otherwise specifically defined herein, each term used herein (and in the recitals above) which is defined in the Credit Agreement shall have the meaning assigned to such term in the Credit Agreement. As of the date hereof, each reference in the Credit Agreement to "this Agreement," "hereunder," "hereof," "herein," or words of like import, and each reference in the other Loan Documents to the Credit Agreement (including, without limitation, by means of words like "thereunder," "thereof" and words of like import), shall mean and be a reference to the Credit Agreement, as amended hereby.

SECTION 2. Amendments to Credit Agreement . Effective as of the Amendment No. 6 Effective Date (as defined below), the Credit Agreement is hereby amended as follows:

(a) Amendments to Section 1.01 .

(i) Section 1.01 of the Credit Agreement is hereby amended by adding the following definition in appropriate alphabetical order:

"Amendment No. 6 Effective Date" means December 22, 2017.

(ii) Section 1.01 of the Credit Agreement is amended by replacing the definition of " Special Intercompany Loans" with the following:

"Special Intercompany Loans" means (i) a loan made within ten (10) days of the Amendment No. 3 Effective Date by the Company to the Parent in an amount not to exceed $55,000,000, (ii) a loan made on the Amendment No. 4 Effective Date by the Company to the Parent in an amount not to exceed $35,000,000, (iii) a loan made on October 11, 2017 by the Company to the Parent in an amount not to exceed $25,000,000, and (iv) a loan made within ten (10) days of the Amendment No. 6 Effective Date by the Company to the Parent in an amount not to exceed $20,000,000.

(b) Section 6.04(d) of the Credit Agreement is amended so that it reads, in its entirety, as follows:

(d) (i) loans or advances made by any Loan Party to any Subsidiary and made by any Subsidiary to a Loan Party or any other Subsidiary, provided that (A) any such loans and advances made by a Loan Party to a Subsidiary that is not a Loan Party shall be evidenced by a promissory note pledged pursuant to the Security Agreement and (B) the amount of such loans and advances made by Loan Parties to Subsidiaries that are not Loan Parties (together with outstanding investments permitted under clause (B) to the proviso to Section 6.04(c) and outstanding Guarantees permitted under the proviso to Section 6.04(e) and excluding any Special Intercompany Loan) shall not exceed $5,000,000 at any time outstanding (in each case determined without regard to any write-downs or write-offs) and (ii) the Special Intercompany Loans, provided that (x) each Special Intercompany Loan shall be evidenced by a promissory note pledged pursuant to the Security Agreement and (y) the original promissory notes evidencing the Special Intercompany Loans referenced in clauses (iii) and (iv) of the definition of "Special Intercompany Loans" shall be delivered to the Administrative Agent within thirty (30) days (or such later date as agreed to by the Administrative Agent in its sole discretion) after the Amendment No. 6 Effective Date;

SECTION 3. Conditions Precedent. This Amendment shall become effective on the date (such date, the "Amendment No. 6 Effective Date") the following conditions precedent shall have been satisfied:

(a) receipt by the Administrative Agent of signatures to this Amendment from the parties listed on the signature pages hereto; and

(b) the Administrative Agent shall have received from the Borrowers (or the Administrative Agent shall be satisfied with arrangements made for the payment thereof) all other costs, fees, and expenses owed by the Borrowers to the Administrative Agent in connection with this Amendment, including, without limitation, reasonable attorneys' fees and expenses, in accordance with Section 9.03 of the Credit Agreement.

SECTION 4. Miscellaneous.

(a) Representations and Warranties. To induce the Administrative Agent and Lenders to enter into this Amendment, the Borrowers hereby represent and warrant to the Administrative Agent and the Lenders that all representations and warranties of the Borrowers contained in Article III of the Credit Agreement or any other Loan Document are true and correct in all material respects with the same effect as though made on and as of the Amendment No. 6 Effective Date (except with respect to representations and warranties made as of an expressed date, which representations and warranties are true and correct in all material respects as of such date).

(b) No Offset. To induce the Administrative Agent and Lenders to enter into this Amendment, the Borrowers hereby acknowledge and agree that, as of the date hereof, and after giving effect to the terms hereof, there exists no right of offset, defense, counterclaim, claim, or objection in favor of the Borrowers or arising out of or with respect to any of the loans or other obligations of the Borrowers owed by the Borrowers under the Credit Agreement or any other Loan Document.

(c) Loan Document. The parties hereto hereby acknowledge and agree that this Amendment is a Loan Document.

(d) Effect of Amendment. Except as set forth expressly hereinabove and in Section 4(m) below, all terms of the Credit Agreement and the other Loan Documents shall be and remain in full force and effect, and shall constitute the legal, valid, binding, and enforceable obligations of the Borrowers, enforceable in accordance with their terms, subject to applicable bankruptcy, insolvency, reorganization, moratorium or other laws affecting creditors' rights generally and subject to general principles of equity, regardless of whether considered in a proceeding in equity or at law.

(e) No Novation or Mutual Departure. The Borrowers expressly acknowledge and agree that (i) this Amendment does not constitute or establish, a novation with respect to the Credit Agreement or any of the other Loan Documents, or a mutual departure from the strict terms, provisions, and conditions thereof, other than with respect to the amendments set forth in Section 2 above and the limited waiver set forth in Section 4(m) below, and (ii) nothing in this Amendment shall affect or limit the Administrative Agent's or any Lender's right to (x) demand payment of the Obligations under, or demand strict performance of the terms, provisions and conditions of, the Credit Agreement and the other Loan Documents (in each case, as amended hereby and subject to the limited waiver set forth in Section 4(m) below), as applicable, (y) exercise any and all rights, powers, and remedies under the Credit Agreement or the other Loan Documents (in each case, as amended hereby and subject to the limited waiver set forth in Section 4(m) below) or at law or in equity, or (z) do any and all of the foregoing, immediately at any time during the occurrence of an Event of Default and in each case, in accordance with the terms and provisions of the Credit Agreement and the other Loan Documents.

(f) Counterparts. This Amendment may be executed in any number of counterparts and by different parties hereto in separate counterparts, each of which when so executed and delivered shall be deemed to be an original and all of which counterparts, taken together, shall constitute but one and the same instrument. This Amendment may be executed by each party on separate copies,

which copies, when combined so as to include the signatures of all parties, shall constitute a single counterpart of this Amendment.

(g) Fax or Other Transmission. Delivery by one or more parties hereto of an executed counterpart of this Amendment via facsimile, telecopy, or other electronic method of transmission pursuant to which the signature of such party can be seen (including, without limitation, Adobe Corporation's Portable Document Format) shall have the same force and effect as the delivery of an original executed counterpart of this Amendment. Any party delivering an executed counterpart of this Amendment by facsimile or other electronic method of transmission shall also deliver an original executed counterpart, but the failure to do so shall not affect the validity, enforceability, or binding effect of this Amendment.

(h) Recitals Incorporated Herein. The preamble and the recitals to this Amendment are hereby incorporated herein by this reference.

(i) Section References. Section titles and references used in this Amendment shall be without substantive meaning or content of any kind whatsoever and are not a part of the agreements among the parties hereto evidenced hereby.

(j) Governing Law. This Amendment shall be governed by and construed in accordance with the internal laws (and not the law of conflicts) of the State of New York, but giving effect to federal laws applicable to national banks.

(k) Severability. Any provision of this Amendment which is prohibited or unenforceable shall be ineffective to the extent of such prohibition or unenforceability without invalidating the remaining provisions hereof in that jurisdiction or affecting the validity or enforceability of such provision in any other jurisdiction.

(l) Reaffirmation of Loan Parties. Each Loan Party (i) consents to the execution and delivery of this Amendment, (ii) reaffirms all of its obligations and covenants under the Loan Documents (including, without limitation, the Collateral Documents and the Loan Guaranty) to which it is a party, and (iii) agrees that, except to the extent amended hereby, none of its respective obligations and covenants under the Loan Documents shall be reduced or limited by the execution and delivery of this Amendment.

(m) Waiver by Lenders of Certain Items. Subject to the satisfaction of the conditions precedent set forth in Section 3 above, the Lenders hereby waive any Default or Event of Default that has occurred and is continuing as of the date hereof solely as a result of the Company making the Special Intercompany Loan referenced in clause (iii) of the definition of "Special Intercompany Loans". This waiver is an accommodation, and the Loan Parties acknowledge and agree that the Lenders shall require strict compliance with the Credit Agreement, as amended by this Amendment, hereafter.

[SIGNATURES ON FOLLOWING PAGES.]

IN WITNESS WHEREOF, the Borrowers, the other Loan Parties, the Administrative Agent and the Lenders have caused this Amendment to be duly executed by their respective duly authorized officers as of the day and year first above written.

BORROWERS:

BIO-REFERENCE
LABORATORIES, INC.
GENEDX, INC.
FLORIDA CLINICAL
LABORATORY, INC.
MERIDIAN CLINICAL
LABORATORY CORP.

By: /s/ Adam Logal
Name: Adam Logal
Title: Director, Vice President

OTHER LOAN PARTIES:

CAREEVOLVE.COM, INC.
BRLI-GENPATH
DIAGNOSTICS, INC.
GENEDX MENA LLC

By: /s/ Adam Logal
Name: Adam Logal
Title: Director, Vice President

JPMORGAN CHASE BANK, N.A.,
Individually as a Lender and as Administrative
Agent, Issuing Bank and Swingline Lender

By: /s/ Eric A. Anderson
Name: Eric A. Anderson
Title: Authorized Officer

THIS 5% CONVERTIBLE PROMISSORY NOTE AND THE SECURITIES ISSUABLE UPON CONVERSION HEREOF HAVE NOT BEEN REGISTERED UNDER THE SECURITIES ACT OF 1933, AS AMENDED (THE "SECURITIES ACT"), OR ANY STATE SECURITIES LAWS, IN RELIANCE UPON AN EXEMPTION FROM REGISTRATION UNDER THE SECURITIES ACT, AND, ACCORDINGLY, MAY NOT BE OFFERED, SOLD, MORTGAGED, PLEDGED, HYPOTHECATED, OR OTHERWISE TRANSFERRED EXCEPT PURSUANT TO AN EFFECTIVE REGISTRATION STATEMENT UNDER THE SECURITIES ACT OR PURSUANT TO AN AVAILABLE EXEMPTION FROM, OR IN A TRANSACTION NOT SUBJECT TO, THE REGISTRATION REQUIREMENTS OF THE SECURITIES ACT AND OTHERWISE IN COMPLIANCE WITH APPLICABLE STATE SECURITIES LAWS.

OPKO HEALTH, INC.
5% CONVERTIBLE PROMISSORY NOTE
(this "Note")

Miami, Florida

$[●] February 27, 2018

This Note is one of a series of 5% Convertible Promissory Notes (collectively, the "OPKO Notes"), issued and sold by OPKO Health, Inc., a Delaware corporation ("Borrower"), in the maximum aggregate initial principal amount of $[●].

FOR VALUE RECEIVED, Borrower hereby promises to pay to [●] ("Lender"), the principal sum of $[●], together with interest, at the applicable rate of interest set forth herein.

1. Payment of Principal and Interest; Interest Rate.

(a) Payment of Principal and Interest. Borrower, shall, subject to the earlier conversion of this Note in accordance with Section 5, pay to Lender the outstanding principal balance under this Note, together with accrued and unpaid interest thereon, on the Maturity Date. Interest on this Note shall accrue at the Applicable Rate from the most recent date to which interest has been paid or, if no interest has been paid, from the date of issuance, until the principal hereunder, and accrued and unpaid interest thereon, shall have been paid in full.

(b) Interest Rate; Determination. Interest shall accrue on the unpaid principal balance of this Note at the per annum rate equal to 5.0%, calculated on the basis of a 365/366 day year and the actual number of days elapsed (the "Applicable Rate").

2. Maturity Date. Subject to the earlier conversion of this Note in accordance with Section 5, the unpaid principal balance (including all accrued and unpaid interest thereon) shall be due and payable on February 27, 2023 (the "Maturity Date").

3. Manner of Payment. All amounts due and payable under this Note shall be paid in U.S. Dollars and shall be paid to Lender by wire transfer of immediately available funds in accordance with the instructions set forth on the signature page hereto. Lender may modify such instructions by delivering notice thereof to Borrower in accordance with Section 13.

Borrower shall be entitled to deduct and withhold from any payment, such amounts as may be required to be deducted and withheld under applicable Law, including, without limitation, any such deduction and withholding with respect to the making of such payment under the Internal Revenue Code of 1986, as amended, and all rules and regulations promulgated thereunder or any other applicable tax law or regulation.

If any payment under this Note shall become due and payable on a Saturday, Sunday, or a bank or legal holiday, then such payment shall be made on the next succeeding Business Day, without additional interest, premium or penalty.

4. Redemption. Borrower may redeem all or any part of the then issued and OPKO Notes (the "Redemption Right"). Borrower may exercise the Redemption Right by delivering notice to all Holders of Borrower's exercise of the Redemption Right (the "Redemption Notice"), which Redemption Notice shall contain the following: (i) the date on which Borrower will redeem the OPKO Notes, which shall be a date no fewer than 30 days, and no more than 60 days, immediately following the date of the Redemption Notice (the "Redemption Date"); (ii) the aggregate principal amount of OPKO Notes to be redeemed; (iii) the Redemption Price, including a reasonably detailed calculation thereof; and (iv) instructions for a Holder to deliver such Holder's OPKO Notes to Borrower and receive in exchange therefor the Redemption Price for each $1,000 principal amount of such Holder's OPKO Notes so delivered. At any time prior to 5:00 p.m. New York time on the date immediately preceding the Redemption Date, a Holder may elect to convert such Holder's Notes in accordance with Section 5(b). Any Redemption Notices shall be applied ratably to the Holders of all OPKO Notes issued based on each Holder's then-current OPKO Note holdings, provided that any voluntary conversions by a Holder subsequent to the date of the Redemption Notice and prior to the Redemption Date shall be applied against such Holder's pro rata allocation, thereby decreasing the aggregate amount redeemed hereunder if less than all of the OPKO Notes are redeemed.

5. Note Conversion; Redemption.

(a) Conversion. Subject to the terms and provisions hereof, this Note shall convert into shares of Borrower's common stock, par value $0.01 ("Common Stock"), as set forth in this Section 5.

(b) Optional Conversion. At any time prior to the Maturity Date, Lender may deliver to Borrower written notice of Lender's election to convert all or any portion of the principal amount of this Note, together with accrued but unpaid interest thereon, into shares of Common Stock (a "Conversion Notice"), in which case such aggregate principal amount of this Note, together with such accrued and unpaid interest thereon, indicated in the Conversion Notice (the "Conversion Amount") shall convert into a number of shares of Common Stock equal to the Conversion Amount, divided by the Conversion Price then in effect.

(c) Method of Conversion. Conversion of this Note pursuant to Section 5 shall take place at any time during the usual business hours of Borrower at its principal office or at such other time

and place as Borrower and Lender may agree, by the surrender for cancellation of this Note and, if so required, by a written instrument or instruments of transfer in form reasonably satisfactory to Borrower duly executed by Lender. Borrower shall pay any applicable transfer tax. This Note shall be deemed to have been converted as of the close of business on the Conversion Date, and Lender shall be treated for all purposes as the holder of record of such number of Common Stock, as provided in this Section 5, on Borrower's books and records as of the close of business on the Conversion Date.

(d) Share Issuance. Borrower shall issue and deliver, on or prior to the fifth (5^{th}) Business Day after the Conversion Date, to Lender or to the nominee of Lender, at the address of Lender on the books of Borrower or as otherwise directed by Lender in writing, a certificate evidencing the Common Stock to which Lender shall be entitled, and Borrower shall register such Common Stock in its share registry.

(e) Reserved Common Stock. Borrower shall at all times keep authorized and approved under its Amended and Restated Certificate of Incorporation, as may be amended from time to time, solely for the purpose of effecting the conversion of this Note and the other OPKO Notes, such number of shares of Common Stock issuable upon the conversion of this Note and the other OPKO Notes in accordance with their terms, and shall take all such action as may be required from time to time in order that it may validly and legally issue the Common Stock upon such conversion.

(f) Adjustment to Conversion Price.

(i) Adjustment for Share Splits and Combinations. If Borrower shall at any time or from time to time after the date hereof effect a subdivision of the outstanding shares of Common Stock, then the Conversion Price in effect immediately before such subdivision shall be multiplied by a fraction (i) the numerator of which is the total number of shares of Common Stock issued and outstanding immediately prior to the time of such subdivision, and (ii) the denominator of which is the total number of shares of Common Stock issued and outstanding immediately following such subdivision. Conversely, if Borrower shall at any time or from time to time after the date hereof combine the outstanding shares of Common Stock into a smaller number of shares, then the Conversion Price in effect immediately before the combination shall be multiplied by a fraction (i) the numerator of which is the total number of shares of Common Stock issued and outstanding immediately prior to the time of such combination, and (ii) the denominator of which is the total number of shares of Common Stock issued and outstanding immediately following such combination. Any adjustment pursuant to this Section 5(f)(i) shall become effective at the close of business on the date the subdivision or combination becomes effective.

(ii) Adjustment for Dividends and Distributions. If Borrower at any time or from time to time after the date hereof makes, or fixes a record date for the determination of holders of Common Stock entitled to receive, a dividend or other distribution payable in Common Stock, then, in each such event, the Conversion Price that is then in effect shall be decreased as of the time of such issuance or, in the event such record date is fixed, as of the close of business on such record date, by multiplying the Conversion Price then in effect by a fraction (i) the numerator of which is the total number of shares of Common Stock issued and outstanding immediately prior to the time of such issuance or the close of business on such record date, and (ii) the denominator of which is the total number of shares Common Stock issued and outstanding immediately prior to the time of such issuance or the close of business on such record date

plus the number of shares of Common Stock issued or issuable in payment of such dividend or distribution;provided, however, that if such record date is fixed and such dividend is not fully paid or if such distribution is not fully made on the date fixed therefor, then the Conversion Price shall be recomputed accordingly as of the close of business on such record date, and thereafter the Conversion Price shall be adjusted pursuant to this Section 5(f)(ii) to reflect the actual payment of such dividend or distribution.

(iii) Adjustment for Reclassification, Exchange and Substitution. If at any time or from time to time after the date hereof the Common Stock issuable upon the conversion of this Note is changed into the same or a different number of shares of any class or classes of shares, whether by recapitalization, reclassification or otherwise (other than an acquisition or asset transfer or a subdivision or combination of shares or share dividend or a reorganization, merger, consolidation or sale of assets provided for elsewhere in this Section 5(f)), then in any such event Lender, upon conversion of this Note in circumstances in which Common Stock would otherwise be issuable, shall instead be entitled to receive upon such conversion, the kind and amount of shares and other securities and property receivable upon such recapitalization, reclassification or other change by holders of the number of shares of Common Stock into which this Note would have been converted (assuming the conversion thereof) immediately prior to such recapitalization, reclassification or change, all subject to further adjustment as provided herein or with respect to such other securities or property by the terms thereof.

(iv) Reorganizations, Mergers, Consolidations or Sales of Assets. If any Organic Change shall be effected in such a way that holders of Common Stock shall be entitled to receive (either directly or upon subsequent liquidation) shares, securities or assets in respect of or in exchange for their shares of Common Stock, then lawful and adequate provisions shall be made whereby Lender shall thereupon have the right to receive, upon the basis and upon the terms and conditions specified herein and in lieu of Common Stock immediately theretofore receivable upon the conversion of this Note, such shares, securities or assets as may be issued or payable in respect of or in exchange for the number of outstanding shares of Common Stock that would have been immediately theretofore receivable upon conversion of this Note had such Organic Change not taken place, and in the case of any reorganization or reclassification appropriate provisions shall be made with respect to the rights and interests of Lender whereby the provisions hereof (including, without limitation, provisions for adjustments to the Conversion Price) shall thereafter be applicable, as nearly as may be, in relation to any shares, securities or assets thereafter deliverable upon the exercise of such conversion rights.

(v) Certificate of Adjustment. In each case of an adjustment or readjustment of the Conversion Price pursuant to Section 5(f), Borrower, at its expense, shall compute such adjustment or readjustment in accordance with the provisions hereof and prepare a certificate showing such adjustment or readjustment, and shall mail such certificate, by first class mail, postage prepaid, to Lender at in accordance with Section 13. The certificate shall set forth such adjustment or readjustment, showing in reasonable detail the facts upon which such adjustment or readjustment is based.

(g) Fractional Shares; Aggregation. No fractional shares of Common Stock shall be issued upon conversion of this Note. If conversion of this Note would result in the issuance of any fractional

shares of Common Stock, then Borrower shall, in lieu of issuing any fractional share, round up to the nearest whole share.

6. Representations and Warranties. Borrower represents and warrants to Lender, on the date hereof, that:

(a) It is duly incorporated and validly existing under the Laws of the State of Delaware;

(b) It has full power and legal right to execute and deliver this Note and to perform its obligations hereunder and its execution and delivery of this Note, and the performance by it of its obligations hereunder, have been duly authorized by all necessary corporate action and do not conflict with any applicable Law or material contractual restriction binding upon or affecting it or any of its property or assets;

(c) This Note constitutes the legal, valid and binding obligations of Borrower, enforceable against Borrower in accordance with its terms, except as the enforcement hereof may be limited by bankruptcy, insolvency, or other Laws affecting the enforcement of creditors' rights generally and subject to the applicability of general principles of equity; and

(d) Except for such filings or other actions that have been made or taken on or prior to the date hereof, no consent, approval or authorization of, or registration, declaration or filing with, any Governmental Authority or other Person is required as a condition to or in connection with the due and valid execution, delivery and performance by Borrower of this Note.

7. Affirmative Covenants. So long as this Note remains outstanding, Borrower shall:

(a) comply in all material respects with applicable Laws, such compliance to include, without limitation, paying before the same become delinquent all taxes, assessments and governmental charges imposed upon it or upon its property, except for good faith contests for which adequate reserves are maintained or any noncompliance which would not reasonably be expected to have a material adverse effect on Borrower;

(b) provide to Lender, as soon as possible and in any event within five (5) Business Days after the occurrence of each event which is an Event of Default, a written notice setting forth the details of such event and the action which Borrower proposes to take with respect thereto; and

(c) maintain its corporate existence in compliance with all applicable Laws, except to the extent that any failure to comply with the foregoing would not reasonably be expected to have a material adverse effect on Borrower.

8. Events of Default. The occurrence of any of the following events shall constitute an "Event of Default" under this Note:

(a) Failure by Borrower to pay when due an installment of principal, interest or other amount owing under this Note or any other OPKO Note on or before the date such payment is due, and such failure continues for five (5) consecutive Business Days;

(b) Borrower fails to comply with or perform any other term, obligation, covenant or condition contained in this Note and which failure shall continue for ten consecutive days following written notice of such default by Lender to Borrower;

(c) Any representation or warranty made by Borrower in this Note shall prove to have been incorrect in any material respect when made and which would reasonably be expected to impair the enforceability of this Note by Lender against Borrower;

(d) Borrower or any Subsidiary of Borrower shall (i) commence a voluntary case under any applicable bankruptcy, insolvency or other similar Law now or hereafter in effect; (ii) consent to the entry of an order for such relief in an involuntary case under any applicable bankruptcy, insolvency or other similar Law now or hereafter in effect; (iii) consent to the appointment of or taking possession by a receiver, liquidator, assignee, trustee, custodian, sequestrator or other similar official for Borrower or such Subsidiary or for all or substantially all of Borrower's or such Subsidiary's assets; or (iv) make any general assignment for the benefit of creditors; or

(e) An involuntary case or other proceeding shall be commenced against Borrower or any Subsidiary of Borrower under any applicable bankruptcy, insolvency or other similar Law now or hereafter in effect, and such involuntary case shall remain undismissed or unstayed for a period of 60 days.

9. Remedies. Upon the occurrence of an Event of Default, all amounts due hereunder, including, without limitation, the unpaid principal balance and accrued and unpaid interest thereon, shall, at Lender's written election, become immediately due and payable upon written notice to Borrower (an "Acceleration Notice"); provided, however, that upon the occurrence of an Event of Default described in Section 8(d) or Section 8(e), all amounts due hereunder, including, without limitation, the unpaid principal balance and accrued and unpaid interest thereon, shall become immediately due and payable automatically and without any Acceleration Notice or demand by Lender. Upon the occurrence of an Event of Default, Lender may additionally exercise any of its other rights and remedies granted hereunder or under applicable Law. Such remedies shall be cumulative and concurrent and may be pursued singly, successively or together, at Lender's option, and as often as the occasion therefore arises.

10. Transfer Restrictions.

(a) Lender covenants that the Purchased Securities will be disposed of only pursuant to an effective registration statement under, and in compliance with the requirements of, the Securities Act or pursuant to an available exemption from the registration requirements of the Securities Act, and in compliance with applicable state securities laws. In connection with any transfer of the Purchased Securities other than pursuant to an effective registration statement or to Borrower, Borrower may require the transferor to provide to Borrower an opinion of counsel selected by the transferor, the form and substance of which opinion shall be reasonably satisfactory to Borrower, to the effect that such transfer does not require registration under the Securities Act. Notwithstanding the foregoing, Borrower hereby consents to and agrees to register on the books of Borrower and with its Transfer Agent, without any such legal opinion, except to the extent that the transfer agent requests such legal opinion, any transfer of the Purchased Securities by an Lender to an Affiliate of such Lender, provided that such transfer does not involve a "sale" within the meaning

of Section 2(a)(3) of the Securities Act and provided that such Affiliate does not request any removal of any existing legends on any certificate evidencing the Purchased Securities.

(b) Lender agree to the imprinting, until no longer required by thisSection 10, of the legends, in substantially the following form, on any certificate or other instrument evidencing any of the Purchased Securities:

> THESE SECURITIES HAVE NOT BEEN REGISTERED WITH THE SECURITIES AND EXCHANGE COMMISSION IN RELIANCE UPON AN EXEMPTION FROM REGISTRATION UNDER THE SECURITIES ACT OF 1933, AS AMENDED (THE "SECURITIES ACT"), OR UNDER ANY APPLICABLE STATE SECURITIES LAWS AND, ACCORDINGLY, MAY NOT BE OFFERED OR SOLD EXCEPT PURSUANT TO AN EFFECTIVE REGISTRATION STATEMENT UNDER THE SECURITIES ACT OR PURSUANT TO AN AVAILABLE EXEMPTION FROM, OR IN A TRANSACTION NOT SUBJECT TO, THE REGISTRATION REQUIREMENTS OF THE SECURITIES ACT AND IN COMPLIANCE WITH APPLICABLE STATE SECURITIES LAWS.

Certificates or another instrument evidencing the Purchased Securities shall not be required to contain such legend or any other legend following any sale of such Purchased Securities pursuant to (i) an effective registration statement under the Securities Act, or (ii) Rule 144 if Lender provides Borrower with a legal opinion (and the documents upon which the legal opinion is based) reasonably acceptable to Borrower to the effect that the Purchased Securities have been sold under Rule 144. Borrower will no later than five (5) Business Days following the delivery by Lender to Borrower or the Transfer Agent (if delivery is made to the Transfer Agent a copy shall be contemporaneously delivered to Borrower) of (x) a legended certificate representing the applicable Purchased Securities (other than the OPKO Notes) and any necessary instruments of transfer and (y) evidence reasonably satisfactory to Borrower and its counsel of the occurrence of any of (i) or (ii) above (including any applicable Lender and broker representation letters and the delivery of any legal opinion referred to therein, as applicable), deliver or cause to be delivered to such Lender (or a transferee of such Lender, as applicable) a certificate or book-entry (including shares transferred via DWAC or similar methodology by DTC) representing such Purchased Securities (other than the OPKO Notes) that is free from all restrictive and other legends.

11. Collection Costs. Borrower shall pay all reasonable costs and expenses of the collection of this Note (including, without limitation, all reasonable and documented fees and expenses of Lender's attorneys) paid or incurred by Lender and irrespective of whether an Action has been commenced against Borrower.

12. Lost, Stolen, Destroyed or Mutilated Note. Upon receipt of evidence reasonably satisfactory to Borrower of the loss, theft, destruction or mutilation of this Note, Borrower will issue a new Note of like tenor and amount and dated the date to which interest has been paid, in lieu of such lost, stolen, destroyed

or mutilated Note, and in such event Lender agrees to indemnify and hold Borrower harmless in respect of any such lost, stolen, destroyed or mutilated Note.

13. Notices. All notices, requests and other communications to any party hereunder shall be in writing (including facsimile or similar writing) and shall be given to such party at such party's address set forth in this Note, or such other address as such party may hereinafter specify for the purpose of this Section 13 to the party giving such notice. All notices, requests and other communications shall be deemed received on the date of receipt by the recipient thereof if received prior to 5:00 p.m. in the place of receipt and such day is a Business Day in the place of receipt. Otherwise, any such notice, request or communication shall be deemed not to have been received until the next succeeding Business Day in the place of receipt. Any notice, request or other written communication sent by e-mail shall be confirmed by certified mail, return receipt requested, posted on the same Business Day, or by personal delivery, whether courier or otherwise, made on the same Business Day as such e-mail transmissions.

14. Certain Definitions. As used in this Note:

(a) "Acceleration Notice" has the meaning set forth in Section 9.

(b) "Action" means any claim, action, cause of action or suit (whether in contract, tort or otherwise), litigation (whether at Law or in equity, whether civil or criminal), controversy, assessment, arbitration, investigation, hearing, charge, complaint, demand, notice or proceeding to, from, by or before any Governmental Authority.

(c) "Affiliate" means with respect to any Person, any other Person, directly or indirectly, through one or more intermediaries, controlling, controlled by, or under common control with such Person, including, without limitation, (i) in respect of any Person which is a limited or general partnership, its partners, affiliated partnerships managed by the same management company or managing (general) partner or by an entity which controls, is controlled by, or is under common control with, such management company or managing (general) partner; (ii) in respect of any Person which is a limited liability company, its members, affiliated limited liability companies managed by the same management company or managing (general) partner or officer or board of directors or by an entity which controls, is controlled by, or is under common control with, such management company or managing (general) partner or officer or board of directors; and (iii) the beneficiaries of any Person which is a trust.

(d) "Applicable Rate" has the meaning set forth in Section 1(b).

(e) "Borrower" has the meaning set forth in the Recitals.

(f) "Business Day" means a day (other than a Saturday) on which banks are open for business in Miami, Florida.

(g) "Common Stock" has the meaning set forth in Section 5(a).

(h) "Contractual Obligation" means, with respect to any Person, any contract, agreement, deed, mortgage, lease, license, commitment, promise, undertaking, arrangement, performance

bond, warranty obligation or understanding, whether written or oral and whether express or implied, or other document or instrument (including any document or instrument evidencing or otherwise relating to any Debt), to which or by which such Person is a party or otherwise subject or bound or to which or by which any property, business, operation or right of such Person is subject or bound.

(i) "Conversion Date" means the date on which Borrower delivers the Conversion Notice to Lender.

(j) "Conversion Notice" has the meaning set forth in Section 5(c).

(k) "Conversion Price" means $5.00, subject to adjustment as provided in Section 5(f).

(l) "Debt" means, with respect to any Person, all obligations (including all obligations in respect of principal, accrued interest, penalties, fees and premiums) of such Person, whether direct or indirect, (i) for borrowed money (including overdraft facilities), (ii) for liabilities secured by any charge, lien pledge, security interest, mortgage and any other restriction or covenant with respect to transferability existing on property owned or acquired and subject thereto, (iii) evidenced by notes, bonds, debentures or similar Contractual Obligations, (iv) for the deferred purchase price of property, goods or services, including in connection with the acquisition of any business or non-competition agreement (other than trade payables or accruals incurred in the ordinary course of business consistent with the past customs and practices), (v) under capital leases (in accordance with generally accepted accounting principles in the United States, consistently applied), (vi) in respect of letters of credit and bankers' acceptances, (vii) for Contractual Obligations relating to interest rate protection, swap agreements, factoring, hedging and collar agreements, (viii) in the nature of premiums (prepayment or otherwise) or penalties in connection with the obligations described in clauses (i) through (viii) above, and (ix) in the nature of Guarantees of the obligations described in clauses (i) through (viii) above of any other Person.

(m) "Dollars", "dollars" and "$" refer to U.S. Dollars.

(n) "Event of Default" has the meaning set forth in Section 8.

(o) "Governmental Authority" means any nation or country (including but not limited to the United States) and any state, commonwealth, territory or possession thereof and any political subdivision of any of the foregoing, including but not limited to courts, departments, commissions, boards, bureaus, agencies, ministries or other instrumentalities.

(p) "Guarantee" means, with respect to any Person, (i) any guarantee of the payment or performance of, or any contingent obligation in respect of, any Debt or other liability of any other Person; (ii) any other arrangement whereby credit is extended to any obligor (other than such Person) on the basis of any promise or undertaking of such Person (A) to pay the Debt or other liability of such obligor, (B) to purchase any obligation owed by such obligor, (C) to purchase or lease assets under circumstances that are designed to enable such obligor to discharge one or more of its obligations or (D) to maintain the capital, working capital, solvency or general financial condition of such obligor; and (iii) any liability as a general

partner of a partnership or as a venturer in a joint venture in respect of Debt or other obligations of such partnership or venture.

(q) "Holder" means a Person holding any OPKO Notes, including, for the avoidance of doubt, Lender.

(r) "Laws" means any and all laws (statutory, judicial or otherwise), ordinances, regulations, judgments, orders, directives, injunctions, writs, decrees or awards of any Governmental Authority.

(s) "Lender" has the meaning set forth in the Preamble.

(t) "Maturity Date" has the meaning set forth in Section 2.

(u) "OPKO Notes" has the meaning set forth in the Recitals.

(v) "Organic Change" means any capital reorganization, reclassification, recapitalization, consolidation, merger, sale of all or substantially all of Borrower's assets or other similar transaction.

(w) "Person" means any individual, partnership, joint venture, firm, corporation, association, limited liability company, joint stock company, unincorporated organization, trust or other enterprise or any governmental or political subdivision or any agency, department or instrumentality thereof.

(x) "Purchased Securities" means this Note and the shares of Common Stock issuable upon conversion of this Note.

(y) "Redemption Date" has the meaning set forth in Section 4.

(z) "Redemption Notice" has the meaning set forth in Section 4.

(aa) "Redemption Price" means, for each $1,000 principal amount of OPKO Notes, an amount in cash, in immediately available funds, equal to the sum of 100% of such principal amount, plus accrued and unpaid interest thereon to, but not including, the Redemption Date.

(bb) "Redemption Right" has the meaning set forth in Section 4.

(cc) "Subsidiary" means, with respect to any specified Person, any other Person of which such specified Person will, at the time, directly or indirectly through one or more Subsidiaries, (a) own at least 50% of the outstanding capital stock (or other shares of beneficial interest) entitled to vote generally, (b) hold at least 50% of the partnership, limited liability company, joint venture or similar interests or (c) be a general partner, managing member or joint venturer.

(dd) "Trading Day" means a day on which the Common Stock is traded on the Trading Market.

(ee) "Trading Market" means the primary national securities exchange on which the Common Stock is listed or quoted for trading on the date in question.

15. Miscellaneous.

(i) This Note may be amended or modified only by an instrument in writing signed by Borrower and Holders holding at least 51% of the outstanding aggregate principal amount of the OPKO Notes; provided, however, that, without the consent of Lender, no amendment, supplement or waiver may (1) change the Maturity Date of the principal of, or any installment of interest on, this Note; (2) reduce the principal amount of, or interest on, this Note; (3) change the currency of payment of principal of, or interest on, this Note; (4) impair the right to institute suit for the enforcement of any payment on or after the Maturity Date (or, in the case of a redemption, on or after the Redemption Date) of this Note; (5) waive a default in the payment of principal of, or interest on the this Note; (6) subordinates this Note in right of payment to any other Debt of Borrower; or (7) reduce the percentage or aggregate principal amount of outstanding OPKO Notes the consent of whose Holders is necessary for waiver of compliance with, or amendment to, the provisions of this Note.

(ii) This Note shall be binding upon and inure to the benefit of and be enforceable by the respective successors and permitted assigns of the parties hereto; provided, however, that the Borrower may not assign or transfer any of its rights or obligations hereunder without the prior written consent of Lender. Subject to the terms and conditions of this Note, including, without limitation, the restrictions on transfer of this Note contained herein, Lender may at any time, upon five (5) days' prior written notice to Borrower, assign all or any portion of its rights hereunder to an Affiliate without Borrower's consent.

(iii) No delay or omission on the part of Lender in the exercise of any right or remedy hereunder shall operate as a waiver thereof, and no partial exercise of any right or remedy precludes any other or further exercise thereof or the exercise of any other rights or remedies.

(iv) If any provision of this Note is held to be invalid and unenforceable in any jurisdiction, then, to the fullest extent permitted by Law, (i) the other provisions hereof shall remain in full force and effect in such jurisdiction, and (ii) the invalidity or unenforceability of any provision hereof in any jurisdiction shall not affect the validity or enforceability of such provision in any other jurisdiction.

(v) Borrower hereby waives presentment, demand for payment (except as expressly required herein), protest, notice of protest, notice of dishonor and any and all other notices or demands in connection with the delivery, acceptance, performance, default or enforcement of this Note.

(vi) THIS NOTE SHALL BE GOVERNED BY AND CONSTRUED IN ACCORDANCE WITH THE LAWS OF THE STATE OF NEW YORK WITHOUT GIVING EFFECT TO ANY CHOICE OR CONFLICT OF LAW PROVISION OR RULE THAT WOULD CAUSE THE APPLICATION OF THE LAWS OF ANY OTHER JURISDICTION. BORROWER AND LENDER HEREBY IRREVOCABLY SUBMIT TO THE EXCLUSIVE JURISDICTION OF THE STATE AND FEDERAL COURTS SITTING IN MIAMI-DADE COUNTY FOR THE ADJUDICATION OF ANY

DISPUTE BROUGHT BY BORROWER OR LENDER HEREUNDER, IN CONNECTION HEREWITH OR WITH ANY TRANSACTION CONTEMPLATED HEREBY OR DISCUSSED HEREIN, AND HEREBY IRREVOCABLY WAIVE, AND AGREE NOT TO ASSERT IN ANY SUIT, ACTION OR PROCEEDING BROUGHT BY BORROWER OR LENDER, ANY CLAIM THAT IT IS NOT PERSONALLY SUBJECT TO THE JURISDICTION OF ANY SUCH COURT, OR THAT SUCH SUIT, ACTION OR PROCEEDING IS IMPROPER. EACH PARTY HEREBY IRREVOCABLY WAIVES PERSONAL SERVICE OF PROCESS AND CONSENTS TO PROCESS BEING SERVED IN ANY SUCH SUIT, ACTION OR PROCEEDING BY MAILING A COPY THEREOF VIA REGISTERED OR CERTIFIED MAIL OR OVERNIGHT DELIVERY (WITH EVIDENCE OF DELIVERY) TO SUCH PARTY AT THE ADDRESS IN EFFECT FOR NOTICES TO IT AND AGREES THAT SUCH SERVICE SHALL CONSTITUTE GOOD AND SUFFICIENT SERVICE OF PROCESS AND NOTICE THEREOF. NOTHING CONTAINED HEREIN SHALL BE DEEMED TO LIMIT IN ANY WAY ANY RIGHT TO SERVE PROCESS IN ANY MANNER PERMITTED BY LAW. BORROWER AND LENDER HEREBY WAIVE ALL RIGHTS TO A TRIAL BY JURY.

[signature page follows]

IN WITNESS WHEREOF, the undersigned has executed and delivered this Note as of the date first above written.

OPKO HEALTH, INC.

By:_____
Name:
Title:

Acknowledged and agreed by Lender as of the date first set forth above:

_____

By:_____
Name:
Title:

Payment Instructions for Lender:

If by wire:

Bank: _____
ABA#: _____
Account # _____
Beneficiary: _____

Lender's Address for Notice:

_____
_____
_____

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
BioReference 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 BioReference Laboratories, Inc.

of our reports dated March 1, 2018, 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, 2017.

/s/ Ernst & Young LLP

Miami, Florida
March 1, 2018

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, 2018

/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, 2018

/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, 2017 (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, 2018

/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, 2017 (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, 2018

/s/ Adam Logal

Adam Logal
Senior Vice President, Chief Financial Officer
Chief Accounting Officer and Treasurer