August 26, 2015

OPKO Letter to Shareholders

MIAMI--(BUSINESS WIRE)-- **OPKO Health, Inc. (NYSE:OPK)** today released the following open letter from Phillip Frost, M.D., its Chairman and Chief Executive Officer, to its shareholders:

Dear Shareholder,

I want to take the occasion of OPKO's recently announced acquisition of Bio-Reference Laboratories (Bio-Reference) to present a general overview of the company's present activities. They are many and while, in some respects, they differ greatly from one another, all share a common theme. They all deal with products for large markets in which OPKO has an opportunity to be a leader, and all have potential for long-term growth. We hope to achieve this growth by providing an ever increasing spectrum of medicines and tests, some new and novel, others of already established value, to help physicians provide better care for their patients.

Diagnostics

The strategy behind the recent Bio-Reference acquisition is twofold. First, it is a business whose revenues and profits have grown consistently since its launch by Dr. Marc Grodman in the 1980's, primarily through organic growth, to become the third largest full service reference laboratory in the United States. It has built a reputation of innovation with recognized franchises in women's health, cancer and, more recently, genetics, helping physicians worldwide to diagnose rare genetic disorders and to identify special features of a patient's genetic material to select more effective chemotherapy. Second, it provides an infrastructure for marketing and sales that reaches approximately 10 million patients a year.

Reimbursement is an important factor for the success of diagnostic products and Bio-Reference has a large team of experts who can complement our efforts to be sure that payors recognize the value of our tests for reimbursement purposes.

4KScore® Test. Because the PSA test is associated with frequent false positive results, many men with elevated PSA values are subjected to unnecessary prostate biopsies and, if an indolent, non-life threatening form of prostate cancer is discovered, may be subjected to over treatment. The 4Kscore test is a blood test used to identify men who are at risk for aggressive prostate cancer and are most likely to benefit from a prostate biopsy and treatment, while avoiding prostate biopsies in men who are at low risk of having aggressive disease. Men determined to be at low risk by the 4Kscore have a 98-99% chance to be metastasis free after 20 years of long-term follow up while being monitored. The 4Kscore test has been extensively studied and validated with the results of 12 prospective and retrospective studies involving over 22,000 patients from both the United States and Europe published in peer-reviewed journals.

The 4Kscore test is now recommended in the 2015 National Comprehensive Cancer Network (NCCN) Prostate Cancer Early Detection Guidelines for men with an elevated PSA

and/or abnormal digital rectal examination who require additional information about their risk for high-grade, aggressive prostate cancer prior to performing a first prostate biopsy or a repeat biopsy after a prior negative prostate biopsy.

The reduced costs of eliminating approximately 40% of prostate biopsies resulting from the use of the 4Kscore test to confirm elevated PSA tests has been estimated at $1 billion and, if the costs of downstream treatment interventions are also considered, there could be $2.5 billion additional annual savings to the U.S. health care system.

The OPKO marketing and sales efforts have so far focused primarily on urologists. Over 25% of U.S. urologists who evaluate men for prostate cancer have now ordered the 4Kscore test to help further evaluate a PSA test prior to prostate biopsy. As the 4Kscore test is intended to be used in situations in which a PSA result is suspicious for cancer, we can now, with the much larger Bio-Reference sales force, expand our marketing efforts to primary care physicians and internists who are responsible for prostate cancer screening and who order 93% of all PSA tests. The groundwork for reimbursement for the 4Kscore test has been put into place. We now have an active CPT code for the test, the test is included in the NCCN guidelines, and we are billing Medicare and commercial payors.

Among the many compelling reasons for the acquisition, we believe Bio-Reference will greatly accelerate the commercial success of the 4Kscore test. Bio-Reference has the capacity to dramatically increase the number of 4Kscore tests done each day. They provide national marketing and distribution with a large client services group and a large dedicated sales force that already have strong relationships with primary care physicians. Bio-Reference has over 1,200 phlebotomists and 180 blood-draw centers around the country that can facilitate patient access. Finally, Bio-Reference has robust billing operations and a seasoned national reimbursement team that participates in almost every major commercial insurance plan. Bio-Reference has the expertise and extensive infrastructure to help make the 4Kscore test the new standard for identifying aggressive prostate cancer in men with a suspicious PSA.

Claros Point-of-Care Systems. We have been working on perfecting this point-of-care technology prior to product submission for regulatory approval and the test for PSA is our most advanced candidate. This test, short term, is most important as it complements our plans to expand the utilization of the 4Kscore test. The several hundred man sales force at Bio-Reference who regularly call on primary care physicians and specialists will sell the PSA test and, when a PSA result raises suspicion, the physician can then order a 4Kscore test to help formulate a decision to refer the patient to an urologist.

Following approval of the PSA test, we intend to continue the development and approval of other important diagnostic panels utilizing the Claros 1 platform, including panels focused on renal and men's and women's health, to further expand the menu of laboratory tests and services performed by Bio-Reference.

Renal Disease Products

Rayaldee™. In late July, we announced that the U.S. Food and Drug Administration (FDA) had accepted our New Drug Application (NDA) for Rayaldee™ for full review and set a Prescription Drug User Fee Act (PDUFA) target date of March 29, 2016. As previously reported, this NDA is supported by data from two randomized, double-blind, placebo-

controlled studies and one open-label extension study conducted in the targeted patient population at a total of 105 U.S. sites. These studies met all primary efficacy and safety endpoints.

Rayaldee has been developed for the prevention and treatment of secondary hyperparathyroidism (SHPT) in patients with stage 3 or 4 chronic kidney disease (CKD) and vitamin D insufficiency. Rayaldee is a proprietary modified-release prohormone formulation designed to gradually correct vitamin D insufficiency while avoiding upregulation of an enzyme which breaks down vitamin D and limits its desired serum parathyroid hormone lowering effect. Gradual elevation of serum total 25-hydroxyvitamin D is intended to prevent excessive elevation of serum calcium and related vascular and renal calcification which contributes heavily to morbidity and mortality in CKD patients. No previous product has been approved for this indication. CKD afflicts over 26 million people in the U.S., including more than 20 million patients with moderate (stages 3 or 4) and severe (stage 5) forms. I believe that Rayaldee will be warmly welcomed by healthcare professionals who care for CKD patients.

Fermagate. Patients with chronic kidney disease also frequently have elevated levels of phosphorus in their blood as a result of decreased kidney excretion capacity. As excess blood phosphorus tends to deposit in soft tissues such as blood vessels, making them more rigid, it is important to normalize blood phosphorus levels. Phosphorus binders are commonly administered orally to bind dietary phosphorus in the GI tract to limit absorption, but a frequent side effect of these “binders” is diarrhea. Our Fermagate is a new “binder” which has successfully completed Phase 2 clinical trials, and has demonstrated a lower incidence of diarrhea. We are currently preparing for Phase 3 trials in the U.S., but are first studying interesting characteristics of Fermagate which may offer additional advantages.

Rolapitant is an NK-1 inhibitor developed to treat nausea and vomiting related to cancer chemotherapy. This was a Phase 3 ready drug obtained from Schering as part of its merger with Merck. After a year of evaluation, we licensed the product to Tesaro, Inc., who successfully completed three Phase 3 studies, meeting all safety and efficacy endpoints, and then submitted an NDA to the FDA. This is expected to be approved early in September 2015, triggering milestone and double digit royalty payments to us. The highly experienced Tesaro team anticipates eventual annual sales of more than $1 billion.

OPKO Biologics

OPKO Biologics, a biopharmaceutical company focused on developing long-acting versions of validated and known therapeutic peptides and proteins, represents the former Prolor Biologics, acquired by us in 2013. Its platform technology involves a carboxyl terminal peptide (CTP) added to a peptide or protein to prolong its biologic half-life.

Human Growth Hormone. The most advanced CTP product under development is a long-acting version of human growth hormone, known as hGH-CTP, for the long-term treatment of children with growth failure due to inadequate secretion of endogenous growth hormone, and for the treatment of hGH deficient adults. Presently, sales of the hGH products injected daily are approximately $3.0 billion worldwide, growing 5% annually.

In December 2014, we entered into an exclusive worldwide agreement with Pfizer Inc. (“Pfizer”) for the development and commercialization of this hGH-CTP product. In connection

with the collaboration, we received up-front payments of $295 million and will receive an additional $275 million upon achievement of development-related milestones. In addition, we will receive initial royalty payments upon the commercialization of hGH-CTP for adult growth hormone deficiency (GHD). Upon the launch of hGH-CTP for pediatric GHD, the royalties will transition to gross profit sharing among all indications for both hGH-CTP and Pfizer's Genotropin®. We will lead clinical development and will be responsible for funding the development programs for adult and pediatric GHD and growth failure in children born small for gestational age (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.

We have completed enrollment in the pivotal Phase 3 study in adults and Pfizer plans to file a Biological License Application (BLA) and Market Authorization Application (MAA) as soon as the 12-month treatment period and data compilation are completed.

All 52 eligible patients in our Phase 2 pediatric study have completed the 12 month mandatory treatment period, the primary time point for efficacy to be evaluated. Preliminary efficacy and safety data at 12-months demonstrate favorable dose responses with all three doses of once weekly injections of hGH-CTP; the safety profile and real time 12-month growth rates are comparable to the active control group given daily Genotropin® injections. It is worth noting that over 90% of the patients have elected to continue receiving the treatment of our weekly hGH-CTP in the open-label phase of the pediatric Phase 2 trial; some for as long as two years, which we believe is an indication of a high acceptance rate by patients. This long-term outcome data provides the basis for the development of a single pivotal Phase 3 study design which has been presented to the FDA, and are in discussions with the EMA (Europe) and PMDA (Japan).

Phase 3 pediatric study activities with our partner Pfizer have commenced and we expect to initiate our Phase 3 pediatric study next year **using drug product manufactured by Pfizer and a pen injection device selected by Pfizer**. Utilizing the same drug supply and source and same pen device in our Phase 3 trial that will be used in commercializing our product will provide for smoother regulatory approval, lower costs of goods, greater quality control and seamless and rapid launch after completion of our Phase 3 study and receipt of regulatory approval. We cannot stress enough the advantage of having Pfizer as our partner, not only for commercial penetration, but also for their experience in bringing growth hormone products to market with their relationships with pediatric endocrinologists, given their two decades of sales and marketing of Genotropin®, a leader in the $3.0 billion daily hGH market.

Factor VIIa-CTP is our novel, long-acting recombinant Factor VIIa for the treatment of hemophilia patients. It also utilizes CTP technology to extend its biologic half-life without the use of polymers, encapsulation techniques, or nanoparticles, all of which have been reported to cause local injection site reactions or other challenges. Currently, Factor VIIa therapy is available only as an intravenous formulation which, due to Factor VIIa's short half-life, usually requires multiple injections to treat a bleeding episode. Pre-clinical studies of intravenous and subcutaneous injections of Factor VII-CTP in hemophilia animal models demonstrated its prolonged duration of action and significantly increased survival. Successful subcutaneous injection in human trials will be important to permit patients to be

treated prophylactically rather than in response to the bleeding events that cause permanent damage to certain tissues and organs. In February 2015, our IND application was approved by the FDA to conduct a Phase 2a study of Factor VII-CTP for the intravenous treatment of bleeding episodes in hemophilia A or B patients with inhibitors to Factor VIII or Factor IX. We expect to begin dosing patients as soon as IRB approvals and external laboratory service contracts are in place. Our Factor VII-CTP has been granted orphan status in the U.S. and Europe. This market, now dominated by Novo Nordisk's NovoSeven® product, which requires frequent injections, enjoys a market of approximately $1.2 to 1.6 billion a year.

Oyxntomodulin, a naturally occurring appetite suppressor, is a peptide hormone secreted by the intestine following food intake. It then induces a feeling of fullness when it reaches the satiety center in the brain. Oxyntomodulin also activates the glucagon-like peptide-1 receptor (GLP1R) and glucagon receptor (GCGR) in the liver. These two effects have been shown to decrease food intake and body weight and control blood glucose levels in overweight human volunteers.

The clinical utility of oxyntomodulin has been limited because of its short biological half-life. We have been developing a long-acting oxyntomdulin, which consists of the **natural** oxyntomodulin molecule linked to a proprietary hydrolysable linker and a commonly used substance to prolong biological half-life. Administration of this proprietary product results in the slow release of the **natural** oxyntomodulin which then targets the satiety center in the brain. Our preclinical studies have shown that a single weekly injection significantly inhibited food intake, reduced body weight, and reduced cholesterol and glucose levels in obese, diabetic animal models. We expect to initiate a Phase 1 trial of our proprietary compound in early 2016.

Early-Stage Products

AntagoNATS Orphan Drug Project. Our gene up-regulating technology utilizing proprietary designed oligonucleotides (AntagoNATS), has been shown in animal models to enhance the expression of mRNAs responsible for the transcription of certain specific genes into functional proteins. The most advanced program is CUR-1916 which has been designed to increase the expression of endogenous SCN1A (sodium channel protein) for the treatment of Dravet Syndrome. Over 75% of Dravet patients are reported to have mutations of SCN1A. Dravet Syndrome is an orphan disease for which, other than symptomatic management with multiple anti-epileptic drugs, there are no viable treatments for the daily uncontrollable seizures in patients as young as 3-6 months old. We have created a Dravet mouse model that carries a human mutation of the SCN1A sequence. Dravet mice have symptoms that mirror Dravet patients; high frequency of severe seizures, low threshold of body temperature elevation to seizure induction, and early death. We have successfully demonstrated that intrathecal injection of CUR-1916 significantly reduced seizure frequency and severity and raised the body temperature threshold to heat induced seizures in Dravet mice. Once the required toxicity studies in animals are completed, we will submit an IND application and request for orphan designation to the FDA.

NK-1 Inhibitor for Pruritus. One of the assets we acquired from Schering (now Merck), as part of its divestiture requirements, in addition to Rolapitant, which was subsequently licensed to Tesaro, was another NK-1 inhibitor molecule which had completed human safety, Phase 1 and Phase 2 studies. While Schering's intention was to develop this drug for other indications, new data about this specific class of compounds indicate that it is very likely to

be effective to treat pruritus (itching) due to various causes. Our compound is long acting with possible once weekly oral dosing and other advantages such as low potential for drug-drug interactions compared to other drugs in its category. We believe that this project could result in a product for which there is a great need, there being no good drug for physicians to use presently. We will be discussing this project more as plans develop.

JNK Inhibitor. We have been supporting various projects at The Scripps Research Institute for several years and one, a JNK inhibitor, has been shown, after studying hundreds of compounds, to be a potent inhibitor of programmed cell death (apoptosis). Dr. Philip LoGrasso, a professor at Scripps, in collaboration with researchers at the Department of Otolaryngology at the University of Miami School of Medicine, found, in a mouse model of hearing loss, that the compound protected against hair cell death from electrode insertion trauma. We plan to continue our work on this potentially important drug project for hearing loss.

New Class of Antibiotics. We believe another project at the Scripps Research Institute supported by us is now bearing fruit. Dennis Wolan, another professor at Scripps, has discovered a chemical pathway unique to all bacteria and mycoplasmae which, because of technical difficulties, has not been exploited previously. Dr. Wolan has now purified various enzymes of the pathway and used them to screen chemical libraries to find inhibitors; several have now been identified. More screening is planned to be followed by medicinal chemistry work for optimization of antibacterial activity.

Adjuvant for Cancer Therapy. We have developed significant proof of concept data in animals for a small glycolipid molecule which binds to the CD1d receptor on dendritic cells to activate invariant natural killer T cells (iNKT) and also induces secretion of T helper cell cytokines. This compound, in combination with chemotherapy agents, has been shown to synergistically increase the survival of lung, breast and liver tumor burdened mice. Our proprietary formulation not only enhances the delivery of this compound, but also increases in vivo potency. Animal studies are on-going with a clinical development program expected to follow.

New Asthma, COPD Drugs. For several years, we have been working on a group of sulfated polysaccharides for the treatment of asthma and chronic obstructive pulmonary disease (COPD). We now have molecules which, in the highly relevant sheep model, appear to be effective given orally or by inhalation. This represents a new class of compounds working with a new and unique mechanism of action for the treatment of asthma and COPD. We plan to initiate pre-clinical toxicology studies shortly and then begin clinical trials.

Operating Subsidiaries

EirGen. Acquired earlier this year, EirGen, located in Waterford, Ireland, will play an important role in the development, manufacturing, and approval of a wide variety of drugs in a variety of dosage forms with an emphasis on high potency products. EirGen currently develops and manufactures products for pharmaceutical companies around the world. Managed by former IVAX employees, EirGen continues to show good revenue and profit growth.

FineTech. Located in northern Israel, FineTech consists of a group of world-class synthetic organic chemists led by Dr. Arie Gutman. They have built an active pharmaceutical

ingredient (API) business specializing in high potency, low volume, high value drugs, complementing the activities of EirGen. They continue to show record revenue and profit growth.

LATAM and Spain. OPKO Spain continues to make progress in spite of a weak local economy. **OPKO Chile** shows growth of sales and profits but these are tempered by currency changes. **OPKO Mexico** is in the process of changing from a model of generic sales, mainly by government tender, to a strategy of branded product sales. This transition is presently limiting profitability.

Financial Update

Our business is going through a significant transformation and as a result, our financial results are evolving into an operating company with substantial revenues. Bio-Reference had fiscal 2014 revenue of $832 million and operating profit of $83.4 million. In looking to their financial performance for 2015, Bio-Reference had revenue of $432 million the first six months of fiscal 2015, an almost 13% increase from the comparable period of 2014. Bio-Reference's operating profit of $30.9 million for the first six months of 2015 represents a 25% increase over their 2014 operating profit. Given Bio-Reference's historical seasonal trends, we expect the second half of 2015 to show continuing growth in earnings and profits. We further expect that the contributions of Bio-Reference, FineTech and EirGen, will create positive EBITDA (earnings before interest, income taxes, depreciation and amortization) for OPKO. Finally, we expect to continue to invest in research and development activities which, if successful, will result in ongoing improvement of our financial performance.

We appreciate your support and confidence and we look forward to sharing further news of our progress.

Sincerely,

Phillip Frost, M.D.

Chairman and Chief Executive Officer

About OPKO Health, Inc.

We are a multi-national biopharmaceutical and diagnostics company that seeks to establish industry-leading positions in large and rapidly growing medical markets by leveraging our discovery, development and commercialization expertise and our novel and proprietary technologies.

SAFE HARBOR STATEMENT

This press release contains "forward-looking statements," as that term is defined under the Private Securities Litigation Reform Act of 1995 (PSLRA), which statements may be identified by words such as "expects," "plans," "projects," "will," "may," "anticipates," "believes," "should," "intends," "estimates," and other words of similar meaning, including statements regarding the market acceptance and growth of our products, expected benefits of the merger with Bio-Reference, the 4Kscore test being the new standard for identifying aggressive prostate cancer, expectations about expected savings from reductions of biopsies and annual healthcare savings to the U.S. healthcare system, that men determined to be at

low risk for aggressive cancer by the 4Kscore have a 98-99% chance to be metastasis free after 20 years, the continued development and approval of diagnostic panels utilizing the Claros 1 platform, the expected timing for clinical trials, approval and launch of our products in development, the belief that Rayaldee will be warmly welcomed by healthcare professionals who care for CKD patients, expected timing of the approval of the NDA for Rolapitant by the FDA and expected payments and sales of Rolapitant, expected payments upon the commercialization of hGH-CTP, expected timing of our phase 3 study of hGH-CTP, the ability to begin dosing patients with Factor VIIa-CTP, the expected timing of a Phase 1 trial of the long-acting oyxntomodulin that we are developing, the belief that the NK-1 inhibitor for pruritus will result in a product for which there is a great need, plans to continue work on a JNK inhibitor for hearing loss, plans to do more screening and medicinal chemistry work for optimization of antibacterial activity, plans for clinical development of adjuvant for cancer therapy, plans for initiating pre-clinical toxicology studies and clinical trials for new asthma and COPD drugs, expected growth in earnings and profits for Bio-Reference, expected contributions of Bio-Reference, FineTech and EirGen to our EBITDA, expected benefits of our research and development activities to our financial performance, as well as other non-historical statements about our expectations, beliefs or intentions regarding our business, technologies and products, financial condition, strategies or prospects.

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 in our filings with the Securities and Exchange Commission, as well as the ability to successfully integrate the acquired businesses; the risk that any potential synergies from the acquisitions may not be fully realized or may take longer to realize than expected; new information arising out of clinical trial results; and the risk that the safety and/or efficacy results of existing clinical trials will not support continued clinical development; as well as risks inherent in funding, developing and obtaining regulatory approvals of new, commercially-viable and competitive products and treatments. In addition, forward-looking statements may also be adversely affected by general market factors, competitive product development, product availability, federal and state regulations and legislation, the regulatory process for new products and indications, manufacturing issues that may arise, patent positions and litigation, among other factors. The forward-looking statements contained in this press release speak only as of the date the statements were made, and 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 the PSLRA.

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