PROVECTUS BIOPHARMACEUTICALS, INC.
Form 10-K
March 13, 2014
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UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 10-K

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

For the fiscal year ended December 31, 2013

¨ **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 000-09410

PROVECTUS BIOPHARMACEUTICALS, INC.

(Exact name of registrant as specified in its charter)

Delaware	**90-0031917**
(State or other jurisdiction of incorporation or organization)	**(I.R.S. Employer Identification No.)**

7327 Oak Ridge Highway, Suite A, Knoxville, Tennessee 37931

(Address of principal executive offices) (Zip Code)

866-594-5999

(Registrant s telephone number, including area code)

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

None

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

Common Stock, par value $.001 per share

(Title of class)

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

Indicate by check mark whether the registrant has submitted electronically and posted on its corporate Web site, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T (§ 232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit and post such files). x Yes ¨ No

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K (§ 229.405 of this chapter) 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. x

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

Large accelerated filer	¨	Accelerated filer	x
Non-accelerated filer	¨ (Do not check if a smaller reporting company)	Smaller reporting company	¨

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Act). ¨ Yes x 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 June 28, 2013 was $77,150,241 (computed on the basis of $0.65 per share).

The number of shares outstanding of the registrant s common stock, par value $.001 per share, as of March 7, 2014 was 172,450,253.

DOCUMENTS INCORPORATED BY REFERENCE

The information required by Part III is incorporated by reference to portions of the definitive proxy statement to be filed within 120 days after December 31, 2013, pursuant to Regulation 14A under the Securities Exchange Act of 1934 in connection with the annual meeting of stockholders to be held on June 16, 2014.

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CAUTIONARY NOTE REGARDING FORWARD LOOKING STATEMENTS

This Annual Report on Form 10-K contains forward-looking statements regarding, among other things, our anticipated financial and operating results. Forward-looking statements reflect our management s current assumptions, beliefs, and expectations. Words such as anticipate, believe, estimate, expect, intend, plan, and similar expressi intended to identify forward-looking statements. While we believe that the expectations reflected in our forward-looking statements are reasonable, we can give no assurance that such expectations will prove correct. Forward-looking statements are subject to risks and uncertainties that could cause our actual results to differ materially from the future results, performance, or achievements expressed in or implied by any forward-looking statement we make. Some of the relevant risks and uncertainties that could cause our actual performance to differ materially from the forward-looking statements contained in this report are discussed below under the heading Risk Factors and elsewhere in this Annual Report on Form 10-K. We caution investors that these discussions of important risks and uncertainties are not exclusive, and our business may be subject to other risks and uncertainties which are not detailed there. Investors are cautioned not to place undue reliance on our forward-looking statements. We make forward-looking statements as of the date on which this Annual Report on Form 10-K is filed with the SEC, and we assume no obligation to update the forward-looking statements after the date hereof whether as a result of new information or events, changed circumstances, or otherwise, except as required by law.

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PART I

ITEM 1. BUSINESS.

General

Provectus Biopharmaceuticals, Inc., a Delaware corporation formed in 2002, together with its six wholly owned subsidiaries and one majority owned subsidiary managed on a consolidated basis, referred to herein as we, us, and our, is a development-stage biopharmaceutical company that is primarily engaged in developing ethical pharmaceuticals for oncology and dermatology indications. Our goal is to develop alternative treatments that are safer, more effective, less invasive and more economical than conventional therapies. We develop and intend to license or market and sell our two prescription drug candidates, PV-10 and PH-10. We also hold patents and other intellectual property which we believe may be used in over-the-counter products, which we refer to as OTC products, and various other non-core technologies. We have transferred all our intellectual property related to OTC products and non-core technologies to our subsidiaries and have designated such subsidiaries as non-core to our primary business of developing our oncology and dermatology prescription drug candidates.

Prescription Drugs

We focus on developing our prescription drug candidates PV-10 and PH-10. We are developing PV-10 for treatment of several life threatening cancers including metastatic melanoma, liver cancer, and breast cancer. We are developing PH-10 to provide minimally invasive treatment of chronic severe skin afflictions such as psoriasis and atopic dermatitis, a type of eczema. We believe that our prescription drug candidates will be safer and more specific than currently existing products. All of our prescription drug candidates are in either the pre-clinical or clinical trial stage.

The table below sets forth our two drug candidates and our progress in developing those candidates for these indications:

PV-10	Prepare for Breakthrough Therapy Designation request 2013 into 2014
Melanoma	Finalized Phase 2 data October 2012 and September 2013
	End-of-Phase 2 FDA meeting April 2010, March 2011, and October 2011
	Phase 2 study completed May 2010
	Phase 2 treatments completed September 2009
	Phase 2 recruitment completed May 2009
	Phase 2 study initiated September 2007
	Orphan drug status January 2007
PH-10	

Psoriasis	Toxicity study research and development for advanced studies 2012, 2013 and into 2014
	Phase 2c randomized study final data collection February 2012
	Phase 2c randomized study initiated December 2010 and completed August 2011
	Phase 2 study completed April 2010
	Phase 2 recruitment completed October 2009
	Replacement Phase 2 initiated July 2009 due to dose regimen change
	Phase 2 study initiated November 2007
PH-10	Toxicity study research and development for advanced studies 2012, 2013 and into 2014
Atopic Dermatitis	
	Phase 2 study completed September 2009
	Phase 2 recruitment completed June 2009
	Phase 2 study initiated June 2008
PV-10	Assessing further development 2013 and 2014 in conjunction with Moffitt Cancer Center research
Breast Cancer	
	Phase 1 study completed July 2008
	Phase 1 initial cohort treatment completed April 2006
	Phase 1 study initiated October 2005
PV-10	Phase 1 protocol expansion September 2012 through 2013 into 2014
Liver Metastasis	Orphan drug status April 2011
	Phase 1 patient accrual and treatment completed January 2011 Phase 1 study initiated October 2009

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PV-10	Moffitt Cancer Center initiates Phase 1 feasibility study to detect immune cell infiltration into melanomas treated by PV-10 in January 2013 into 2014

Mechanism of Action

In addition to clinical trials, patients enrolled in the compassionate use or expanded access program for PV-10 are also receiving PV-10 treatments.

Oncology (PV-10)

We believe our prescription drug candidate PV-10 may afford competitive advantage compared to currently available options for the treatment of certain types of cancer. We are developing PV-10, a sterile injectable form of rose bengal disodium (Rose Bengal), for direct injection into tumors. It is an immuno-chemoablative agent that when injected intralesionally is tantamount to an in situ vaccination following acute and durable necrosis of diseased tissue. Because PV-10 is retained in diseased or damaged tissue but quickly dissipates from healthy tissue, we believe we can develop therapies that confine treatment to cancerous tissue and reduce collateral impact on healthy tissue. We have conducted Phase 1 and Phase 2 studies of PV-10 for the treatment of recurrent and metastatic melanoma, and Phase 1 studies of PV-10 for the treatment of liver and breast cancers, each of which are described in more detail below.

Recurrent Melanoma

A Type C meeting was held with the FDA s Division of Oncology Products 2 on December 16, 2013. The purpose of the meeting was to determine which of the available paths that our novel investigational oncology drug PV-10 will take in pursuit of initial FDA approval and commercialization. PV-10, a 10% solution of rose bengal disodium, is designed to selectively target and destroy cancer cells without harming surrounding healthy tissue, while inducing a secondary tumor-specific immune response. As a result of this meeting, we will submit data from its Phase 2 study in a formal breakthrough therapy designation (BTD) request, and should receive a decision within 60 days of receipt of that request.

With the passage of the Food and Drug Administration Safety and Innovation Act (FDASIA) in July 2012, the Food and Drug Administration (FDA) was given powerful expedited tools to speed patient access to innovative medicines for serious or life-threatening conditions. FDASIA initiatives such as breakthrough therapy designation are designed to accelerate approval for new drugs that show preliminary clinical evidence of a large treatment effect. A key feature of BTD authorizes the FDA to take steps to ensure that the design of the clinical trials are as efficient as practicable, when scientifically appropriate, such as by minimizing the number of patients exposed to a potentially less efficacious treatment. Requests for BTD are reviewed and granted or rejected within 60 days of receipt. As we have previously reported, based on rapid tumor destruction in a positive Phase 2 trial in melanoma patients receiving PV-10 (protocol PV-10-MM-02), we sought input from the FDA regarding our current development plan. FDA guidance encourages sponsors to seek such advice prior to formal request for designation.

We believe that this meeting with the FDA is another significant step forward in streamlining the pathway to initial U.S. approval of PV-10 as the first local agent for recurrent locoregionally advanced melanoma. These patients suffer with troublesome, disfiguring disease that can persist for many years before presenting at distant sites. Our meeting with the FDA established the parameters for submission of a BTD request tailored to addressing the pressing needs of these patients.

The meeting and official meeting minutes provided valuable guidance on a number of issues surrounding the approval path of PV-10:

The FDA agreed with us that treatment of cutaneous and subcutaneous tumors in patients with locally advanced cutaneous melanoma (i.e., recurrent, in-transit or satellite melanoma that has not yet spread from the skin to distant sites) could provide clinical benefit to such patients, particularly if the measured objective responses in patients disease correlated to a demonstrated treatment effect on one or more symptoms of their disease (e.g., pain, infection or significant bleeding).

The FDA agreed to work with us to quantify symptom control in this patient population.

In reference to discussions on the potential for breakthrough therapy designation, FDA advised Provectus to provide objective response rates with adequate information to evaluate the symptomatic treatment effects (e.g. pain, infection, bleeding) in patients presenting with locally advanced cutaneous melanoma who received PV-10 to all lesions.

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The Phase 2 study of PV-10 showed:

- Among all 80 intent-to-treat melanoma patients, 26% achieved a complete response and another 25% achieved a partial response (shrinkage by at least 30%) of their injected study tumors (51% objective response rate, confidence interval 40-63%).

- In the subgroup of melanoma patients that received PV-10 injection into all known disease (28 of the 80 ITT patients), 50% achieved a complete response (71% ORR, CI 51-87%).

- In the subgroup of melanoma patients with locally advanced cutaneous melanoma that received PV-10 injection into all known disease or only had 1 or 2 designated bystander tumors untreated (54 of the 80 ITT patients), a complete response was achieved in 232 of 363 injected tumors (64% of lesions) with the vast majority of these tumors requiring only 1 or 2 injections.

These data show that if a tumor is accessible to PV-10 injection, the drug is likely to destroy that tumor. If approved, PV-10 would be the first tissue-sparing local therapy for recurrent melanoma.

We have continued to observe that the FDA may yet recommend and it may be in our best interest to undertake a small, short bridging study in patients where all tumor burden can be injected. This would allow more frequent dosing than was permitted in the Phase 2 study, presumably akin to the dosing schedule currently used to treat nearly 100 patients under our expanded access protocol, and allow symptomatic endpoints to be prospectively correlated with objective response criteria. We have $18 million in cash reserves and would not require additional capital or the resources of a partner to conduct such a study. If such a study is conducted, it also fits with needs for an international study supportive of licensure in Australia, Europe, China and India.

Non-specific local treatments that temporarily reduce tumor burden, such as surgery and radiation, are the most commonly used cancer therapies today. Furthermore, we believe our clinical and immunologic mechanism data show that it may be possible to delay or prevent melanoma metastasis to distant sites. Measurement of tumor shrinkage via objective response criteria has been considered direct clinical benefit in drug approvals for other skin cancers, and we believe a similar case can be made for PV-10 in locally advanced cutaneous melanoma. As advised by the FDA, we will submit data from the 28 patients in our Phase 2 study who had all existing disease treated in a formal BTD request, and should receive a decision within 60 days of receipt of that request.

While the rapid ablative effect immediately evident in patients treated with PV-10 highlights our path to initial approval, the bystander effect continues to be of scientific interest and studies to quantify systemic tumor-specific immune response in cancer patients are ongoing. This emerging understanding of the secondary effect of tumor ablation with PV-10 is an important foundation for future studies to assess the long-term impact of PV-10 on distant metastasis and possible combination strategies for use of PV-10 in the treatment of cancer patients with more advanced disease.

Ongoing immunologic mechanism of action studies at the Moffitt Cancer Center (Moffitt) have been conducted in 2011, 2012, 2013 and thus far in 2014 to characterize the systemic benefit of PV-10. A feasibility study to detect immune cell infiltration into melanomas treated by PV-10 was commenced in January 2013.

Initial data was presented at the 2012 Society of Surgical Oncology Annual Meeting, confirms that PV-10 immuno-chemoablation of melanoma lesions leads to a systemic response and the induction of systemic anti-tumor immunity. We are assessing whether emerging results from these ongoing studies can be used to support accelerated approval in the U.S. Additionally, data on PV-10 was presented by Moffitt in a poster presentation at the American Association for Cancer Research 2013 Annual Meeting in Washington, DC. The PV-10 combination therapy poster, based upon an abstract entitled Combination of PV-10 immuno-chemoablation and systemic anti-CTLA-4 antibody therapy in murine models of melanoma, authored by Eric Wachter, Savannah Blair, Jamie Singer and Craig Dees, was presented as well.

In August, 2013, Moffitt stated that a single injection (PV-10) may revolutionize melanoma treatment. In their initial study, researchers injected a single dose of PV-10 into mice with melanoma. The result was a significant reduction in the skin cancer lesions, as well as a sizable reduction in melanoma tumors that had spread to the lungs. The researchers said the dye solution appeared to produce a robust anti-tumor immune response and may be safer than existing immunological agents.

Moffitt is currently in the middle of their first human clinical trial of PV-10 for advanced melanoma patients. In addition to monitoring the response of injected melanoma tumors, Moffitt is also measuring the boost in the anti-tumor immune cells of patients after injection. The initial study appears in PLOS ONE, an open-access, peer-reviewed online journal.

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On March 6, 2014, it was reported that PV-10 Immune Mechanism Data to Be Presented at the American Association for Cancer Research Annual Meeting by Moffitt Cancer Center via a Poster Presentation. The poster, based upon abstract #630, entitled Induction of anti-melanoma immunity after intralesional ablative therapy, authored by Hao Liu, Krithika Kodumudi, Amy Weber, Amod A. Sarnaik and Shari Pilon-Thomas, will be presented on Sunday, April 6, 2014.

We also report ongoing progress with our Compassionate Use Program for PV-10 for non-visceral cancers. With nearly 100 patients enrolled in six publicized centers across the U.S. and Australia, the protocol enables subjects to undergo more frequent and extensive treatments of PV-10 over a longer period of time than was allowed under the protocol used for the Phase 2 trials. Its dosage is expected to serve as the blueprint for the treatment of recurrent melanoma in the potential short bridging study and upon potential approval.

We are continuing to assess whether we should conduct any additional work by ourselves, or when to partner with a larger company to further co-develop PV-10, as well as potential paths to accelerated and expedited approval in the U.S. and abroad, including in China and India.

Liver Cancer

According to Global Cancer Facts & Figures, 2nd Edition, liver cancer is the fifth leading cause of deaths related to cancer in the world in men and seventh in women. Approximately 750,000 people are newly diagnosed annually with primary liver cancer, also known as Hepatocellular carcinoma (HCC), with China alone accounting for about 55% of the cases diagnosed each year. The world market for liver cancer drugs is projected to exceed $2.0 billion by 2015 and does not include the full impact of the China market potential.

Early detection is difficult and as a result, most cases reach an advanced metastatic stage and are unresectable. If the cancer cannot be completely removed, the disease is usually deadly within three to six months. Malignant lesions in the liver arising from HCC or metastases from a wide range of cancers represent an ongoing treatment challenge for oncologists. HCC is one of the most common malignancies worldwide, and its incidence is rapidly increasing in the United States. The liver is a common site of metastases from solid tumors, particularly those arising in the gastrointestinal tract. Other tumors, such as lung and breast cancer and melanoma, also readily spread to the liver.

In 2009, we began a Phase 1 study of PV-10 to assess the safety, tolerability and pharmacokinetics of single intralesional injections of PV-10 with subjects with either recurrent hepatocellular carcinoma or cancer metastatic to the liver. In January 2011, we completed patient accrual of all subjects in the Phase 1 study. The primary outcome measure was safety, including systemic and locoregional adverse events. The secondary outcome measures were (i) lesion distribution and retention of PV-10 following injection, (ii) ORR of target and measurable bystander lesions (if present) by modified RECIST, (iii) changes in markers of hepatic function, including ALP, ALT, AST, total bilirubin and GGT, and (iv) pharmacokinetics of PV-10 in the bloodstream following intralesional injection.

Final results for PV-10 as a treatment for liver cancer are very encouraging as they show the treatment was generally well-tolerated, with substantial evidence of efficacy. We believe PV-10 s ability to selectively target and destroy cancer cells without harming surrounding healthy tissue make it a potentially attractive therapy for cancers of the liver, which can be very serious and difficult to treat if they cannot be fully removed through surgery. Based upon the initial results of our PV-10 Phase 1 trial for liver cancer, and the growing confidence we have in PV-10 as a viable treatment for non-resectable liver cancer, we are currently designing a Phase 2 study with the potential for accelerated approval.

In April 2011, we received orphan drug designation by the FDA for Rose Bengal, the active ingredient in PV-10, for the treatment of HCC, the most common form of primary liver cancer.

In September 2012, we commenced an expansion of the Phase 1 study, which we continued in 2013 and thus far in 2014. Drug-drug metabolic interaction nonclinical studies of PV-10 and sorafenib provided the data to support additional work within the regulatory framework for this important indication. We plan to commence a potentially pivotal study in 2014. This study is potentially pivotal since it would be powered to enable accelerated approval under the auspices of a proposed Breakthrough Therapy Designation request for PV-10 to treat primary liver cancer.

We collaborated with XenoTech, a preclinical CRO and pioneer in collaborative research surrounding in vitro drug metabolism and pharmacokinetics (DMPK) services, in writing an article describing a study to determine the potential of rose bengal disodium to cause drug-drug interactions which has been published by Xenobiotica, a peer-reviewed scientific journal that publishes comprehensive research papers on pharmacokinetics (the study of distribution, metabolism, disposition and excretion of drugs). The published research indicated that the risk of PV-10 causing clinically relevant drug-drug interactions is likely minimal. PV-10, a 10% solution of rose bengal that is currently under clinical investigation as a novel cancer therapeutic, is designed to selectively target and destroy cancer cells without harming surrounding healthy tissue, minimizing the potential for systemic side effects.

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The study was undertaken prior to initiation of the now ongoing testing of PV-10 plus sorafenib (cohort 2) in a clinical trial of PV-10 intralesional injection in hepatocellular carcinoma patients taking a stable dose of sorafenib. Sorafenib is a competitive inhibitor of cytochrome P450 (CYP) drug metabolism enzymes and is reliant on the UDP-glucuronosyltransferase (UGT) pathway for efficient clearance. CYP and UGT enzymes help to biotransform small lipophilic drugs like sorafenib into water-soluble excretable metabolites.

Provectus researchers collaborated with XenoTech s experts to design the appropriate in vitro experiments necessary to assess the risk for potential liability when rose bengal is co-administered with other drugs in humans. Rose bengal, known for inducing singlet oxygen on exposure to light, can cause erroneous results in conventional in vitro test systems. These assay artifacts were shown to be test system dependent in DMPK studies. XenoTech scientists successfully tailored experiments to ascertain CYP and UGT inhibition potential in more appropriate model systems.

Breast Cancer

In 2005, we began a Phase 1 study of PV-10 to assess the safety and tolerability of injections of PV-10 into recurrent breast carcinoma. We completed the Phase 1 study in 2008. The primary outcome measure was systemic and locoregional adverse experience. The secondary outcome measures were (i) histopathologic response of PV-10 injected lesions and (ii) wound healing of PV-10 injected lesions.

We are very pleased with the results of this Phase 1 clinical trial, a classic ascending dose study. Its goals were to determine the safety of the treatment and the appropriate dosage. We have also wanted to show that PV-10 has multi-indication potential. We continued to demonstrate this objective in 2011, 2012, 2013, and expect to do so in 2014. We are now in a position for a Phase 2 study in recurrent breast carcinoma with our lead oncology drug product candidate PV-10. We are evaluating potential for further development of PV-10 to treat recurrent breast cancer based on the published data provided by Moffitt as well as interest to address this important indication.

Other Indications

The compassionate use program for PV-10 is only available for cancer indications that do not involve treatment of visceral organs and are not subject to enrollment in ongoing clinical trials. These indications include certain breast cancers, basal cell carcinoma, squamous cell carcinoma, certain head and neck cancers and melanoma. Compassionate use programs provide patients with access to experimental therapeutics prior to FDA approval.

The protocol for the compassionate use program enables subjects to undergo more frequent and extensive treatments of PV-10 over a longer period of time than was allowed under the protocol used for the Phase 2 trial of PV-10. Based on the success of the compassionate use program, its dose regimen is expected to serve as the blueprint for additional PV-10 clinical studies. The majority of patients enrolled in the program have been treated for melanoma, with other patients for other indications such as recurrent squamous cell carcinoma and scalp sarcoma.

Additionally, we are considering a clinical study of PV-10 for pancreatic cancer as well as other solid tumor indications.

Dermatology (PH-10)

Our prescription drug candidate PH-10 is an aqueous hydrogel formulation of Rose Bengal for topical administration to the skin. It is a novel nonsteroidal anti-inflammatory agent that interacts with ambient and other light sources. We are developing PH-10 for the treatment of cutaneous skin disorders, specifically psoriasis and atopic dermatitis, and we believe that PH-10 may be successful in treating other skin diseases. We believe that PH-10 offers a superior

treatment for psoriasis and atopic dermatitis because it selectively treats diseased tissue with negligible potential for side effects in healthy tissue.

We have been actively discussing licensing transactions with a number of potential out licensing partners for PH-10. We believe that our Phase 2c trial of PH-10 for psoriasis will further solidify the commercial viability of PH-10 in these discussions. In August 2011, we completed follow-up of all Phase 2c patients and communicated data of the study to both prospective partners as well as the public market in early 2012.

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Psoriasis

Psoriasis is a common chronic disorder of the skin characterized by dry scaling patches, called plaques, for which current treatments are few and those that are available have potentially serious side effects. There is no known cure for the disease at this time. According to the National Institutes of Health, as many as 7.5 million Americans, or approximately 2.2 percent of the U.S. population, have psoriasis. The National Psoriasis Foundation reports that approximately 125 million people worldwide, 2 to 3 percent of the total population, have psoriasis. It also reports that total direct and indirect health care costs of psoriasis for patients exceed $11 billion annually.

According to the National Psoriasis Foundation, the majority of psoriasis sufferers, those with mild to moderate cases, are treated with topical steroids that can have unpleasant side effects. None of the other treatments for moderate cases of psoriasis have proven completely effective. The 25-30% of psoriasis patients who suffer from more severe cases generally are treated with more intensive drug therapies or PUVA, a light-based therapy that combines the drug Psoralen with exposure to ultraviolet A light. While PUVA is one of the more effective treatments, it increases a patient s risk of skin cancer.

Our Phase 1 study for PH-10 was initiated in April 2001 to evaluate the safety of three different doses of PH-10 in separate patient segment groups. Subjects in the study each received a single dose of PH-10 followed by administration of green light on psoriatic plaques. Subjects were examined post-treatment, with a final follow-up examination at 90 days.

Our Phase 2 study of PH-10 for treatment of psoriasis was initiated in 2009 and completed in April 2010. There were 30 subjects treated in the completed Phase 2 study, and an additional six subjects were treated in an earlier study that was terminated in favor of an increased dosing frequency. Consistent with the preliminary data that we announced in December 2009, 70% of the 30 subjects enrolled in the Phase 2 clinical trial of PH-10 for psoriasis demonstrated improvement in their Psoriasis Severity Index (PSI) scores at the end of four weeks of daily treatment with PH-10. In addition, 86% of subjects reported no or only mild pruritus (itching) by week four of the trial, and no significant safety issues were noted. At the four week interval substantial improvement was observed across all standard disease assessment scores.

During 2010, we initiated a Phase 2c clinical trial of PH-10 for psoriasis. This multicenter, randomized controlled Phase 2c study enrolled 99 subjects at four different sites, which began in December 2010. The subjects were randomized sequentially by center to one of four treatment cohorts, and assessed efficacy and safety of topical PH-10 applied once daily to areas of mild to moderate plaque psoriasis. The primary efficacy endpoint was treatment success, a static endpoint assessed at day 29 after initial PH-10 treatment and defined as 0 or 1 on all Psoriasis Severity Index (PSI) components and 0 or 1 on the Plaque Response scale. The primary safety endpoint was incidence of adverse experiences, including pain and dermatologic/skin toxicity (incidence, severity, frequency, duration and causality). The secondary outcome measures were (i) Psoriasis Severity Index (PSI) score changes at each visit from day 1 pre-treatment, (ii) Plaque Response score changes at each visit from day 1 pre-treatment, and (iii) Pruritus Self-Assessment score changes at each visit from day 1 pre-treatment.

The Phase 2c trial was conducted at four sites in the U.S. including the Mount Sinai School of Medicine in New York City, Wake Research Associates in Raleigh, NC, Dermatology Specialists in Oceanside, CA and International Dermatology Research in Miami, FL. With over 90 subjects, this trial is the largest dermatological trial that we have conducted to date.

The results of this study helped define the parameters necessary for the design of a pivotal Phase 3 trial, and it was an important milestone on the regulatory pathway leading towards commercialization. In addition, we ve held discussions

with a number of potential out licensing partners, and we believe this Phase 2c trial has further solidified the commercial viability of PH-10 in these discussions. We have also continued important toxicity study research and development in 2012, 2013 and thus far in 2014 to prepare for a successful Phase 3 study and to support a successful New Drug Approval filing.

Atopic Dermatitis

Atopic Dermatitis, the most severe and common type of eczema, is a long-term skin disease that causes dry and itchy skin, rashes on the face, inside the elbows, behind the knees, and on the hands and feet. Scratching of the afflicted skin can cause redness, swelling, cracking, weeping clear fluid, crusting, thick skin, and scaling. According to the National Eczema Association, physicians estimate that 65% of eczema patients are diagnosed in the first year of life and 90% of patients experience it before age five. Often the symptoms fade during childhood, though most will have atopic dermatitis for life. The National Eczema Association estimates that atopic dermatitis affects over 30 million Americans.

In 2008, we initiated a Phase 2 study of PH-10 for the treatment of atopic dermatitis. This Phase 2 study assessed whether topical PH-10 applied once daily to mild, moderate or severe atopic dermatitis may ameliorate inflammation of the skin when activated by ambient light. The subjects applied PH-10 daily for 28 days to skin areas affected by atopic dermatitis. The subjects were assessed weekly during the treatment period and for four weeks following the treatment period. The primary outcome measures were (i) treatment success, defined as a score of 0 to 1 at day 28, the end of the study treatment period, by the Investigator s Global Assessment (IGA) scoring system for atopic dermatitis status, and (ii) adverse experience, including pain and dermatologic/skin toxicity (incidence, severity, frequency, duration and causality) during the eight weeks following treatment.

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Data from the subjects indicated that a substantial majority of subjects had improvement in the Eczema Area Severity Index (EASI) during four weeks of treatment. The treatments were generally well tolerated with no significant safety issues identified. At the four week interval substantial improvement was observed across all standard disease assessment scores. We have also continued important toxicity study research and development in 2012, 2013 and thus far in 2014 to prepare for continued development in this important indication and to support a successful New Drug Approval filing.

Other Indications

We have investigated the use of PH-10 for treatment of actinic keratosis (also called solar keratosis or senile keratosis), which is the most common pre-cancerous skin lesion among fair-skinned people and is estimated to occur in over 50% of elderly fair-skinned persons living in sunny climates. We have previously conducted a Phase I clinical trial of PH-10 for actinic keratosis to examine the safety profile of a single treatment using topical PH-10 with green light photoactivation. No significant safety concerns were identified in the study. We have decided to prioritize further clinical development of PH-10 for treatment of psoriasis and atopic dermatitis rather than actinic keratosis at this time since the market is much larger for psoriasis and atopic dermatitis.

We have also conducted pre-clinical studies of PH-10 for use in treating severe acne vulgaris. Moderate to severe forms of the disease have proven responsive to several photodynamic regimens, and we anticipate that PH-10 can be used as an advanced treatment for this disease. Our pre-clinical studies show that the active ingredient in PH-10 readily kills bacteria associated with acne. This finding, coupled with our clinical experience in psoriasis, atopic dermatitis, and actinic keratosis, suggests that therapy with PH-10 will exhibit no significant side effects and will afford improved performance relative to other therapeutic alternatives. If correct, this would be a major advance over currently available products for severe acne.

The active ingredient in PH-10 is photoactive in that it reacts to light of certain wavelengths thereby potentially increasing its therapeutic effects. We believe that photodynamic treatment regimens can deliver a higher therapeutic effect at lower dosages of active ingredient, thus minimizing potential side effects including damage to nearby healthy tissues. PH-10 is especially responsive to green light, which is strongly absorbed by the skin and thus only penetrates the body to a depth of about three to five millimeters. For this reason, in the past we have investigated PH-10 combined with green-light activation, for topical use in surface applications where serious damage could result if medicinal effects were to occur in deeper tissues.

Over-the-Counter Pharmaceuticals

We have designated our subsidiary that holds our OTC products, GloveAid and Pure-ific, Pure-Stick, Pure N Clear as non-core. The potential further development and licensure of our OTC products would likely be facilitated by selling a majority stake of the underlying assets of the non-core subsidiary holding the OTC products. This transaction would likely be accomplished through a non-core spin-out process, which would enable the non-core subsidiary to become a separate publicly held company. The new public entity could then raise funds without diluting the ownership of the then current shareholders of the Company.

GloveAid

Personnel in many occupations and industries now use disposable gloves daily in the performance of their jobs, including airport security personnel, food handling and preparation personnel, health care workers such as hospital and blood bank personnel, laboratory researchers, police, fire and emergency response personnel, postal and package delivery handlers and sorters, and sanitation workers.

Accompanying the increased use of disposable gloves is a mounting incidence of chronic skin irritation. To address this market, we have developed GloveAid, a hand cream with both antiperspirant and antibacterial properties, to increase the comfort of users hands during and after the wearing of disposable gloves. During 2003, we ran a pilot scale run at the manufacturer of GloveAid.

Pure-ific

Our Pure-ific line of products includes two quick-drying sprays, Pure-ific and Pure-ific Kids, that immediately kill up to 99.9% of germs on skin and prevent regrowth for six hours. We have determined the effectiveness of Pure-ific based on our internal testing and testing performed by Paratus Laboratories H.B., an independent research lab. Pure-ific products help prevent the spread of germs and thus complement our other OTC products designed to treat irritated skin or skin conditions

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such as acne, eczema, dandruff and fungal infections. Our Pure-ific sprays have been designed with convenience in mind and are targeted towards mothers, travelers, and anyone concerned about the spread of sickness-causing germs. During 2003 and 2004, we identified and engaged sales and brokerage forces for Pure-ific. We emphasized getting sales in independent pharmacies and mass (chain stores) markets. The supply chain for Pure-ific was established with the ability to support large-scale sales and a starting inventory was manufactured and stored in a contract warehouse/fulfillment center. In addition, a website for Pure-ific was developed with the ability for supporting online sales of the antibacterial hand spray. During 2005 and 2006, most of our sales were generated from customers accessing our website for Pure-ific and making purchases online. We discontinued our proof-of-concept program in November 2006 and have, therefore, ceased selling our OTC products. We now intend to license the Pure-ific product, a strategy we have been discussing with interested groups. Additionally, we also intend to sell a majority stake in the underlying assets via a non-core spin-out transaction, as discussed below.

On December 15, 2011, we sold Units to accredited investors which included shares of common stock in Pure-ific and a warrant to purchase 3/4 of a share of the Company s common stock. A total of 666,666 Units were sold for gross proceeds of $500,000 resulting in the sale of a 33% non-controlling interest in Pure-ific. At the time of the sale and as of December 31, 2011, the carrying value of the net assets in Pure-ific was $0. The sale also resulted in the issuance of warrants to purchase 500,000 shares of the Company s common stock at an exercise price of $1.25 per share with a five-year term. We intend to use the proceeds, after deducting offering expenses of approximately $56,500, to spin-off Pure-ific as a new publicly-traded company, a process we have initiated but have not yet completed. Network 1 Financial Securities, Inc., served as placement agent for the offering.

Acne

Our acne products Pure-Stick and Pure N Clear work by decreasing the production of fats, oils and sweat that create an environment conducive to unchecked growth of bacteria. Secondly, the products also act to reduce the number of bacteria already present. Pure-Stick and Pure N Clear represent new formulations of proven, safe ingredients that achieve both steps required to successfully treat acne. Since Pure-Stick and Pure N Clear are applied topically to affected areas there are no safety concerns with healthy skin. The unique combinations have allowed the Company to secure patent protection for these products.

Medical Devices

We have non-core medical device technologies that we believe may address two major markets:

- cosmetic treatments, such as reduction of wrinkles and elimination of spider veins and other cosmetic blemishes; and
- therapeutic uses, including photoactivation of PH-10, other prescription drugs and non-surgical destruction of certain skin cancers.

We expect to further develop our non-core medical devices through partnerships with, or selling our assets to, third-party device manufacturers or, if appropriate opportunities arise, through acquisition of one or more device manufacturers. Additionally, the Company also intends to sell a majority stake in the underlying assets via a non-core spin-out transaction.

Photoactivation

Our clinical tests of PH-10 for dermatology have in the past utilized a number of commercially available lasers for activation of the drug. This approach has several advantages, including the leveraging of an extensive base of installed devices present throughout the pool of potential physician-adopters for PH-10. Access to such a base could play an integral role in early market capture. However, since the use of such lasers, which were designed for occasional use in other types of dermatological treatment, is potentially too cumbersome and costly for routine treatment of the large population of patients with psoriasis, we have begun investigating potential use of other types of photoactivation hardware, such as light booths. The use of such booths is consistent with current care standards in the dermatology field, and may provide a cost-effective means for addressing the needs of patients and physicians alike. We anticipate that such photoactivation hardware would be developed, manufactured, and supported in conjunction with one or more third-party device manufacturers.

Laser-Based Treatment of Melanoma

We have conducted extensive research on ocular melanoma at the Massachusetts Eye and Ear Infirmary (a teaching affiliate of Harvard Medical School) using a new laser treatment that may offer significant advantage over current treatment options. A single quick non-invasive treatment of ocular melanoma tumors in a rabbit model resulted in elimination of over 90% of tumors, and may afford significant advantage over invasive alternatives, such as surgical excision, enucleation, or

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radiotherapy implantation. Ocular melanoma is rare, with approximately 2,000 new cases annually in the U.S. However, we believe that our extremely successful results could be extrapolated to treatment of primary melanomas of the skin, which have an incidence of over 60,000 new cases annually in the U.S. and a 6% five-year survival rate after metastasis of the tumor. We have performed similar laser treatments on large (averaging approximately 3 millimeters thick) cutaneous melanoma tumors implanted in mice, and have been able to eradicate over 90% of these pigmented skin tumors with a single treatment. Moreover, we have shown that this treatment stimulates an anti-tumor immune response that may lead to improved outcome at both the treatment site and at sites of distant metastasis. From these results, we believe that a device for laser treatment of primary melanomas of the skin and eye is nearly ready for human studies. We anticipate partnering with, or selling our assets to, a medical device manufacturer to bring it to market in reliance on a 510(k) notification. For more information about the 510(k) notification process, see Federal Regulation of Therapeutic Products below.

Research and Development

We continue to actively develop projects that are product-directed and are attempting to conserve available capital and achieve full capitalization of our company through equity and convertible debt offerings, generation of product revenues, and other means. All ongoing research and development activities are directed toward maximizing shareholder value and advancing our corporate objectives in conjunction with our OTC product licensure, our current product development and maintaining our intellectual property portfolio.

Research and development costs totaling $3,595,555 for 2013 included payroll of $1,459,057, consulting and contract labor of $1,317,472, lab supplies and pharmaceutical preparations of $310,160, legal of $262,720, insurance of $161,268, rent and utilities of $78,512, and depreciation expense of $6,366. Research and development costs totaling $5,005,459 for 2012 included payroll of $2,536,818, consulting and contract labor of $2,008,270, lab supplies and pharmaceutical preparations of $47,808, legal of $231,430, insurance of $97,728, rent and utilities of $77,238, and depreciation expense of $6,167. Research and development costs totaling $8,807,896 for 2011 included payroll of $6,182,147, consulting and contract labor of $2,238,765, lab supplies and pharmaceutical preparations of $57,467, legal of $161,068, insurance of $92,859, rent and utilities of $68,234, and depreciation expense of $7,356.

Production

We have determined that the most efficient use of our capital in further developing our OTC products is to license the products. The Company has been discussing this strategy with interested groups. Additionally, the Company also intends to sell a majority stake in the underlying assets via a non-core spin-out transaction.

Sales

We have not had any significant sales of any of our OTC products, though we commenced limited sales of Pure-ific, our antibacterial hand spray in 2004 through 2006, in a proof-of-concept program. We discontinued our proof-of-concept program in 2006 and have, therefore, ceased selling our OTC products. We will continue to seek additional markets for our products through existing distributorships that market and distribute medical products, ethical pharmaceuticals, and OTC products for the professional and consumer marketplaces through licensure, partnership and asset sale arrangements, and through potential merger and acquisition candidates.

In addition to developing and selling products ourselves on a limited basis, we are negotiating actively with a number of potential licensees for several of our intellectual properties, including patents and related technologies. To date, we have not yet entered into any licensing agreements; however, we anticipate consummating one or more such licenses in the future.

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Intellectual Property

Patents

We hold a number of U.S. patents covering the technologies we have developed and are continuing to develop for the production of prescription drugs, non-core technologies and OTC pharmaceuticals. All patents material to an understanding of the Company are included and a cross reference to a discussion that explains the patent technologies and products is identified for each patent in the following table:

U.S. Patent No	Title and Cross Reference	Issue Date	Expiration Date
5,829,448	Method for improved selectivity in activation of molecular agents; see discussion under Medical Devices in Description of Business	November 3, 1998	October 30, 2016
5,832,931	Method for improved selectivity in photo-activation and detection of diagnostic agents; see discussion under Medical Devices in Description of Business	November 10, 1998	October 30, 2016
5,998,597	Method for improved selectivity in activation of molecular agents; see discussion under Medical Devices in Description of Business	December 7, 1999	October 30, 2016
6,042,603	Method for improved selectivity in photo-activation of molecular agents; see discussion under Medical Devices in Description of Business	March 28, 2000	October 30, 2016
6,331,286	Methods for high energy phototherapeutics; see discussion under Oncology in Description of Business	December 18, 2001	December 21, 2018
6,451,597	Method for enhanced protein stabilization and for production of cell lines useful production of such stabilized proteins; see discussion under Material Transfer Agreement in Description of Intellectual Property	September 17, 2002	April 6, 2020
6,468,777	Method for enhanced protein stabilization and for production of cell lines useful production of such stabilized proteins; see discussion under Material Transfer Agreement in Description of Intellectual Property	October 22, 2002	April 6, 2020
6,493,570	Method for improved imaging and photodynamic therapy; see discussion under Oncology in Description of Business	December 10, 2002	December 10, 2019
6,495,360	Method for enhanced protein stabilization for production of cell lines useful production of such stabilized proteins; see discussion under Material Transfer Agreement in Description of Intellectual Property	December 17, 2002	April 6, 2020
6,519,076		February 11, 2003	October 30, 2016

	Methods and apparatus for optical imaging; see discussion under Medical Devices in Description of Business		
6,525,862	Methods and apparatus for optical imaging; see discussion under Medical Devices in Description of Business	February 25, 2003	October 30, 2016
6,541,223	Method for enhanced protein stabilization and for production of cell lines useful production of such stabilized proteins; see discussion under Material Transfer Agreement in Description of Intellectual Property	April 1, 2003	April 6, 2020
6,986,740	Ultrasound contrast using halogenated xanthenes; see discussion under Oncology in Description of Business	January 17, 2006	September 9, 2023
6,991,776	Improved intracorporeal medicaments for high energy phototherapeutic treatment of disease; see discussion under Oncology in Description of Business	January 31, 2006	May 5, 2023

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U.S. Patent No	Title and Cross Reference	Issue Date	Expiration Date
7,036,516	Treatment of pigmented tissues using optical energy; see discussion under Medical Devices in Description of Business	May 2, 2006	January 28, 2020
7,201,914	Combination antiperspirant and antimicrobial compositions; see discussion under Over-the-Counter Pharmaceuticals in Description of Business	April 10, 2007	May 15, 2024
7,338,652	Diagnostic agents for positron emission imaging; see discussion under Oncology in Description of Business	March 4, 2008	September 25, 2025
7,346,387	Improved selectivity in photo-activation and detection of molecular diagnostic agents; see discussion under Medical Devices in Description of Business	March 18, 2008	October 30, 2016
7,353,829	Improved methods and apparatus for multi-photon photo-activation of therapeutic agents; see discussion under Medical Devices in Description of Business	April 8, 2008	April 23, 2020
7,384,623	A radiosensitizer agent comprising tetrabromoerythrosin; see discussion under Oncology in Description of Business	June 10, 2008	August 25, 2019
7,390,668	Intracorporeal photodynamic medicaments for photodynamic treatment containing a halogenated xanthene or derivative; see discussion under Dermatology in Description of Business	June 24, 2008	March 6, 2021
7,402,299	Intracorporeal photodynamic medicaments for photodynamic treatment containing a halogenated xanthene or derivative; see discussion under Dermatology in Description of Business	July 22, 2008	October 2, 2025
7,427,389	Diagnostic agents for positron emission Imaging; see discussion under Oncology in Description of Business	September 23, 2008	July 7, 2026
7,648,695	Improved medicaments for chemotherapeutic treatment of disease; see discussion under Oncology in Description of Business	January 19, 2010	July 6, 2021
7,863,047	Improved intracorporeal medicaments for photodynamic treatment of disease; see discussion under Dermatology in Description of Business	January 4, 2011	October 30, 2016
8,470,296	Improved intracorporeal medicaments for high energy photodynamic treatment of disease; see discussion under Dermatology in Description of Business	June 25, 2013	June 28, 2022
8,530,675	Process for the synthesis rose bengal and related xanthenes; see discussion under Oncology in Description of Business	September 10, 2013	July 13, 2031
8,557,298	Chemotherapeutic agents for cancer; see discussion under Oncology in Description of Business	October 15, 2013	June 23, 2020

We continue to pursue patent applications on numerous other developments we believe to be patentable. We consider our issued patents, our pending and patent applications, and any patentable inventions which we may develop to be extremely valuable assets of our business.

Material Transfer Agreement

We have entered into a Material Transfer Agreement dated as of July 31, 2003 with Schering-Plough Animal Health Corporation, which we refer to as SPAH , the animal-health subsidiary of Schering-Plough Corporation, a major

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international pharmaceutical company which is still in effect. Under the Material Transfer Agreement, we will provide SPAH with access to some of our patented technologies to permit SPAH to evaluate those technologies for use in animal-health applications. If SPAH determines that it can commercialize our technologies, then the Material Transfer Agreement obligates us and SPAH to enter into a license agreement providing for us to license those technologies to SPAH in exchange for progress payments upon the achievement of goals.

The Material Transfer Agreement covers four U.S. patents that cover biological material manufacturing technologies (i.e., biotech related). The Material Transfer Agreement continues indefinitely, unless SPAH terminates it by giving us notice or determines that it does not wish to secure from us a license for our technologies. The Material Transfer Agreement can also be terminated by either of us in the event the other party breaches the agreement and does not cure the breach within 30 days of notice from the other party. We cannot assure you that SPAH will determine that it can commercialize our technologies or that the goals required for us to obtain progress payments from SPAH will be achieved.

The Company has received no progress payments in relation to its Material Transfer Agreement with SPAH. Progress payments could potentially total $50,000 for the first cell line for which SPAH uses our technology and $25,000 for each use of the same technology thereafter. We do not know how many cell lines SPAH may have and we currently have no indication from SPAH that it intends to use any of our technologies in the foreseeable future.

Additionally, the Company also intends to sell a majority stake in these underlying assets via a non-core spin-out transaction.

Competition

In general, the pharmaceutical and biotechnology industries are intensely competitive, characterized by rapid advances in products and technology. A number of companies have developed and continue to develop products that address the areas we have targeted. Some of these companies are major pharmaceutical companies and biotechnology companies that are international in scope and very large in size, while others are niche players that may be less familiar but have been successful in one or more areas we are targeting. Existing or future pharmaceutical, device, or other competitors may develop products that accomplish similar functions to our technologies in ways that are less expensive, receive faster regulatory approval, or receive greater market acceptance than our products. Many of our competitors have been in existence for considerably longer than we have, have greater capital resources, broader internal structure for research, development, manufacturing and marketing, and are in many ways further along in their respective product cycles.

While it is possible that eventually we may compete directly with major pharmaceutical companies, we believe it is more likely that we will enter into joint development, marketing, or other licensure arrangements with such competitors. Eventually, we believe that we will be acquired.

We also have a number of market areas in common with traditional skincare cosmetics companies, but in contrast to these companies, our products are based on unique, proprietary formulations and approaches. For example, we are unaware of any products in our targeted OTC skincare markets that are similar to our Pure-ific product. Further, proprietary protection of our products may help limit or prevent market erosion until our patents expire.

Federal Regulation of Therapeutic Products

All of the prescription drugs we currently contemplate developing will require approval by the FDA prior to sales within the United States and by comparable foreign agencies prior to sales outside the United States. The FDA and

comparable regulatory agencies impose substantial requirements on the manufacturing and marketing of pharmaceutical products and medical devices. These agencies and other entities extensively regulate, among other things, research and development activities and the testing, manufacturing, quality control, safety, effectiveness, labeling, storage, record keeping, approval, advertising and promotion of our proposed products. While we attempt to minimize and avoid significant regulatory bars when formulating our products, some degree of regulation from these regulatory agencies is unavoidable. Some of the things we do to attempt to minimize and avoid significant regulatory bars include the following:

Using chemicals and combinations already allowed by the FDA;

Using drugs that have been previously approved by the FDA and that have a long history of safe use; and

Using chemical compounds with known safety profiles

The regulatory process required by the FDA, through which our drug or device products must pass successfully before they may be marketed in the U.S., generally involves the following:

Preclinical laboratory and animal testing;

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