Piramal Life Sciences

knowledge action care

ANNUAL REPORT 2009-2010

Board of Directors

Ajay G. Piramal, Chairman

Dr. (Mrs.) Swati A. Piramal, Vice-Chairperson

Gautam Doshi

Sir Ravinder Maini

Dr. R. A. Mashelkar

Prof. Goverdhan Mehta

N. Santhanam

Dr. Somesh Sharma, Managing Director

Auditors

Price Waterhouse & Co.

Bankers

Axis Bank Limited

Calyon Bank

HDFC Bank Limited

ICICI Bank Limited

Kotak Mahindra Bank Limited

Yes Bank Limited

Central Bank of India

IndusInd Bank Limited

Registered Office

Piramal Tower,
Ganpatrao Kadam Marg,
Lower Parel,
Mumbai 400 013, India.

The Vision

To discover, develop and commercialize innovative drugs to address still unmet medical needs to reduce the burden of disease.

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Chairman's Letter

Dear Shareholders,

Warm greetings to you all.

The momentum of FY2009 has continued into FY2010. We continue to move firmly towards our goal of reducing the burden of disease by finding new and affordable cures for unmet medical needs. Committed to the Group's values - knowledge, action and care, we continue to focus upon nurturing innovation and breakthrough thinking to impact the lives of millions, in dynamic, nimble footed delivery and in making quality drugs accessible.

The global drug discovery and development industry is at cross roads. The ever increasing cost of bringing drug to the market and increased scrutiny from the FDA has resulted in large pharmaceutical companies being extremely selective about the candidates that they work on. Countries on the other hand, due to increased cost of healthcare, are making all efforts to contain costs by encouraging generic drugs. As a result, patent protected life of drugs has been decreasing. There has been clear shift in trend to focus more on efficient ways of bringing a new drug to the market. Multi-national pharmaceutical companies are looking at alliances to maximize R&D productivity.

All these developments augur well for nascent drug discovery and development industry in India. The cost of conducting pharmaceutical research in India is low as compared to that in western geographies. The industry in India also benefits from condensed timeline of recruiting patients in India due to availability of treatment-naïve patients. With the trend of highly experienced and knowledgeable drug discovery and development scientists returning to India, the drug discovery and development industry in India is on the verge of taking off.

During the year we completed Phase I study of a new, orally active glucose lowering compound, P1736, in The Netherlands. Our programmes being done in collaborations with our partners - Eli Lilly and Merck are progressing well. We have commenced Phase I trial of a new experimental drug molecule P2202, the second compound from Eli Lilly, for diabetes-metabolic syndrome in Canada. For our collaboration agreement with Merck, we will be starting the pre-clinical development of a new candidate very soon.

Overall, we are moving steadily towards our goal of being the first Indian company to discover, develop and launch a new drug globally.

We wish to express our gratitude to our employees who embody the spirit of PLSL and to you, our stockholders, for your ongoing support.

Warm regards,

Ajay G. Piramal
Chairman

Date : 27th April, 2010

Management Discussion & Analysis

Review of the year ended 31 March 2010 :

BUSINESS STRATEGY :

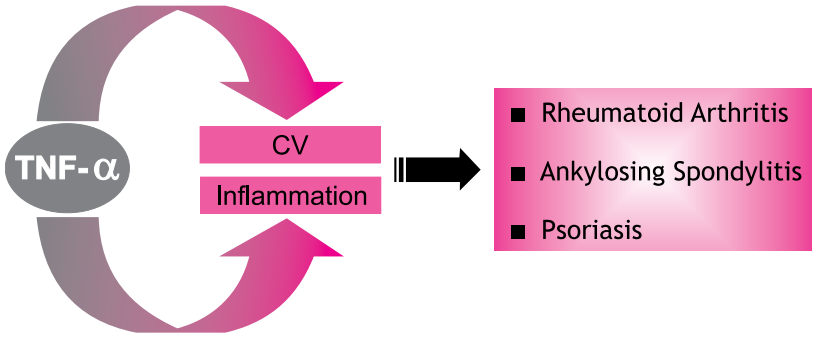
PLSL is a product focused biopharmaceutical company specializing in the discovery and development of novel small-molecule drugs. The Company's strategy is to rapidly discover and optimize compounds to meet important unmet clinical needs in the target markets of cancer, metabolic disorder, inflammatory, and infectious diseases. PLSL has assembled a world-class scientific team and established a dominant position in drug discovery and development through the use of PLSL proprietary technologies. The key elements of PLSL's strategy includes:

- Identify a robust portfolio of lead candidates that can be developed to address unmet medical needs in targeted market segments
- Establish seamless development capabilities from discovery through launch and further expedite product path to clinic
- In cases where the candidate involves orphan drug status, niche indications, or accelerated clinical trials, PLSL plans to develop the candidate through launch
- Establish corporate partnerships in target markets
  - The Company plans to seek partnerships and collaborations for late stage development and commercialization
- Expand clinical pipeline through in-licensing
  - PLSL intends to widen its pipeline by in-licensing drug candidates allowing the Company multiple "shots on goal"
- Manufacturing, marketing and distribution strategy
  - While PLSL has established capabilities in these areas, the Company is open to outsourcing to third parties on a need basis

Identify a robust portfolio of lead candidates

PLSL's discovery strategy is to be an "early follower" by working on precedented targets that have been validated by leaders with late-stage, potentially first-in-class development candidates. The Company has chosen not to work on classes of drugs where there are five or more competitors with candidates at a similar level of development. Moreover, in selecting drug candidates PLSL hopes to address pathways indicated in multiple applications.

Multiple application of TNF-α as a target



In addition to medicinal chemistry efforts, PLSL plans to leverage India's bio-diversity and vast pool of knowledge in traditional medicinal systems such as Ayurveda (an administration of herbal, herbo-mineral or herbo-animal combinations) to source for drug lead molecules. The Company has a unique and diverse collection of natural product extracts from microbes and plants from rare habitats in India, collected over a period of last three decades. With 6,060 plant extracts and 49,744 microbial strains in its library the Company has arguably the largest and most diverse collection of plant extracts and microbial strains in India. PLSL's discovery

efforts in this segment include evaluation and investigation of medicinal extracts/preparations from herbs and plants as practiced in rural/tribal areas, or as cited in ancient Ayurvedic texts. PLSL hopes to bring herbal medication to the world by applying modern science and clinical validation techniques.

This approach has proven to be significantly less expensive and more rewarding compared to the current, more common strategy of mass-screening vast combinatorial libraries of "druggable" compounds.

PLSL natural product extracts

Natural product extracts	Number
Plant extracts	6,060
Microbial strains	49,744

Establish seamless development capabilities from discovery through launch

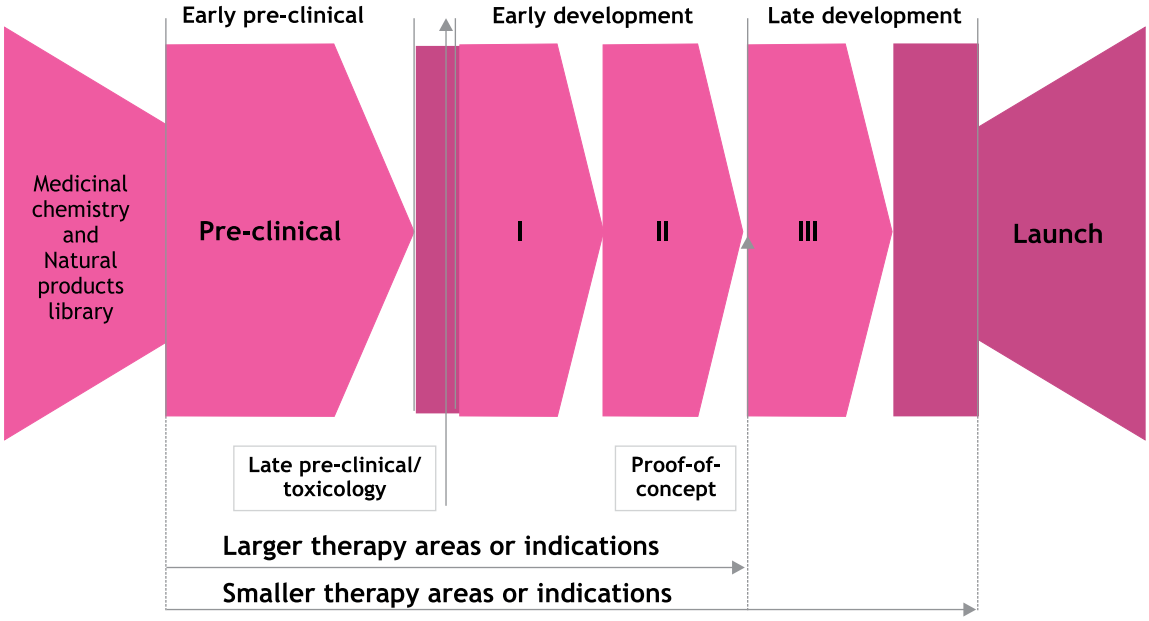
PLSL plans to be a vertically integrated drug development company, with the capability to develop drug candidates from early discovery through clinical development and launch worldwide.

Headquartered in Mumbai, India, PLSL has the advantage of a large, "treatment naïve" patient pool, lower clinical trial and overhead expenses, as well as availability of skilled clinicians. As a result, the Company is able to conduct discovery and development operations with a highly reduced expense base in comparison with larger pharmaceutical companies based in the US and Europe.

Discovery → Early Development (I & II) → Late Development (III) → Launch

PLSL believes it has the necessary infrastructure in place to develop molecules through launch and commercialization.

PLSL commercialization strategy



Establish corporate partnerships in target markets

PLSL will develop new chemical entities (NCEs) or plant extracts from early discovery through Phase II clinical trials in India and other countries that afford an opportunity for early commercialization.

Discovery → Early Development (I & II) → Out-license/partnership

In cases where the program or product requires larger clinical trials, PLSL will either out-license to global pharmaceutical companies post Proof-of-Concept, or establish a partnership with a pharma company for late-stage development in which the two Companies will co-develop the compound on a shared risk and reward basis. PLSL will concurrently continue Phase III trials in India.

Expand clinical pipeline through in-licensing

As an innovative pharmaceutical company, PLSL is committed to widening its pipeline, with both organic and in-licensed drug candidates. By in-licensing, the Company hopes to enhance the probability of success of its pipeline by increasing its "shots on goal."

PLSL has in-licensing relationships with the following partners, based on the described risk-reward sharing mechanism

- Eli Lilly & Co.
- Merck & Co.
- Pierre Fabre Laboratories (only discovery)
- A top-five global pharmaceutical Company (to be disclosed)

R&D Agreement with Eli Lilly & Co.

In January 2007, PLSL signed a drug development agreement with Eli Lilly & Co. to develop and commercialize a select group of Lilly's pre-clinical drug candidates spanning multiple therapeutic areas. As the initial phase of this agreement, Eli Lilly has out-licensed two patented pre-clinical compounds to PLSL indicated in metabolic diseases.

- PLSL is responsible for the design and execution of global clinical development through completion of Phase II trials, including process chemistry, formulation, IND-enabling non-clinical toxicology studies and human clinical trials
- Eli Lilly is responsible for Phase III development, registration, and global drug launch (excluding India and certain South Asian countries)
- PLSL will receive the following:
  - » Milestone payments (total of US$100mm) on successful completion of Phase I, II and III
  - » Percentage royalty on global sales upon successful launch
  - » Exclusive marketing rights for India and certain neighboring countries

R&D Agreement with Merck & Co.

In November 2007, Merck and PLSL entered into a research and development collaboration agreement to discover and develop new drugs for two new oncology targets provided by Merck.

- PLSL will be responsible for carrying out an integrated drug discovery program from lead identification through pre-clinical candidate selection, followed by investigational new drug (IND)-enabling non-clinical studies and human clinical trials demonstrating proof-of-concept, primarily for oncology
- Merck will have an option to advance the most promising drug candidates into late stage clinical trials and to commercialize these drug candidates
- PLSL will receive the following:
  - » Up to US$175mm in milestone payments per target associated with development progress
  - » Royalties on global sales upon successful launch of the product
  - » Marketing rights for India and certain neighboring countries upon successful launch

R&D Agreement with Pierre Fabre Laboratories

In January 2008, PLSL entered into a collaboration agreement with Pierre Fabre Laboratories for research in oncology.

- The Pierre Fabre Group will provide its expertise in research and target screening in oncology while PLSL will make available its natural products base to facilitate pharmacological characterization of new molecules

Drug Discovery Collaborations

PLSL also has a number of drug discovery collaborations with partners including:

- Eli Lilly, USA
- Merck & Co., USA
- Pierre Fabre labs, France
- NIH, USA

- Oncotest GmbH, Germany
- DBT, Govt of India
- National Institute of Oceanography, Goa, India
- Indian Institute of Chemical Biology, Kolkata, India
- IIIM, Jammu-Tawi, India
- IIT, Mumbai, India
- Apollo Hospital, Chennai, India
- NCCS, Pune, India

Manufacturing strategy

PLSL has strong in-house process chemistry capabilities to manufacture up to kilogram quantities of NCE candidates to provide active pharmaceutical ingredients ("API") for GLP toxicology and Phase I clinical trials. API requirements for later stage clinical trials including commercial scale manufacturing will be out-sourced to Indian vendors (including the parent company, PHL) through a competitive bidding process.

In addition, PLSL has in-house pre-formulation and formulation development capabilities. Manufacture of formulated drug products is outsourced to Indian vendors with USFDA approved formulation plants.

Pipeline Overview :

Oncology Pipeline

Program	Discovery	Preclinical	Phase 1	Phase 2	Phase 3	Trial Location
P276 - CDKs	*Head & Neck Cancer*					India
	Multiple Myeloma Phase I / II					India
	Mantle Cell Lymphoma					US, India
	Malignant Melanoma					Australia
P276 Combination with Gemcitabine	*Pancreatic cancer Phase I / II*					India
P276 Combination with Radiation	*Head and Neck cancer Phase I / II*					India
P1446 – CDKs	*Phase I*					Canada
	Phase I					India
NPB-001-05-Bcr-Abl	*Chronic Myeloid Leukemia Phase I / II*					India
PI3 Kinase	*Lead Selection*					
Microbial Leads	*Lead Selection*					
Target X - Merck	*Lead Selection*					
Target Y - Merck	*Lead Selection*					

Note : NPB-001-05 is a Phytopharmaceutical

Inflammation Pipeline

Program	Discovery	Preclinical	Phase 1	Phase 2	Phase 3	Trial Location
NPS31807 - TNFα	*Rheumatoid Arthritis - Phase II Completed*					India
	Rheumatoid Arthritis - Phase II Completed					India
	Psoriasis - Phase II Completed					India
P979 - TNFα	*Tox Quantity Under Manufact*					
P3914 - NSAID	*Preclinical*					
IL6	*Lead Optimization*					
TNFα	*Lead Optimization*					

Note: NPS31807 is a phytopharmaceutical

Metabolic Disorder Pipeline

Program	Discovery	Preclinical	Phase 1	Phase 2	Phase 3	Trial Location
P1736 – Non-PPARγ	*Phase II*					Netherlands
P1201 – Lilly	*Phase I*					Netherlands, France
P2202 – Lilly	*Phase I*					Canada
DGAT1	*Lead Selection*					

Infectious Diseases Pipeline

Program	Discovery	Preclinical	Phase 1	Phase 2	Phase 3	Trial Location
NPH30907 Dermatophytes	*Phase II Completed*					India
PP9706642 – Anti-HSV2	*Preclinical*					
PM181104 – MRSA/VRE	*Toxicity*					

Note: NPH30907 and PP9706642 are Phytopharmaceuticals

Clinical Stage programs

Oncology-CDK Inhibitors

Disease Background

Cancer continues to be a killer disease throughout the world and is the second leading cause of death after cardiovascular disease. All multiplying cells have to go through a process called as 'cell cycle'. The Cyclin dependent kinase (Cdk) complexes play an important role in regulation of cell cycle progression. Dysregulation of the cell cycle is considered to be one of the important mechanisms of cancer development. In human cancers, genetic and epigenetic events result in over expression of Cyclins or absent or diminished levels of Cdk inhibitors, which provide tumor cells a selective growth advantage. Inhibiting the Cyclins/Cdks therefore offers a potential mechanism for treatment of cancer.

P276

P276 is a novel potent small molecule flavone derived selective Cdk4-D1, Cdk1-B and Cdk9-T inhibitor, with potent cytotoxic effects against tumor cell lines. Anti-tumor activity of P276-00 has also been demonstrated in cellular assays and in rodent tumor models. Phase I study of P276 conducted in India and Canada has been completed. A phase II study in squamous cell carcinoma of head and neck (most common cancer in men in India) is ongoing at several centers in India. In addition, two phase II study in mantle cell lymphoma and malignant melanoma have been initiated in USA, India, and Australia respectively. A phase I/II study in multiple myeloma (cancer of a specific type of white blood cells) is ongoing across five centers in India. Furthermore, since most of the cancers require multiple therapeutic modalities for their effective management, we also have initiated studies of P276 in combination with gemcitabine (which is already approved for the treatment of pancreatic cancer) and in combination with radiation for head and neck cancer in India.

P1446

P1446 is a novel, selective, potent and orally active inhibitor of Cdk4-D1, Cdk1-B and Cdk9-T. This molecule would serve as a back-up molecule for P276. Studies with a variety of cancer cell lines suggest that P1446 effectively inhibits proliferation of and induces cytotoxicity in both cisplatin sensitive and resistant cells without any significant cytotoxicity to normal human cells. Oral administration of P1446 resulted in significant inhibition of tumor growth in rodent tumor models. Studies conducted in-house indicate a need of prolonged oral administration of P1446 for sustained effect. The phase I studies of P1446 are ongoing in Canada, and India.

Chronic myeloid leukemia - NPB001

Disease Background

Chronic myeloid leukemia or CML, a disease of blood cells, is clinically characterized by an excessive multiplication of variety

of cells in the peripheral blood accompanied by overgrowth of the cells even in the bone marrow. The hallmark of CML is the Philadelphia (Ph) chromosome, which is the result of a reciprocal translocation between chromosomes 9 and 22. It encodes for a new, abnormal gene called BCR-ABL that produces BCR-ABL tyrosine kinase, an abnormal protein that leads to the overproduction of immature, poorly functioning white blood cells in CML. CML accounts for almost 15% of all leukemias with 4000-5000 new cases being diagnosed in the US alone every year. Allogeneic stem cell transplantation is the most effective cure for CML till date. However, its widespread application in patients of CML is thwarted due to the limited availability of matching donors and its suitability only to patients less than 65 years of age, who can withstand the toxic effects of transplantation. The current medical therapy of CML includes tyrosine kinase inhibitors such as imatinib mesylate, dasatinib, nilotinib, interferon-α and cytoreductive agents such as hydroxyurea, busulfan, cytarabine and their combinations. Although effective and durable, the emergence of resistance and intolerability to tyrosine kinase inhibitors is the biggest drawback of continued therapy with them.

NPB001 is a phytopharmaceutical administered as an oral suspension. It has demonstrated tyrosine kinase inhibitor properties. Preclinically it has demonstrated cell death and inhibition of cell proliferation in BCR-ABL positive imatinib sensitive as well as resistant cell lines with specific inhibition of the BCR-ABL tyrosine kinase. It has also shown efficacy in the rodent models by decreasing the size of implanted tumor. A combined phase I/II study of NPB001 in patients of chronic myeloid leukemia who are resistant/intolerant to the current standard of care is ongoing to determine the safety, tolerability and efficacy of the drug. In addition, based on its action against one more protein c-kit, a phase II study of NPB001 in c-kit positive gastro intestinal stromal tumor (GIST) patients is also being planned.

Inflammation - NPS31807

Disease Background

Rheumatoid arthritis (RA), is a chronic, systemic, inflammatory disease affecting 1% of general population and leads to significant disability and a consequent reduction in the quality of life. TNF-α is one of the major mediator and has a potential role in the establishment of inflammation in the joints and its eventual destruction. The novel drugs useful in Rheumatoid Arthritis are targeted against TNF-α. At present the more successful treatment options for RA include monoclonal antibodies (Infliximab) and receptor fusion proteins (Etanercept) which apart from having to be administered by injection have significant adverse effects. They are not only very costly but also lead to reactivation of Tuberculosis. Our RA program was initiated to develop a safe oral anti TNF-α drug that can safely be used for long duration early in the course of disease.

NPS31807 is a phytopharmaceutical and is being developed for the treatment of chronic inflammatory disorders where TNF-α plays pivotal role including Rheumatoid Arthritis, Psoriasis, Inflammatory Bowel Disease and Ankylosing Spondylitis. NPS31807 has demonstrated inhibitory activity against TNF-α, IL – 1, IL-6 and IL-8 in various cellular and animal experiments. It has shown to be acting by inhibition of an important protein, NF kB, which plays a role in the synthesis / release of TNF-α. We have completed phase II studies of NPS31807 in RA and Psoriasis. The studies have been planned for other inflammatory disorders.

Metabolic Disorders

Disease Background

Metabolic Syndrome

The metabolic syndrome is a cluster of the metabolic risk factors: diabetes and raised fasting plasma glucose, abdominal obesity, high cholesterol and high blood pressure. International Diabetes Federation (IDF) has estimated that around 20-25 per cent of the world's adult population have the metabolic syndrome and they are twice as likely to die from and three times as likely to have a heart attack or stroke compared with people without the syndrome. In addition, people with metabolic syndrome have a five fold greater risk of developing type2 diabetes. They would add to the 230 million people worldwide who already have diabetes, one of the most common chronic diseases worldwide. The primary management for the metabolic syndrome is a healthy lifestyle. In people for whom lifestyle change is not enough and who are considered to be at high risk for cardiovascular disease, and diabetes, drug therapy will be required to treat the metabolic syndrome. However, specific pharmacological agents are not available. There is a definite need for a treatment that could modulate the underlying mechanisms of the metabolic syndrome as a whole and thereby reduce the impact of all the risks factors and the long term metabolic and cardiovascular consequences.