



Piramal Life Sciences
knowledge action care



ANNUAL REPORT 2008-2009

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., Mumbai.

Bankers

Axis Bank Limited

Calyon Bank

HDFC Bank Limited

ICICI Bank Limited

Kotak Mahindra Bank Limited

Yes Bank Limited

Registered Office

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

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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 FY2008 has continued into FY2009. Our core values of Knowledge, Action and Care continue to inspire us to find new solutions for unmet medical needs. Knowledge propels us to discover new solutions, Action drives us to reduce the time and cost of research, and Care ensures that we are focused on end patient outcomes to reduce the burden of disease.

The global drug discovery and development industry is intensely competitive. Business models are changing rapidly to factor in decreased success ratios of discovering new drugs. Following the Global Credit Crisis, funding for research has been extremely difficult to come by. This has resulted in slower progress of many of the ongoing projects. It has now become important to do the R&D projects in an extremely cost effective manner. Piramal Life Sciences Limited (PLSL) focuses on nurturing innovation and breakthrough thinking to impact the lives of millions, in dynamic, nimblefooted delivery and in making quality drugs accessible worldwide.

During the year, we made steady progress in our discovery and development program. We initiated two Phase II studies and two Phase I/II study for our lead cancer molecule P276-00. Our back-up compound to P276 – P-1446A-05 has also moved into clinical trials stage. Today we have a pipeline of 12 drug candidates with 8 of them in clinical trials.

Our programmes being done in collaborations with our partners - Eli Lilly and Merck are progressing well. We are nearing the completion of the Phase I trial of P1201-07, which is the first Eli Lilly compound. We have also initiated Phase I clinical trials on the second compound under this partnership – P2202. For our collaboration agreement with Merck, we have started the process of lead identification in the targets given by Merck.

Overall, we are moving steadily as per our ambition of being the first Indian company to discover, develop and launch a new pharmaceutical drug globally.

We are thankful of our employees for their ingenuity and perseverance. We are grateful to you, our stockholders, for your vote of confidence and continued interest in our endeavors.

Warm regards,

Ajay G. Piramal
Chairman

Date : 25th April, 2009

Management Discussion & Analysis

Review of the year ended 31 March 2009 :

BUSINESS STRATEGY :

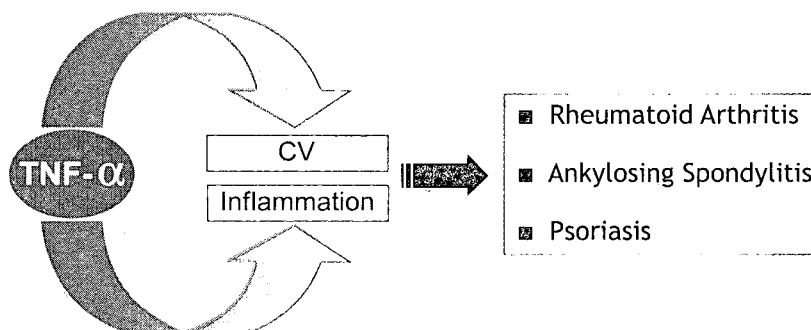
PLSL is a product focused biopharmaceutical company specializing in the discovery and development of novel small-molecule drugs. The Company's strategy is to rapidly discover and optimize compounds to meet important unmet clinical needs in the target markets of cancer, metabolic disorder, inflammatory, 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 strategy
 - While PLSL has established capabilities in this area, 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 6,270 plant extracts and 43,260 microbial strains in its library

MANAGEMENT DISCUSSION & ANALYSIS

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	6,270
Microbial strains	43,260

Establish seamless development capabilities from discovery through launch

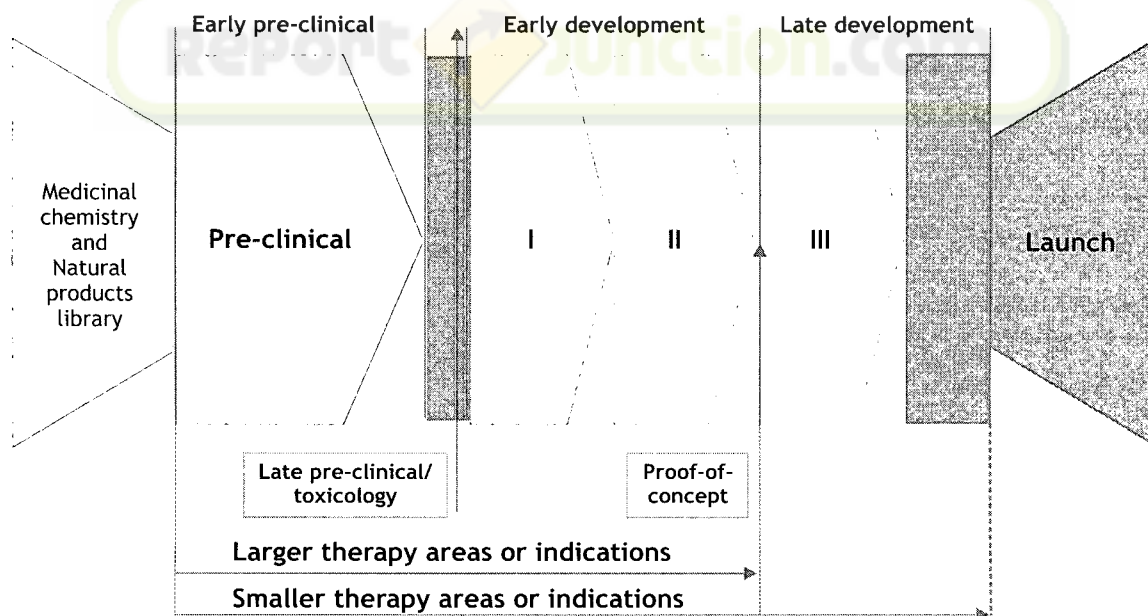
PLSL plans to be a vertically integrated drug development company, with the capability to develop drug candidates from early discovery through clinical development and launch worldwide.

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.

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. During the last year, PLSL has nearly completed the Phase I study of the first compound – P1201-07. PLSL has also initiated a Phase I study of the second compound - P2202 in Canada during the last year.

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. During the year, we have started the process of lead identification in these two new targets.

Drug Discovery Collaborations

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

- Dana Farber Cancer Centre, USA
- National Institute of Health, USA (NIH)
- Oncotest, Germany
- De Montfort University, UK
- NCCS, Pune
- Indian Institute of Chemical Biology, Kolkata (IICB)
- National Institute of Oceanography, Goa (NIO)
- Indian Institute of Science, Bangalore (IISc)
- Department of Biotechnology (DBT) of the Government of India
- Indian Institute of Integrative Medicine, Jammu (IIIM)
- IIT, Mumbai
- Apollo Hospital, Chennai
- NCAOR, Goa

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 Update:

We have initiated the following new clinical trials:

- Phase II trials of P276 for Mantle Cell Lymphoma in USA.
- Phase II trial of P276 for head and neck cancer in India.
- Phase I/II Combination trials of P276 for Pancreatic, and Head and Neck Cancer in India.
- Phase I trial of New Cancer Molecule P-1446A-05 in India and Canada.
- Phase I trial of a new experimental drug molecule P2202 for diabetes-metabolic syndrome in Canada.

MANAGEMENT DISCUSSION & ANALYSIS

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
	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 - TNF α	Rheumatoid Arthritis - Phase II Completed					India
	Rheumatoid Arthritis - Phase II Completed					India
	Psoriasis - Phase II Completed					India
P979 - TNF α	Tox Quantity Under Manufact.					
P3914 - NSAID	Preclinical					
IL6	Lead Optimization					
TNF α	Lead Optimization					

Note : NPS31807 is a phytopharmaceutical

Diabetes & Metabolic Disorder Pipeline

Program	Discovery	Preclinical	Phase 1	Phase 2	Phase 3	Trial Location
P1736 - Non-PPAR γ	Phase I					Netherland
P1201 - Lilly	Phase I					Netherland, France
P2202 - Lilly	Phase I					Canada
DGAT1	Lead selection					

Anti-Infective 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. The study has shown initial efficacy signals in the form of stable disease. We have initiated, a phase I/II study in multiple myeloma (cancer of a specific type of white blood cells) across five centers in India. Importantly, 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, one phase II study in mantle cell lymphoma has been initiated in USA and another phase II study in malignant melanoma is about to be initiated in Australia. 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 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 India and Canada.

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 has been initiated to determine the safety, tolerability and efficacy of the drug.

MANAGEMENT DISCUSSION & ANALYSIS

In addition, based on its action against one more protein c-kit, once a phase II dose is determined from the current study, 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 κ B, which plays a role in the synthesis / release of TNF- α . We have completed phase II studies of NPS31807 in RA and Psoriasis. The study is being planned to initiate a larger phase II study in psoriasis patients, and a phase II trial in patients having Inflammatory Bowel Disease.

Tinea - NPH30907

Disease Background

Tinea, also known as Ringworm, is a common contagious fungal infection of the skin. Tinea is also a common infection in domestic animals, especially cattle and cats. Humans can contract tinea from animals; cats, cattle and dogs are common sources owing to close association with humans. A number of different species of fungi cause tinea. Dermatophytes of the genera Trichophyton and Microsporum are the most common causative agents.

NPH30907, a phytopharmaceutical topical formulation showed good anti-dermatophyte activity against panel of microorganisms. We have completed clinical study to prove the efficacy of 5% NPH30907 cream as an anti-dermatophyte formulation in patients with localized tinea lesions and are exploring options to commercialize the same.

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.

Type 2 - Diabetes Mellitus

Type 2 Diabetes Mellitus is an emerging worldwide health crisis with an incidence rate of 300 million by 2025 as predicted by WHO. Type 2 Diabetes Mellitus (T2DM) or Non-insulin dependent diabetes (NIDDM) accounts for about 90%-95% of the diabetic population. In the US, 20.8 million people, i.e. about 7% of the total population suffers from diabetes. The recent statistics published