

For immediate release  
November 25, 2003

## PLIVA's Fourth R&D Day in London

### Highlights

- Broad portfolio of over 60 generic molecules for EU and USA entry in development
- Almost 600 new submissions of new generics worldwide in 2003
- Two equivalent biological products, erithropoetin and G-CSF, in clinical development stage
- Strong entrance into R&D-driven specialty arena:
  - PLD-165 for type II diabetes
  - PLD-179 for non-obstructive bladder urinary retention
  - PLD-180 for treatment of amyotrophic lateral sclerosis (ALS)
- Successful progress of NCEs in clinical development:
  - PLD-116 first PhaseII study successfully completed
  - PLD-118 first PhaseII study successfully completed; second PhaseII study enrolling patients
  - PLD-147 PhaseI enrolling patients

PLIVA d.d. ("PLIVA") will today host its fourth R&D Day in London, where it will update investors and analysts on the most recent developments in its R&D pipeline.

Radan Spaventi, Vice-President of PLIVA's Management Board and CSO, commented: "I am pleased to say that PLIVA is continuing to deliver upon the promises made to investors. The progress shown in our R&D pipeline clearly shows that PLIVA is successfully developing a wide range of generic, specialty & NCE products. We believe that this strong pipeline will ensure sustainable growth as well as the transition to a non-azithromycin dependent business by 2006."

Zelimir Vuksic, Vice-President of PLIVA's Management Board and President of Pharmaceuticals, added: "With our third quarter results, our pharmaceuticals business clearly showed that PLIVA began to deliver the organic growth that investors have been expecting from us. With over 700 registrations pending market approval, and more than 60 molecules continuously in development, we believe that we will only continue to prove our strategy a success in the future."

### 1. Generics

During the course of 2003, PLIVA further proved its competence in the development of generics and specialty products and effective value chain integration. PLIVA continued to maintain its highly competitive level of R&D productivity, which has averaged over 500 submissions annually, since its initial commitment to developing its generics business in 1999. Furthermore, 2003 was an important year for the company, as it brought with it the first wave of approvals across the CEE and Western Europe (WE) regions. These approvals validate PLIVA's generics strategy, whose cornerstone until now has been Europe. Following PLIVA's expansion into the US in 2002, we expect an increasing number of submissions in the US in the upcoming years.

From January through November 2003, PLIVA submitted 590 applications globally, consisting of 30 molecules or 105 products. A total of 61, 37, and 7 products were filed in CEE, WE and the US respectively (12, 14, and 4 molecules respectively). During this period, marketing approvals for 7

molecules were granted in CEE, 18 in WE, and 2 in the US. These approved molecules include *ciprofloxacin*, *carvedilol*, *gabapentin*, *risperidone*, *ondansetron*, *venlafaxine*, *torasemide* in the CEE region; *ondasetron*, *torasemide*, *ciprofloxacin*, *citalopram*, *dacarbazine*, *desmopressin acetate*, *enalapril*, *fluconazole*, *ranitidine*, *minocycline*, *gabapentin*, *omeprazole*, *polyfax*, *polytrim*, *piroxicam*, *primidon*, *simvastatin* in WE; and, *fluconazole* and *torasemide* in the US. PLIVA has over 600 pending registrations, with 518 pending approvals in CEE, 120 in WE and 9 in the US.

PLIVA is also successfully developing **Equivalent Biologicals**, proving its expertise in molecular biology, formulation and finished form and bulk production. The **erithropoetin** clinical program is currently ongoing in Croatia, with first approval expected in 2004. The **G-CSF** program should also enter clinical development by early 2004, with first approval expected in 2005 in Croatia.

Furthermore, launch of PLIVA's first cytostatic products is expected in 2004 in WE and the US.

In line with its strategy of vertical integration, PLIVA has a number of active pharmaceutical ingredients (APIs) in development, such as *irinotecan*, *oxaliplatin*, *alendronate*, *pantoprazole* and *acarbose*.

## 2. NCE & Specialty Pharmaceuticals

PLIVA has made substantial progress in advancing its NCE projects:

Development of **PLD-118**, a novel oral antifungal compound, is continuing with the second in a series of Phase II studies currently enrolling patients. Results from the first Phase II study indicated that the compound is likely to be safe and effective in HIV-infected patients with oropharyngeal candidiasis. Additional dose refinement is being evaluated in a second Phase II study in this indication. This study is designed as a dose escalating, comparative, randomized, single-blind study where 84 patients in 10 sites in Russia will be enrolled. The dosing regimen includes doses of 200mg, 300mg, 400mg and 500mg b.i.d./14 days and the control comparator treatment will be fluconazole 100mg o.d./14 days. Preliminary results of this study are expected in the 1H2004. Preparations for studies in additional indications such as vaginal candidiasis are currently in progress.

Development of **PLD-116** has continued, with a first safety and efficacy study performed on male and female patients with left-sided mild-to-moderate ulcerative colitis completed during 2003. The compound was administered as a daily enema for 14 days. Preliminary results from this placebo-controlled study suggest that the compound is likely to be safe in these patients. Efficacy data demonstrate that patients who received PLD-116 had statistically significant decrease in their disease activity at the end of treatment. This response was greater than that observed in patients who received placebo, but due to a small sample size, this difference did not reach statistical significance. Activities on producing additional formulations of the compound are planned in order to expand possible use of the drug. The same compound is also in a preclinical evaluation stage for the treatment of wound healing.

**PLD-117** completed Phase I, where the compound demonstrated potential for a good safety and tolerability profile. However, due to the streamlining of the pipeline, PLIVA has decided to seek a partner for further development of this molecule.

**PLD-147**, a novel orally active platinum-based cytostatic compound, is currently being developed for the treatment of solid tumors. Current findings indicate that the compound is more potent in human and mouse cell lines in comparison to satraplatin (currently in Phase III clinical trials – orally bioavailable) and cisplatin. The compound was also shown to be as effective as satraplatin in animal tumor models and active in cisplatin resistant tumors. The study is currently enrolling patients. In parallel to the Phase I clinical trial, additional preclinical studies are ongoing.

**PLD-177** (previously PLR-13), a representative of a new compound class, is in development for the treatment of asthma. The compound has a novel mode of action resembling corticosteroid activity and selective affinity to lung tissue. Such properties result in potent activity in suppressing inflammation in rat models for asthma and very good safety profile as compared to current corticosteroids. Start of Phase I development is planned for 1Q2005, following completion of ongoing feasibility study in inhaler device. There was also steady progress in PLR-8, aimed at developing a new class of molecules for the treatment of respiratory inflammation disorders.

Within **PLR-14**, PLIVA is developing small molecule inhibitors of TNF-alpha production through inhibition of cytokine transcription. These molecules are intended for the treatment of rheumatoid arthritis and other inflammatory diseases responsive to TNF-alpha inhibition treatment. The current lead compound exhibits good activity in adjuvant arthritis mouse model as well as analgesic activity. The lead compound is not genotoxic and has acceptable toxicity and pharmacokinetic profile in animals.

**PLD-146**, a broad-spectrum macrolide project being developed in collaboration with GlaxoSmithKline is successfully ongoing with significant progress being made.

In line with our specialty strategy, PLIVA has added three new projects to its pipeline at different stages of development. These include PLD-165 for type II diabetes, PLD-179 for urinary retention and PLD-180 for amyotrophic lateral sclerosis (ALS). If proven to be successful, PLIVA believes these projects can be marketable starting in 2006.

**PLD-165** is a late stage project for which PLIVA acquired the interests, including intellectual property rights and other human drug-related assets from Ergo Science Corporation. The product has an approvable letter from the FDA. Within this project, PLIVA is developing a treatment for type II diabetes, a metabolic disorder resulting in insulin resistance and glucose intolerance. Progress of disease is often connected with risk factors such as hypertension and obesity, and number of diseases and/or disorders (persistent infections, retinopathy, kidney failure, etc.). This type of diabetes affects approximately 16 million people in the US alone, and the incidence is increasing. The total US market for non-insulin products to treat type II diabetes was USD 5.4bn (IMS) in 2002 with an increasing trend.

PLD-165 is a known drug being developed in a new indication, type II diabetes, for oral, once a day administration and is expected to enter the market by 2007. The main properties of this compound are effective lowering of blood sugar, triglycerides and free fatty acid levels. Protocol for the required safety study is prepared and the major milestone is the FDA meeting that will take place in early 2004.

**PLD-179** is currently on the market and indicated for non-obstructive bladder urinary retention due to acute post-operative, postpartum or neurogenic bladder weakness. PLIVA is developing a novel buccal delivery system for PLD-179, whose properties include fast-acting, reduced response time and fewer gastrointestinal side effects. A human pharmacokinetic/safety study is currently in progress, and NDA clinical trials are expected for 2H2004. Projected market entry date for this project is 2006.

A third new project under the code-name **PLD-180** was recently added to the pipeline. Within this project, PLIVA is developing an existing drug in a new indication for the treatment of amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's disease. ALS is a progressive fatal disease with death occurring typically within 3-5 years following first diagnosis. The ALS patient population in the US is 20,000, with 5,000 new cases diagnosed and 5,000 deaths occurring each year. There is currently no cure for this disease, while current treatment is directed towards slowing down its progression and increasing life expectancy and quality of life (the only approved drug for ALS indication is Rilutek). The drug that PLIVA is developing as PLD-180, has a well-established safety and tolerability profile, and is being formulated in a new fast-dissolve dosage form. A blinded study in a mouse model of ALS is showing encouraging results. The drug has a potential for orphan drug

status with expected launch earliest by 2007. Leading experts in the ALS community will assist in further development of the project.

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***Calendar of upcoming events\****

Year 2003 Results ..... February 2004

*\* Provisional timetable; changes possible. For up-to-date calendar, please refer to our website: [www.pliva.com](http://www.pliva.com)*

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