Pharmaceutical Technologies

2012
PLIVA annually manufactures:

- 5.5 billion tablets
- 30 million injections
- 10 million tubes of creams and ointments
DEAR READERS,

There are only a few companies in Croatia or worldwide which can take pride in the long tradition that PLIVA can. Its history dates back to as early as 1921 when the Kaštel factory in Karlovac started to manufacture domestic herb extracts. In its more than 90-year long history PLIVA has manufactured hundreds of different high quality medicines and made an exceptional contribution to the treatment of patients in Croatia and globally. Its experts, researchers and scientists have also greatly contributed to science and technology developments.

After decades of intensive research and considerable investments in new technologies, production facilities and equipment and into research and development of both branded and generic medicines, PLIVA is today the largest pharmaceutical company in Croatia and one of the country's leading exporters. Since 2008 PLIVA has operated as a member of Teva, one of the largest pharmaceutical companies in the world, and PLIVA's site in Zagreb has become one of the strategic productions sites for the Teva Group. PLIVA has state-of-the-art development and production capacities and offers a broad portfolio of generic medicines with superior therapeutic solutions to a great number of European and international markets. The production site in Zagreb is mainly engaged in the production of tablets, which are delivered to the most demanding international markets. Furthermore, the project of increasing current production capacities for oral solid forms is underway. Injections and semi-solid products, i.e. creams and ointments, are also manufactured in Zagreb. Eighty percent of medicines are intended for exports.

PLIVA annually manufactures about 5.5 billion tablets and capsules, 30 million injections and 10 million tubes of creams and ointments. With more than 90 different molecules, PLIVA manufactures about 1000 various products for the US, European Union and other markets, and records a stable sales growth.

About 1000 people work in production operations in Zagreb and more than a quarter have university qualifications. Special thanks go to these people, without whose efforts, engagement, expertise and commitment to the achievement of increasingly ambitious business plans and goals PLIVA's success would not be possible.

PLIVA CROATIA

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PLIVA MILESTONES

In Karlovac, the companies ISIS (Zagreb) and Chinoin (Budapest) found the company Kaštel D.D., Pliva’s predecessor. The production of domestic herb extracts begins.

1921

The production of injections, syrups and tablets begins.

1923

Production moves to the current site in Zagreb, which employs about 60 people, of whom ten are tertiary qualified.

1927

PLIVA’s oxytetracycline production plant receives approval by the US Food and Drug Administration (FDA), the first of more than 30 DMF submissions approved by the FDA.

1965

Pliva’s oxytetracycline production plant receives approval by the US Food and Drug Administration (FDA), the first of more than 30 DMF submissions approved by the FDA.

1971

Production in the new facility for finished dosage forms starts. One hundred and thirty-two new medicines are manufactured, of which 58 on the basis of original formulations.

1980

Pliva’s original macrolide antibiotic azithromycin is patented.

1988

Azithromycin is launched under Pliva’s brand name Sumamed.

PAGE 04

/// PHARMACEUTICAL TECHNOLOGIES
VLADIMIR PRELOG, PH.D., NOBEL PRIZE WINNER FOR CHEMISTRY IN 1975, JOINS THE COMPANY AND BEGINS RESEARCH IN KAŠTEL D.D.

KAŠTEL D.D. BECOMES ONE OF THE FIRST SULPHONAMIDE PRODUCERS IN THE WORLD. STREPTAZOL, PATENTED UNDER NUMBER 13726 AND LAUNCHED IN 1937 IN THE FORM OF TABLETS AND INJECTIONS, ACHIEVES GREAT SUCCESS


THE PLIVA RESEARCH INSTITUTE IS FOUNDED

AZITHROMYCIN IS LAUNCHED UNDER PFIZER’S BRAND NAME ZITHROMAX ON US AND WESTERN EUROPE MARKETS

PRODUCTION IN THE NEW ORAL SOLID FORMS FACILITY STARTS

A NUMBER OF RECONSTRUCTIONS TAKE PLACE TO THE PRODUCTION FACILITIES FOR INJECTIONS AND CREAMS

PLIVA BECOMES A MEMBER OF THE TEVA GROUP, THE LARGEST GENERIC PHARMACEUTICAL COMPANY WORLDWIDE

THE PRODUCTION OF VITAMIN C, BASED ON IN-HOUSE PATENTED TECHNOLOGY, BEGINS

OXYTETRACYCLINE AND VITAMIN B6 PRODUCTION STARTS

THE PRODUCTION OF ORAL SOLID FORMS STARTS

A NUMBER OF RECONSTRUCTIONS TAKE PLACE TO THE PRODUCTION FACILITIES FOR INJECTIONS AND CREAMS

PLIVA BECOMES A MEMBER OF THE TEVA GROUP, THE LARGEST GENERIC PHARMACEUTICAL COMPANY WORLDWIDE

A NEW INVESTMENT CYCLE, ONE OF THE BIGGEST IN THE COMPANY’S HISTORY. OVER THE NEXT SEVERAL YEARS, THE NEW PRODUCTION FACILITY FOR ACTIVE PHARMACEUTICAL INGREDIENTS WILL BE BUILT AT PLIVA’S SITE IN SAVSKI MAROF. THE EXPANSION OF PRODUCTION CAPACITIES FOR ORAL SOLID FORMS AND INJECTIONS AND THE INTRODUCTION OF NEW TECHNOLOGIES TO THE PRODUCTION AND PACKAGING OF FINISHED DOSAGE FORMS ARE UNDERWAY AT THE PRILAZ BARUNA FILIPOVIĆA SITE
Although PLIVA’s history starts with the establishment of the joint-stock company and factory Kaštel in Karlovac in 1921, manufacturing at PLIVA’s current site in Savski Marof dates back to as early as 1878, when the baron Dumreicher opened a factory and refinery for spirits and baker’s yeast. This factory was recognised as a pioneer in the industrialisation and economic development of Croatia for that time, and was subsequently renamed Žumberak, and in 1967 its name changed to PLIVA, Savski Marof site. The first president of the Board of the Joint-Stock Company Kaštel was Prof. Gustav Janaček, Ph.D. who, in cooperation with Eugen Ladany, Ph.D., started the production of pharmaceutical and galenical preparations thus paving the way for the modern production of medicinal products in this region. A team of enthusiasts, guided by a passion for science and its values, started with researching and developing new medicines soon after the establishment of Kaštel. Organised research work at PLIVA started in 1936 in cooperation with Prof. Vladimir Prelog from the University of Zagreb, later a Nobel Prize Laureate for chemistry. In 1936 Kaštel launched and patented sulfanilamide, an active substance with bacteriostatic effects, under the name Streptazol and thus became one of the first sulfonamide manufacturers in the world. The production of vitamin C started in 1953 and it was based on the in-house patented technology. The production of oxytetracycline and vitamin B6 started
soon after. In the middle of the fifties PLIVA had galenic, tablet and injection departments, and in 1952 it founded its own Research Institute. The department for the preparation of production worked on granulation, granulate drying and tablettting. Although it had modest equipment, some tablets were sugar coated even back then. In addition to finished dosage forms, PLIVA currently also manufactures a large number of active pharmaceutical ingredients.

The discovery of azithromycin, the first azalide antibiotic, was a landmark in both PLIVA’s history and the history of the entire Croatian pharmaceutical industry. This discovery made PLIVA one of the few pharmaceutical companies with an in-house developed original medicine and Croatia one of only nine countries with its own antibiotic. Thanks to its outstanding therapeutic properties, Sumamed has become and remained one of the most successful blockbuster medicines worldwide.

Until about twenty years ago PLIVA was a typical local company, generating about 75% of its revenues from medicines on the domestic market. Following its successful privatisation, expansion to new markets and business operations in a number of countries, PLIVA was transformed from a local player into a strong regional player and one of the most well-known brands in Central and Eastern Europe.

The investment cycle reached its peak in the nineties with the opening of the new production facilities for azithromycin in Savski Marof and oral solid forms in Zagreb, as well as the opening of the New Research Institute. The main focus in PLIVA’s business at that time was its internationalisation. Following its shift to the generic business, PLIVA became a member of the US-based company Barr in 2006, and again changed its owner in 2008 when it became a member of the Israeli Teva. PLIVA, now a member of the Teva Group, is the largest pharmaceutical company in Croatia and the leading pharmaceutical company in Southeast Europe.
Quality is the guiding principle for all PLIVA employees and its entire business operations. Since medicinal products are special purpose products, they have to be safe and efficient and meet appropriate quality specifications and all marketing authorisation requirements. The entire process – from purchase of active pharmaceutical ingredients to product release from the factory and its transportation to wholesalers or hospitals – is meticulously controlled and consistently in full accordance with current Good Manufacturing Practice (cGMP) standards.

Experts from PLIVA’s Quality Assurance work in laboratories with state-of-the art equipment and use leading edge analytical instruments, methods and technologies.

PLIVA’s production site in Zagreb specialises in the production of oral solid forms, sterile forms, creams and ointments. Thanks to approvals by the US Food and Drug Administration (FDA), the British Medicines and Healthcare Products Regulatory Agency (MHRA) and those of other relevant European agencies, PLIVA is among manufacturers complying with the highest global quality standards required for international markets. Operations in Zagreb play a very important role in the Teva Group and the production site in Zagreb is one of the strategic production sites for the entire Teva Group.
Finished dosage forms, such as tablets, film coated tablets, capsules, dry syrups, dry and liquid injections, creams, ointments, gels and suppositories, are manufactured at PLIVA's site in Zagreb.

The production is highly automated and follows a gravity flow principle in separate and independent production modules.

The production facility also houses high-rack storage, with a fully automated system for delivery and dispatch of raw materials, semi-finished products and finished products either from the reception area to the warehouse or individual production rooms, or from high-rack storage and individual production lines to the in-process finished products warehouse.

All PLIVA's production facilities meet the highest production standards and requirements of the relevant regulatory authorities in the markets for which the products are intended, including the most demanding American market.

The safety of production processes and employees is very high and complies with all necessary work safety and environmental standards.
The production process starts with the delivery of palletised raw materials from the automated raw materials warehouse to weighing rooms on the fifth floor. The weighed raw materials are then delivered by gravity flow to bins located on the filling stations beneath the weighing rooms, which open automatically when weighing begins. The bins are then automatically transported to the sixth floor where their contents are mixed in a specially constructed homogenisation device. All materials from bins are vertically transported via specially designed openings in floors or ceilings of production rooms. After mixing, bins are again automatically transported to the fifth floor for granulation, whereby the powdery mixture of raw materials turns into granules using the appropriately prepared binders. The bins with granulates are transported using the automatic material handling system to the area above the modules situated on the third floor and intended for regranulation or sieving. Once regranulation and homogenisation (if necessary) are finished, granulates are automatically transported to the first floor, which houses the appropriate modules for tabletting complying with all GMP requirements. After tabletting, some tablets are film or sugar coated in line with prescribed technological procedures. After coating, film coated tablets are released from the coating machine to reception containers, which are then transported to packaging lines.

This production is specific because it is carried out in completely sterile conditions and the organisation of work is adjusted to stringent requirements set for the production of these sterile products. The process begins with the weighing of raw materials and continues with the sterile manufacture of solutions, sterile filtration into special containers or directly to the filling line, for glass ampoules or vials, depending on a product. Ampoules are sealed on the filling line and transferred to the next production phase. For products requiring terminal sterilisation, ampoules are sterilised in steam sterilisers after filling. For products undergoing freeze drying, products are filled into glass bottles, which are then placed in the freeze-dryer for conversion of the solution from liquid to powdery form. After the freeze drying of bottles or terminal sterilisation of ampoules, the bottles and ampoules are inspected on the machine for visual inspection. The product is then labelled, packed and prepared for transportation to the packaging plant.
This production includes the production of creams, ointments, gels and suppositories. The production process starts with heating of the binder, then excipients are added to the binder and the process finishes with the adding of active substances to the prepared mixture. The mixture, which is then heated, cooled and kept at temperatures defined for each individual product, is automatically discharged from the machine, filled into appropriate metal containers and transported to the filling machine for plastic or aluminium tubes, depending on a product. Filled, closed, labelled and inspected tubes are machine packed into individual and then collective cardboard boxes and prepared for transportation to the warehouse.

The activities are carried out on several floors of a single facility. The packaging of injections in ampoules is carried out on the third floor. After production on the second floor, the ampoules are automatically transported to labelling machines, where they are labelled individually and each given a batch number and expiry date. Labelled ampoules are packed into plastic blisters, and then into individual and collective cardboard boxes. The packaging of solid forms (tablets, film coated tablets and capsules) is carried out on the ground floor and on the first floor. These products are packed on highly automated packaging lines into plastic blisters or bottles and, to a lesser extent into glass bottles, and then into cardboard packaging.

All parts of the packaging plant are connected to other plants with the common automated system for transportation of materials, which transports packaging materials and semi-finished products intended for packaging to and from the production plant. This high level automation also enables high level control and security in warehousing and handling printed packaging material. This is especially important in the production of pharmaceuticals which requires a high level of safety and protection against counterfeiting.
PLIVA is the only pharmaceutical company in Croatia with fully integrated production. Vertical integration enables superior attention to be given to the quality of all products.

**A BROAD PRODUCT PORTFOLIO**

A broad product portfolio is divided into several therapeutic groups, the major ones being: cardiovascular, gastrointestinal, anti-infectives, oncology, musculoskeletal, neurological and psychiatric diseases.

**COOPERATION WITH THE ACADEMIC AND SCIENTIFIC COMMUNITY**

PLIVA regularly collaborates with leading Croatian scientific and higher education institutions, especially with the Faculty of Pharmacy and Biochemistry, Faculty of Chemical Engineering and Technology, Faculty of Science and the Ruđer Bošković Institute. PLIVA’s experts and scientists contribute to the work of the scientific community by attending and organising scientific and professional symposia, participating in the work of professional societies and associations and through significant publishing efforts. They also partly organise lectures or teach at universities as guest professors or are mentors to students whose research for their bachelor theses also includes work in PLIVA’s laboratories.
As part of their subject “Industrial Pharmacy”, the fifth year students from the Faculty of Pharmacy and Biochemistry visit PLIVA to familiarise themselves with laboratory work and production of oral solid forms, which are especially important for the understanding of the overall process of production of medicinal products.

For the first time the students from the Faculty of Pharmacy and Biochemistry participated in the Case Study Competition 2011. They had to be very creative in developing a communication strategy for contraception methods and protection of reproductive health of adolescents, as well as in improving methods and tools for communicating key messages.

**COOPERATION WITH PHARMACISTS**

PLIVA’s pilot project intended for on-line training of pharmacists, the first of this kind in Croatia, is about to start. Pharmacists are increasingly expected to share the knowledge of pharmacy and medicine with end users, i.e. to educate them about the importance of prevention and appropriate treatment.

Quick and easy access to reliable and credible clinical information is important for pharmacists in advising individual patients, especially given the current trends of focusing on personalised medicine and healthcare.

**PHARMACISTS AT PLIVA**

PLIVA currently employs more than 100 pharmacists, working in various segments: from research and development, through to production and regulatory affairs and commercial operations. They are an important part of the entire system and one of the basic employee profiles that we hire.
Basic production and packaging processes for oral solid forms (tablets, capsules)
Production of freeze-dried sterile forms in bottles

Control of production environment

Preparation

Production of water for injection

Weighing

Additional preparation

- Filter integrity control

PREPARATION OF SOLUTION

Sterile filtration

- pH control
- Bioburden control

- Filter integrity control

FREEZE DRYING

Filling

- Filling volume control

Al capping

Sterilisation of Al caps

Visual inspection

Stoppering

Sterilisation and drying of stoppers

Labelling

- Stopper and cap position control
- Label identification
- Print data control
- Labelling control

Transport to packaging

Washing and sterilisation of bottles