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University of Zagreb
Faculty of Economics & Business

PHARMACEUTICAL INDUSTRY – CASE OF CROATIA

Final Thesis

Luka Kolobarić

Zagreb, September 2019

University of Zagreb
Faculty of Economics & Business

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Final Thesis

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Zagreb, September 2019.

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SUMMARY

The impact that the pharmaceutical industry, as one of the most important and most profitable industries in the world, has on the economic and social aspect of the Croatian economy has prompted a deeper exploration of this topic. The aim of the paper is to describe the principles of operation and business of the pharmaceutical industry in Croatia. The motive for further study of the topic is to explain the economic consequences of doing business in this industry in Croatia. The topic will be presented initially by explaining the terms pharmacy and pharmaceutical industry, the historical description of pharmacy as a science and profession, and the development of the pharmaceutical industry worldwide. The focus is then placed on the Republic of Croatia, the beginnings of the pharmaceutical industry in Croatia, the legal frameworks in which the pharmaceutical industry operates today, and the current state of the domestic pharmaceutical market (employees, average salaries, major economic indicators, and consumption and turnover of medicines). In the next part, it will be about pharmaceutical companies in Croatia. The operations of the three largest companies in Croatia will be presented; PLIVA Ltd, Belupo JSC and JGL JSC. At the end of the paper, we will critically reflect on the data collected and draw conclusions about the paper presented.

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1. INTRODUCTION

1.1 The objective of the thesis

The subject of this thesis is the analysis of the pharmaceutical industry in the Republic of Croatia. The aim is to explain more closely the concept of pharmacy and pharmaceutical industry, historical development and the current situation in Croatia. The impact of the pharmaceutical industry in the Republic of Croatia and the work of the largest companies in the sector will be analyzed.

Historical overview, number of employees, average gross and net salaries, major economic indicators, turnover and consumption of medicines are some of the aspects of the pharmaceutical industry that are one of the most important economic factors on the global scene.

1.2 Data sources and methods of collection

In this paper, professional literature in the field of business operations of companies was used as the main source of data. As this paper deals with the Croatian pharmaceutical industry, some of the literature is taken from official reports. The reports have been issued by the competent authorities of the Croatian Medicines and Medical Devices Agency (Croatian: Agencija za lijekove i medicinska sredstva Hrvatske, HALMED), the Financial Agency of Croatia (Croatian: Financijska Agencija, FINA) and the Central Bureau of Statistics of the Republic of Croatia (Croatian: Državni zavod za statistiku, DZS). Some of the literature was downloaded from the Internet, from the official websites, where it is was possible to find a good source of information about the pharmaceutical companies' business and the impact they have on the economies of the countries in which they operate.

1.3 Content and structure of paper

The paper is divided into 5 chapters. The first chapter is an introduction, where the subject and objectives of the paper, the sources of data and methods of collection, and the content and structure of the paper are presented.

The second part is the historical development of the pharmaceutical industry, which shows the conceptual definition of the terms pharmacy and pharmaceutical industry, the development of pharmacy throughout history in the world, the development of the pharmaceutical industry and the current state of the global pharmaceutical industry.

The third part presents the pharmaceutical industry in the Republic of Croatia. The historical overview and the beginning of the industry in Croatia are presented, the current legal framework for the functioning of the industry in Croatia, the number of employees in the pharmaceutical industry sector, the average gross and net salaries, and the main economic indicators. Also, drug consumption and turnover are reported, according to regulatory authorities.

The fourth part of this paper presents a list of pharmaceutical companies in Croatia. The three largest pharmaceutical companies in Croatia - PLIVA Ltd, Belupo JSC and JGL JSC - were selected for a detailed business analysis.

The paper ends with fifth part, where conclusions on the topic are presented.

2 PHARMACEUTICAL INDUSTRY THROUGH HISTORY

2.1 The terms Pharmacy and Pharmaceutical Industry

The word pharmacy is a version of the early French word *pharmacie*, which meant a substance either in the form of food or medicine with a laxative effect, and the French took it from the medieval Latin term *pharmacia*, which in turn was derived from the Greek term *pharmakon* (Greek: *Φάρμακον*) which literally in translation, it means "medicine, poison, magic." Accordingly, today's modern definition describes pharmacy (apothecary) as the art and science of finding, designing and manufacturing medicinal preparations, and of monitoring and recording their effects and side effects (Thomas, 2008, p. 98).

It is a highly regulated profession in the field of biomedicine and health, whose main (but not the only) employees are pharmacists, with a profile of higher or secondary education. Pharmacy, as a science, discipline and business field, can be divided into several different groups today, such as public pharmacy, hospital pharmacy, clinical pharmacy, pharmaceutical

industry, nuclear pharmacy, military pharmacy, medical biochemistry and laboratory diagnostics, and a number of other fields and discipline.

According to such a division, the pharmaceutical industry is one part of the pharmacy, which deals with the predominantly synthetic part of the pharmacy, through the discovery, development, production and marketing of medicinal substances in the form of pharmaceutical preparations (McGuire, Bode and Zahn, 2007, p. 334). While pharmacy is the center of research and action in most cases, it has a human body and a cure, and all the environmental factors that can affect the two concepts; the pharmaceutical industry is narrowly specialized in medicines and pharmaceuticals, and their life cycle. The pharmaceutical industry can engage in the production of innovative, new medicinal products or the generic production of medicines (medicines whose patent rights have expired, which enables other legal entities to manufacture and market them).

The pharmaceutical industry is today a powerful economic factor in many countries, as it is one of the industries with the greatest impact on the economy. Among the 50 largest companies in the world with the highest revenues, there are two that deal exclusively with the pharmaceutical industry; AmerisourceBergen Corporation with more than \$ 167.939 billion in revenue and Cardinal Health, Inc. with a revenue more than \$ 136.80 billion USD (Murphy et al., 2019).

The largest global leaders in the pharmaceutical industry today are the markets of the United States (US), European Union (EU) and Japan.

The pharmaceutical industry in Croatia also has a strong position as one of the great drivers of the economy. The Government of the Republic of Croatia has recognized this type of industry as a strategic and valuable investment: *"The pharmaceutical industry in Croatia has a long tradition. Because of its know-how and an experienced workforce, a successful development of the industry and related sectors in the future is assured. Furthermore, the pharmaceutical industry is one of the sectors of the Croatian economy where investment in research and development is extensive."* (Ministry of Economy, 2019).

Figure 1. Infographic showing pharmaceutical industry data nowadays in Croatia

PHARMACEUTICAL INDUSTRY

of Croatia in numbers

NOWADAYS IN CROATIA

DATA

number of
pharmaceutical
companies



50

number of
employees



4,357

average gross
salary in euros



1,913

share in total
exports



7%

Source: data obtained from Central Bureau of Statistics, 2018

2.2 Pharmacy and Pharmaceutical Industry until the 19th century

Pharmacy has an ancient history and one could say it is old as man himself. The oldest records of pharmacy date back to the 6th century BC, referring to ancient records of Sanskrit medicines. Records of medicines and medicinal substances can be found throughout the Old World, especially in Mesopotamia and Egypt, whose civilizations have a valuable historical heritage. In particular, the so-called *Ebers Papyrus*, an ancient Egyptian record dating from 1550 BC. which describes pharmacological knowledge and procedures of the time. Chinese history also encompasses a number of works and records, most of which relate to herbal preparations, with the oldest records dating back to the 1st century BC. Since ancient times, the pharmacist has been positioned in the Japanese culture for the highest place in the health care system, as evidenced by records that already in the 8th century describe the role and tasks of the person performing the duties of pharmacist. The profession is regulated to such a person, and is placed above other related activities, such as doctors or acupuncturists, and even in the hierarchy and above the emperor's personal doctors (Titsingh , 1834, p. 434).

In the Middle East, more precisely in Baghdad, the first pharmacies opened as early as the 8th century. Rich Greek history was fertile ground for both the historical heritage of medicine and pharmacy, so we know of Diocles of Carystus, a famous ancient scientist who studied the medicinal properties of plants and is historically located in the 4th century BC. However, the most famous Greek contribution to ancient pharmacy was made by Pedanius Dioscorides, writing the monumental work *De Materia Medica*, (Latin, On Medicinal Substances), which would serve as the basis for all later medieval texts on medicinal substances.

Ancient Rome was also a place where pharmacy has its deep roots in the works of many physicians and philosophers. Aelius Galenus or Claudius Galenus, often Anglicized as Galen and better known as Galen of Pergamon was a Greek physician, surgeon and philosopher in the Roman Empire. Arguably the most accomplished of all medical researchers of antiquity, Galen influenced the development of various scientific disciplines, including anatomy, physiology, pathology, pharmacy and neurology, as well as philosophy and logic. Galen is considered the father of medicine and pharmacy, as these two sciences were part of the same field until the 13th century. Galen's original Greek texts gained renewed prominence during the early modern period. In the 1530s, Belgian anatomist and physician Andreas Vesalius

took on a project to translate many of Galen's Greek texts into Latin. Vesalius's most famous work, *De humani corporis fabrica*, was greatly influenced by Galenic writing and form (Dear, 2019).

The Middle Ages represented a tremendous advance in the development of pharmacy and medicine, as a science and profession. In the Middle Ages there was a rapid development of botany and chemistry, which directly resulted in new trends in the pharmaceutical industry. A new discipline is emerging, pharmacology, which is inextricably linked to pharmacy. Pharmacology is actually a branch of biology, which deals with the mechanism of action of a drug, a medicinal product made by man, present in nature or endogenous substances (Vallance and Smart, 2006). In particular, these new trends in pharmaceutical business have been seen in the cultures of today's Middle East. Notable pharmacists and pharmacy-related workers in the Middle Ages include Abu al-Qasim al-Zahrawi who pioneered in the preparation of medicines by sublimation and distillation. His *Liber servitoris* is of particular interest, as it provides the reader with recipes and explains how to prepare the *simples* from which were compounded the complex drugs then generally used. Sabur Ibn Sahl, was, however, the first physician to initiate pharmacopoeia, describing a large variety of drugs and remedies for ailments. Al-Biruni wrote one of the most valuable Islamic works on pharmacology, entitled *Kitab al-Saydalah* (Arab, The Book of Drugs), in which he detailed the properties of drugs and outlined the role of pharmacy and the functions and duties of the pharmacist. Avicenna, too, described no less than 700 preparations, their properties, modes of action, and their indications. He devoted in fact a whole volume to simple drugs in The Canon of Medicine. Avicenna represents one of the most notable pharmacists in the Middle Ages (Levery, 2005).

Figure 2. Physician and Pharmacist, illustration from *Medicinarius* (1505) by Hieronymus Brunschwig.



Source: Wikipedia,

<https://en.wikipedia.org/wiki/Pharmacy#/media/File:Legenogapotekeren.jpg>

After the 5th century fall of the Western Roman Empire, medicinal knowledge in Europe suffered due to the loss of Greek medicinal texts and a strict adherence to tradition, although an area of Southern Italy near Salerno remained under Byzantine control and developed a hospital and medical school, which became famous by the 11th century (Sneader , 2014).

In the early 11th century, Salerno scholar Constantinos Africanus translated many Arabic books into Latin, driving a shift from Hippocratic medicine towards a pharmaceutical-driven approach advocated by Galen (Sneader, 2014). In medieval Europe, monks typically did not speak Greek, leaving only Latin texts such as the works of Pliny available until these translations by Constantinos. In addition, Arabic medicine became more widely known due to Muslim Spain.

During the 12th century in Europe, shops that were like a concept of a modern pharmacy started opening. The workers in the shops were often called apothecaries, chemists and pharmacists. The pharmacy profession was still considered the same as the physician's profession, without clean boundaries on what were the roles and obligations of those health workers. That was the situation until the year 1231, when the Holy Roman Emperor Frederick

II issued the infamous *Edict of Salerno* (in literature also referred as Constitution of Salerno). This was the first law that made the first legally fixed separation of the occupations of physician and apothecary. Physicians were forbidden to double as pharmacists and the prices of various medicinal remedies were fixed. This became a model for regulation of the practice of pharmacy throughout Europe (Rashdall, 1895, p. 85). Historians and pharmacist consider this year as the beginning of the modern-day pharmacy and medicine practice; a birth-year of pharmacy.

The *Edict of Salerno* made it possible to continue with legal boundaries in opening and managing pharmacy-like shops through Europe. It is not known which establishment was the first of this kind in Europe. Some argue that it is Italy, claimed to have been set up in 1221 in the Church of Santa Maria Novella in Florence, which now houses a perfume museum. but the oldest pharmacy that is still working is located in Trier, Germany. Croatian pharmacy history also has deep roots, as there is a pharmacy still operating in Dubrovnik, Croatia, located inside the Franciscan monastery, opened in 1317; as well as the one opened in Trogir. Notable pharmacies include the one in the Town Hall Square of Tallinn, Estonia, dating from at least 1422. The medieval Esteve Pharmacy, located in Llívia, a Catalan enclave close to Puigcerdà, also now a museum, dates back to the 15th century, keeping albarellos from the 16th and 17th centuries, old prescription books and antique drugs.

Figure 3. Sign of the Town Hall Pharmacy in Tallinn, operating continuously from at least 1422



Source: Wikipedia, https://en.wikipedia.org/wiki/Pharmacy#/media/File:Raeapteek_sign.jpg

Pharmaceutical science improved markedly in the 16th and 17th centuries. In 1546 the first pharmacopoeia or collected list of drugs and medicinal chemicals with directions for making pharmaceutical preparations, appeared in Nürnberg, Germany. Previous to this time, medical preparations had varied in concentration and even in constituents. Other pharmacopoeias followed in Basel (1561), Augsburg (1564), and London (1618). The London Pharmacopoeia became mandatory for the whole of England and thus became the first example of a national pharmacopoeia. Another important advance was initiated by Paracelsus, a 16th-century Swiss physician-chemist. He admonished his contemporaries not to use chemistry as it had widely been employed prior to his time in the speculative science of alchemy and the making of gold. Instead, Paracelsus advocated the use of chemistry to study the preparation of medicines.

From 1231 until the 19th century, pharmacy as a science and profession grew and developed according to world changes. Pharmacist became notable members of the society with a major influence on science, art and social circumstances. Pharmaceutical sciences started developing, as well as different specialized pharmaceutical disciplines such as: community pharmacy, hospital and ambulatory pharmacy, pharmacognosy... Pharmaceutical industry is a part of pharmacy practice that we can trace back to the 19th century and the beginning of pharmaceutical research and opening first pharmaceutical factories.

2.3 Pharmaceutical Industry from the 19th century until today

As we are able to trace the beginning of the pharmaceutical industry back to the first apothecaries, it is possible to say that the role distributing botanical drugs such as morphine and quinine to wholesale manufacture in the mid-1800s can be considered as the beginning of industrial pharmacy. Rational drug discovery from plants started particularly with the isolation of morphine, analgesic and sleep-inducing agent from opium, by the German apothecary assistant Friedrich Sertürner (Sneader, 2014). By the late 1880s, German dye manufacturers had perfected the purification of individual organic compounds from tar and other mineral sources and had also established rudimentary methods in organic chemical synthesis. The development of synthetic chemical methods allowed scientists to systematically vary the structure of chemical substances, and growth in the emerging science of pharmacology expanded their ability to evaluate the biological effects of these structural changes.

In 1820 quinine (malaria treatment) was isolated from cinchona bark and colchicine (gout treatment) from autumn crocus. In 1833 atropine (variety of uses) was purified from *Atropa belladonna*, and in 1860 cocaine (local anesthetic) was isolated from coca leaves. Isolation and purification of these medicinal compounds was of tremendous importance for several reasons. First, accurate doses of the drugs could be administered, something that had not been possible previously because the plants contained unknown and variable amounts of the active drug. Second, toxic effects due to impurities in the plant products could be eliminated if only the pure active ingredients were used. Finally, knowledge of the chemical structure of pure drugs enabled laboratory synthesis of many structurally related compounds and the development of valuable drugs.

Pain relief has been an important goal of medicine development for millennia. Prior to the mid-19th century, surgeons took great pride in the speed with which they could complete a surgical procedure. Faster surgery meant that the patient would undergo the excruciating pain for shorter periods of time. In 1842 ether was first employed as an anesthetic during surgery, and chloroform followed soon after in 1847. These agents revolutionized the practice of surgery. After their introduction, careful attention could be paid to prevention of tissue damage, and longer and more-complex surgical procedures could be carried out more safely. Although both ether and chloroform were employed in anesthesia for more than a century, their current use is severely limited by their side effects; ether is very flammable and explosive, and chloroform may cause severe liver toxicity in some patients. However, because pharmaceutical chemists knew the chemical structures of these two anesthetics, they were able to synthesize newer anesthetics, which have many chemical similarities with ether and chloroform but do not burn or cause liver toxicity (Dailey, 2018).

In the prevention of infectious diseases, an even more important innovation took place near the beginning of the 19th century with the introduction of smallpox vaccine. In the late 1790s the English surgeon Edward Jenner observed that milkmaids who had been infected with the relatively benign cowpox virus were protected against the much more deadly smallpox. After this observation he developed an immunization procedure based on the use of crude material from the cowpox lesions. This success was followed in 1885 by the development of rabies vaccine by the French chemist and microbiologist Louis Pasteur. Widespread vaccination programs have dramatically reduced the incidence of many infectious diseases that once were common. Indeed, vaccination programs have eliminated smallpox infections. The virus no longer exists in the wild, and, unless it is reintroduced from caches of smallpox virus held in

laboratories in the United States and Russia, smallpox will no longer occur in humans. A similar effort is under way with widespread polio vaccinations; however, it remains unknown whether the vaccines will eliminate polio as a human disease (Encyclopaedia Britannica: Pharmaceutical industry).

In the latter part of the 19th century a number of important new classes of pharmaceuticals were developed. In 1869 chloral hydrate became the first synthetic sedative-hypnotic (sleep-producing) drug. In 1879 it was discovered that organic nitrates such as nitroglycerin could relax blood vessels, eventually leading to the use of these organic nitrates in the treatment of heart problems. In 1875 several salts of salicylic acid were developed for their antipyretic (fever-reducing) action. Salicylate-like preparations in the form of willow bark extracts (which contain salicin) had been in use for at least 100 years prior to the identification and synthesis of the purified compounds. In 1879 the artificial sweetener saccharin was introduced. In 1886 acetanilide, the first analgesic-antipyretic drug (relieving pain and fever), was introduced, but later, in 1887, it was replaced by the less toxic phenacetin. In 1899 aspirin (acetylsalicylic acid) became the most effective and popular anti-inflammatory, analgesic-antipyretic drug for at least the next 60 years. Cocaine, derived from the coca leaf, was the only known local anesthetic until about 1900, when the synthetic compound benzocaine was introduced. Benzocaine was the first of many local anesthetics with similar chemical structures and led to the synthesis and introduction of a variety of compounds with more efficacy and less toxicity (Encyclopaedia Britannica: Pharmaceutical industry).

In the late 19th and early 20th centuries, a number of social, cultural, and technical changes of importance to pharmaceutical discovery, development, and manufacturing were taking place. One of the most important changes occurred when universities began to encourage their faculties to form a more coherent understanding of existing information. Some chemists developed new and improved ways to separate chemicals from minerals, plants, and animals, while others developed ways to synthesize novel compounds. Biologists did research to improve understanding of the processes fundamental to life in species of microbes, plants, and animals. Developments in science were happening at a greatly accelerated rate, and the way in which pharmacists and physicians were educated changed (Anderson, 2005, p. 119).

Prior to this transformation the primary means of educating physicians and pharmacists had been through apprenticeships. While apprenticeship teaching remained important to the education process (in the form of clerkships, internships, and residencies), pharmacy and

medical schools began to create science departments and hire faculty to teach students the new information in basic biology and chemistry. New faculty were expected to carry out research or scholarship of their own. With the rapid advances in chemical separations and synthesis, single pharmacists did not have the skills and resources to make the newer, chemically pure drugs. Instead, large chemical and pharmaceutical companies began to appear and employed university-trained scientists equipped with knowledge of the latest technologies and information in their fields (Encyclopaedia Britannica: Pharmaceutical industry).

As the 20th century progressed, the benefits of medical, chemical, and biological research began to be appreciated by the general public and by politicians, prompting governments to develop mechanisms to provide support for university research. In the United States, for instance, the National Institutes of Health, the National Science Foundation, the Department of Agriculture, and many other agencies undertook their own research or supported research and discovery at universities that could then be used for pharmaceutical development. The symbiotic relationship between large public institutions carrying out fundamental research and private companies making use of the new knowledge to develop and produce new pharmaceutical products has contributed greatly to the advancement of medicine (Encyclopaedia Britannica: Pharmaceutical industry).

The next great advance in the development of drugs for treatment of infections came in the 1930s, when it was shown that certain azo dyes, which contained sulfonamide groups, were effective in treating streptococcal infections in mice. One of the dyes, known as Prontosil, was later found to be metabolized in the patient to sulfanilamide, which was the active antibacterial molecule. In 1933 Prontosil was given to the first patient, an infant with a systemic staphylococcal infection. The infant underwent a dramatic cure. In subsequent years many derivatives of sulfonamides, or sulfa drugs, were synthesized and tested for antibacterial and other activities.

One of the biggest discoveries in the history of the pharmaceutical industry was the discovery of penicillin. The first description of penicillin was published in 1929 by the Scottish bacteriologist Alexander Fleming. Fleming had been studying staphylococcal bacteria in the laboratory at St. Mary's Hospital in London. He noticed that a mold had contaminated one of his cultures, causing the bacteria in its vicinity to undergo lysis (membrane rupture) and die. Since the mold was from the genus *Penicillium*, Fleming named the active antibacterial substance penicillin. At first the significance of Fleming's discovery was not widely

recognized. It was more than 10 years later before British biochemist Ernst Boris Chain and Australian pathologist Howard Florey, working at the University of Oxford, showed that a crude penicillin preparation produced a dramatic curative effect when administered to mice with streptococcal infections (Encyclopaedia Britannica: Pharmaceutical industry).

A notable moment in the history of pharmaceutical industry was the discovery of insulin and the work of Paul Langerhans, that led to opening doors for isolation and production of hormones; a new era for the pharmaceutical industry.

The pharmaceutical industry has become a large and very complex enterprise. At the end of the 20th century, most of the world's largest pharmaceutical companies were located in North America, Europe, and Japan; many of the largest were multinational, having research, manufacturing, and sales taking place in multiple countries. Since pharmaceuticals can be quite profitable, many countries are trying to develop the infrastructure necessary for drug companies in their countries to become larger and to compete on a worldwide scale. The industry has also come to be characterized by outsourcing. That is, many companies contract with specialty manufacturers or research firms to carry out parts of the drug development process for them. Others try to retain most of the processes within their own company. Since the pharmaceutical industry is driven largely by profits and competition—each company striving to be the first to find cures for specific diseases—it is anticipated that the industry will continue to change and evolve over time (Encyclopaedia Britannica: Pharmaceutical industry).

3 PHARMACEUTICAL INDUSTRY IN CROATIA

3.1 Development of Pharmacy in Croatia

It is already stated that Croatia has a very old history regarding pharmacy and pharmaceutical practice. First pharmacies were opened on the Croatian coast, by the influence of Venice. By the 18th century small city pharmacies were operating in all of Croatia. The birth of the Croatian pharmaceutical industry can be traced back to opening of the first drug factory in a small place named Pregrada. That was the place where Adolf Alfons Thierry, a pharmacist from Pregrada, built the first building intended only for pharmaceutical purposes. In the front of the building he placed a pharmacy called: *K angjelu čuvaru* (At the guardian angel), and

behind the building there were factory facilities. That was the first chemistry and pharmaceutical company in South-East Europe. By the beginning of the 20th century, more than 60 drugs were manufactured at that facility, and the most notable were Thierry's digestion balsam and wound ointment. (Flegar and Inić, 2017).

Later, in 1921 in a small place Kaštel, near Karlovac another pharmaceutical company was founded by the name of *Kaštel*. The company has expanded its drug assortment with the years and started with the productions of drugs and vaccines. Then the name of the company was changed to PLIVA, which is an abbreviation from the slogan in Croatian: *Proizvodnja lijekova i vakcina* (Manufacture of Drugs and Vaccines). The headquarters of the company were moved to Zagreb, where the production was conducted. The biggest success of Pliva was in 1980, when a group of Pliva experts: Slobodan Đokić, Gorjana Radoboja-Lazarevski, Zrinka Tamburašev and Gabrijela Kobrehel discovered a molecule called azitromicin, which was later patented as the antibiotic Sumamed, one of the best-selling antibiotics in the world. It was patented and manufactured in 1981. Sumamed was sold across the whole world, from the United States to Europe and Russia. In 2005 the Sumamed patent ended, which allowed other companies to manufacture it (Azithromycin: A world best-selling antibiotic – Pliva).

3.2 Legal framework for Pharmaceutical Industry in Croatia

The pharmaceutical industry is a tertiary activity that falls under activity classification Part 24.4. Manufacture of pharmaceutical, chemical and vegetable products for medical purposes. The pharmaceutical industry in the Republic of Croatia is subject to the following regulations:

- The Law on Medicines
- The Law on Medical Devices
- Law Implementing Regulation (EU) 2017/745 on Medical Devices and Regulation (EU) 2017/746 on In vitro Diagnostic Medical Devices
- Law on the Implementation of Regulation (EU) No 1095/2010. 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials of medicinal products for human use and repealing Directive 2001/20 / EC
- Law on Amendments to the Law on Veterinary Medicinal Products

The competent authority responsible for medicines, medicinal products and homeopathic medicines in accordance with the laws and regulations of the Republic of Croatia is the Agency for Medicinal Products and Medical Devices of the Republic of Croatia (HALMED), which is responsible to the Ministry of Health of the Republic of Croatia. HALMED's headquarters are in Zagreb. All legal entities wishing to market medicinal products, vaccines and medical devices in the Republic of Croatia are obliged to register in the register of HALMED related to the sector they are dealing with and are subject to the control of HALMED. In this regard, there are several sectors of the pharmaceutical industry in the Republic of Croatia.

These are:

- Wholesale of medical devices (523 legal entities registered with HALMED)
- Wholesale medical products and medicines (no legal entity registered with HALMED)
- Wholesale medicines (108 legal entities registered with HALMED)
- Wholesale veterinary medicinal products (no legal entity is registered with HALMED)
- Production license (23 legal entities registered with HALMED)
- Manufacturers, importers and wholesalers of active substances (14 legal entities registered with HALMED)
- Medical products and pharmaceuticals (139 legal entities registered with HALMED)
- Retail medical products (744 legal entities registered with HALMED)
- Mediation (2 legal entities registered with HALMED)
- Production of veterinary medicinal products (no legal entity is registered with HALMED) (HALMED, 2019).

Therefore, a large number of legal entities, enterprises are located in the pharmaceutical industry sector or are directly related to marketing in the field of pharmaceuticals and pharmaceuticals.

Today, the pharmaceutical industry, both in Croatia and in the European Union, and in most countries of the world, is a highly regulated profession, with clear rules and procedures. Being an industry that spends most of its resources on research & development (R&D), the

innovation of pharmaceutical companies is one of the most important determinants of their business.

The main product of the pharmaceutical industry is medicine, whether the new original medicine or its generic version. The brand name drug is a product of a pharmaceutical company that is based on a new active substance. Specifically, each drug consists of two components; the first is the active substance of the drug (the one that has an effect on the human body), and the second is the excipients (substances that are added to maintain the required physico and chemical properties as well as stability). A generic drug, on the other hand, is a drug that contains the same active substance but is not made by the original drug manufacturer but by another pharmaceutical company. A series of tests and analyses show that there is no difference in the effect of brand name and generic drugs (Desai et al., 2019).

A legal entity, a pharmaceutical company that produces a new active substance, has the right to register and patent it in the form of a new drug. It is estimated that it takes approximately 12 years for the drug to be released into free circulation from the first studies. This is because of a series of laboratory and clinical tests that need to be performed on the new active substance in order to establish its safety profile. Pharmaceutical companies are investing enormous material and financial resources in the process, which is why they retain the right to patent a new drug for about 20 years after the entry of a new active substance into the free market (Götzsche, 2018). Upon expiration of such a patent, all other pharmaceutical companies have the right to manufacture their own medicine, which contains the active substance the same as the brand name drug. These are generic drugs on the market.

The production of a new drug or new active substance is also regulated by various legal solutions, both in the Republic of Croatia and in the European Union, of which Croatia is a full member, and is subject to the directives of the European Commission, the European Medicines Agency (EMA) and its permanent bodies:

- Committee for Medicinal Products for Human Use (CHMP)
- Pharmacovigilance Risk Assessment Committee (PRAC)
- Committee for Medicinal Products for Veterinary Use (CMVP)
- Committee for Orphan Medicinal Products (COMP)
- Committee on Herbal Medicinal Products (HMPC)
- Committee for Advanced Therapies (CAT)

- Pediatric Committee (PDCO)

The process of manufacturing a new drug can be divided into several parts:

- Preclinical research (approximately 3.5 years) - The pharmaceutical company conducts tests before the drug is even tested in humans, to verify its biological effect.
- Investigational New Drug Application (30 days) - a pharmaceutical company submits to the regulatory authority a request for a drug test in humans, which includes comprehensive documentation of the substance type, tests, toxic and biological effects, etc. If the regulatory authority does not refuse the request, the drug can be tested on people.
- Phase I clinical trials (approximately 1 year) - examines the effects of the drug, its characteristics and the impact on 20 to 80 healthy volunteers
- Phase II clinical trials (approximately 2 years) - include a much larger number of people and people with the disease for which the drug is intended
- Phase III clinical trials (approximately 3 years) - large trials in approximately 3,000 individuals, where all adverse drug reactions are recorded. This phase precedes the final registration of the medicinal product by the regulatory authority and its placing on the market.
- New Drug Application (approximately 2.5 years) - The pharmaceutical company collects all documentation and information known about the drug and submits a registration request to the regulatory authority, which is a document of approximately 100,000 pages.
- Phase IV clinical trials (lasts for the entire duration of the drug use) - performed on all patients after marketing authorization is granted. It's part of the pharmaceutical industry called pharmacovigilance - monitoring the side effects of post-registration medicines. This phase is also referred to as the post-marketing phase (Bahadur, 2008).

Because the development of a new drug may be interrupted at any time by the above stages, therefore, investments in the development of new drugs are accompanied by certain risks.

3.3 Number of Employees

According to the National Classification of Activities, the area of the pharmaceutical industry is classified in category C. MANUFACTURING (DZS, 2018).

According to the Central Bureau of Statistics, and data for the end of March 2019, there were 21,050 registered legal entities in this category, with 14,657 active ones. Almost all of them were profit ones, except for 3 active legal entities. State ownership in this sector holds 0.5% of the total number of active legal entities, while 96.8% is private property. Mix ownership holds 1.6% of this category. The number of employees in this category is as follows: 0 employees (3,571 legal entities), 1-9 (8,070), 10-49 (2,211), 50-249 (644), 250-449 (97), 500 and more (64). There are 244 active joint stock companies, 11,305 active limited liability companies, 2,895 active simple limited liability companies, 3 active public trade companies, 44 active major foreign trade subsidiaries or individual traders and 5 active other legal forms (DZS, 2019).

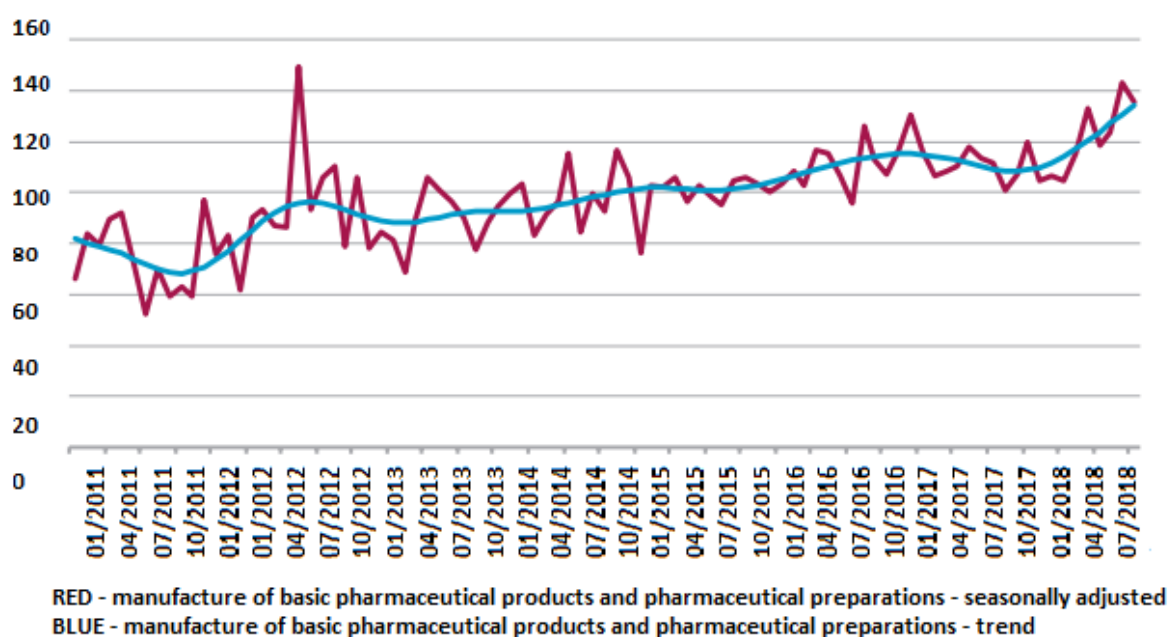
In the Republic of Croatia, data are available from the Central Bureau of Statistics on the number of employees in legal entities in the category of production of basic pharmaceutical products and pharmaceutical preparations. As can be seen in Table 1, there is an increase in the number of employees in this category, after a large decrease in the number of employees due to the global economic events that followed after 2009 and the recessionary crisis. In 2012, the lowest number of employees in this category (3,664 persons) is recorded, followed by an increase in the number of employees annually. However, the figures still did not reach the record levels recorded in 2000, when the number of employees in this category was 5,220 (data not shown in the table).

Year	2006	2007	2008	2009	2010	2012	2011	2013
Number of employees	3,900	4,149	4,897	4,225	3,843	3,664	3,918	3,939

Table 1. Number of persons in paid employment in legal entities in the category of production of basic pharmaceutical products and pharmaceutical preparations in the Republic of Croatia for the period from 2006 to 2013, DZS data

Tajana Barbić in her sector analysis *Farmaceutska industrija* (2019) states that the number of employees in the sector continued to increase beyond 2013, reaching 4,354 in 2016, again falling slightly to 4,332 in 2017, to increase again in the first six months of 2018. to 4,413 people. In July 2018, the number of employees in the Republic of Croatia was 0.3% lower than in the same month of 2017. In the same period, the total number of employees in the pharmaceutical industry decreased by 1.2%. The number of female employees, who traditionally make up almost 60% of the total number of employees in the pharmaceutical industry, also fell by 1.2% year-to-year in July 2017. However, from January to July this year, the number of employees in the pharmaceutical industry increased by 1.9%. Faster production growth than employee growth has resulted in an 8.9% increase in labor productivity in this industry from January to July 2018. It is interesting to note that of the total 4,332 employees in the pharmaceutical industry at the end of 2017; more than 89% of them are employees of the three largest companies in the sector (Barbić, 2019, p. 4).

Figure 4. Manufacture of basic pharmaceutical products and pharmaceutical preparations, original indices (2015 = 100)

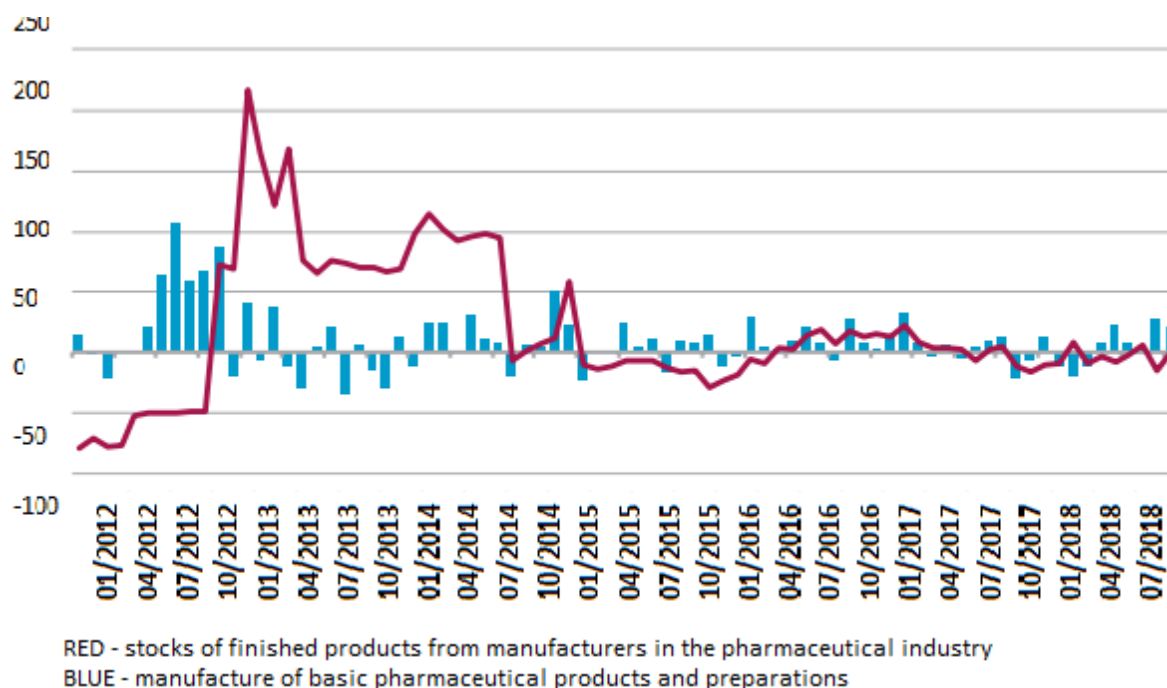


Source: Barbić, 2019, p. 4

Figure 4. shows that in the period of 2011 to July 2017, the manufacture of basic pharmaceutical products and pharmaceutical preparations has a growth trend, with almost a 75% increase in the observed period. It should be emphasized that the described trends in the

movement of inventories in the first seven months of this year are contrary to the trends from the previous year in the same period when inventories were growing.

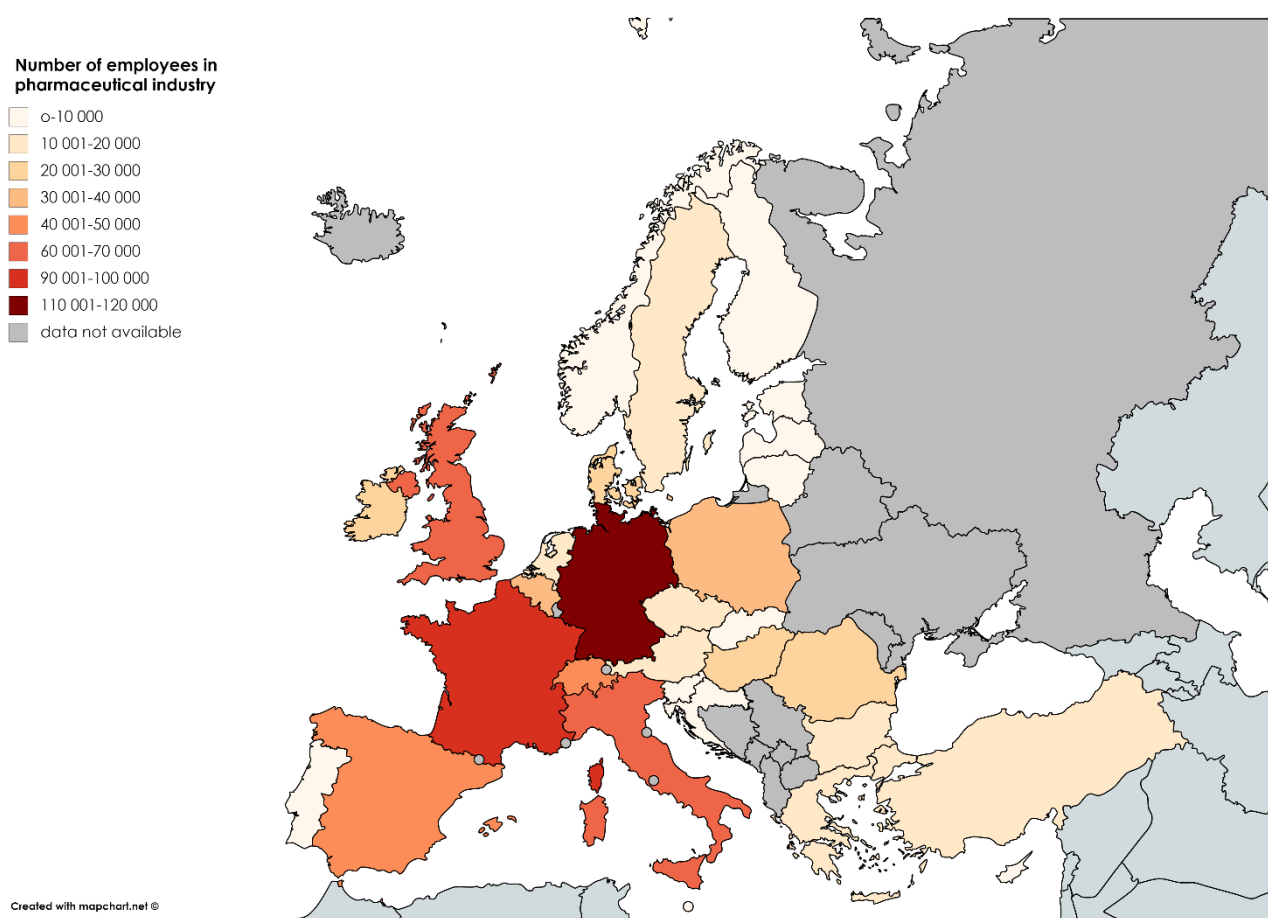
Figure 5. Manufacture of basic pharmaceutical products and preparations and inventories of finished products by manufacturers, year-to-year change rates



Source: Barbić, 2019, p.4

The pharmaceutical industry has maintained its position as one of the leading high-tech industries in Europe according to the European Federation of Pharmaceutical Industries Association (EFPIA) (The Pharmaceutical Industry in Figures, 2018) whose production in 2017 is estimated at 258 billion euros. In the same year, the pharmaceutical industry employed 750,000 people, of whom 115,000 were highly skilled in R&D activities. In 2016, the number of employees in this sector in Europe was 747,607, of which 45 percent were employed in pharmaceutical companies in Germany, France, the United Kingdom and Italy. Croatian companies in the pharmaceutical industry employed 0.8% of the total number of employees in the European pharmaceutical industry (The Pharmaceutical Industry in Figures, 2018).

Figure 6. Number of employees in pharmaceutical industry in European countries



Source: data obtained from The Pharmaceutical Industry in Figures, 2018

Unlike the Central Bureau of Statistics, EFPIA data shows slightly different figures related to the pharmaceutical industry in Croatia. Namely, according to EFPIA and full members of EFPIA, it is stated that in 2016 in Croatia the pharmaceutical industry employs about 6,000 people.

3.4 Average Net and Gross Earnings

In the Republic of Croatia, data from the Central Bureau of Statistics on average paid off net and gross salaries in legal entities in the category of production of basic pharmaceutical products and pharmaceutical preparations are available. As can be seen in Table 2, there has been an increase in the average net wage paid in the pharmaceutical industry, after a slight decrease due to the events related to the recession crisis (2009). The lowest average net salary

in this sector was measured in 2000, when it amounted to 5,118 Croatian kuna (Croatian: hrvatska kuna, HRK). This information is not shown in the table.

Year	2006	2007	2008	2009	2010	2012	2011	2013
Average monthly net wage	7,403	7,245	7,814	7,751	7,997	8,086	8,230	8,450

Table 2. Average monthly net earnings in Croatian Kuna (HRK) of legal persons in the manufacturing category of basic pharmaceutical products and pharmaceutical preparations in the Republic of Croatia for the period 2006 to 2013, DZS data

The average gross earnings of legal persons employed in the pharmaceutical industry are shown in Table 3.

Year	2006	2007	2008	2009	2010	2012	2011	2013
Average monthly gross wages	11,637	11,359	12,245	11,920	12,246	12,385	12,779	13,188

Table 3. Average monthly gross earning in Croatian Kuna (HRK) of legal entities employees in the production category of basic pharmaceutical products and pharmaceutical preparations in the Republic of Croatia for the period 2006 to 2013, DZS data

According to Barbić (2019), the average gross earnings of employees in the pharmaceutical industry in June 2018 increased by 5.2% compared to June 2017, reaching HRK 14,632. In June 2018, the gross wages of employees in the production of basic pharmaceutical products and preparations were 89% higher than the average gross wage paid in the manufacturing industry. In the same month, the gross wage in the pharmaceutical industry was 72% higher than the average gross wage in the economy.

3.5 Main economic indicators

At the year-to-year level, producer prices in the pharmaceutical industry have fallen in all months of 2018. In July, producer prices in the pharmaceutical industry decreased by 0.1% year-to-year. In the foreign market, producer prices in the pharmaceutical industry also decreased by 0.1% compared to July 2017, while the domestic market recorded a decline of

0.6% in the same period. Production prices in the total manufacturing industry are on the rise in 2018.

Consumer prices in the pharmaceutical industry increased by 1.1% year-to-year between January and June 2018. In the same period, total consumer prices increased by 1.4%. In July 2018, consumer prices in the pharmaceutical industry grew by 1.7%, while total consumer prices at the year-on-year level in July 2018 increased by 2.1%.

Year	2016	2017	I-VI 2018
Production activity (%)	12	0.4	10
Average number of employees	4,354	4,332	4,413
Average gross salary (HRK)	13,553	13,433	14,632
Consumer prices (%)	2.2	1.6	1.1
Export (in millions HRK)	6,760.8	8,587.2	3,560.9
Import (in millions HRK)	9,379.0	8,371.5	4,423.8
Foreign trade balance (in millions HRK)	-2,618.2	215.7	-862.9

Table 4. Main indicators of the pharmaceutical industry in Croatia (basic pharmaceuticals and pharmaceuticals) (Barbić, 2019)

In the first half of 2018, there was an increase in foreign trade in medical and pharmaceutical products on a year-on-year basis on the import side, which increased by 12.6% year-to-year. On the other hand, exports of medical and pharmaceutical products decreased by 12.2% year-to-year in the first half of this year. Consequently, foreign trade in medical and pharmaceutical products abroad generated a deficit of HRK 862.9 million, while a surplus of HRK 125.6 million was achieved in the first half of 2017. In comparison, during the same period, exports of goods at the economy level increased 2.5%, while imports increased by 6.0%, leading to a 11.7% year-to-year increase in the foreign trade deficit. Medical and pharmaceutical products worth HRK 3.6 billion were exported in the first half of 2018, which is 6.9% of total merchandise exports. Imports of medicines to Croatia reached HRK 4.4 billion in the first six months of 2018. During this period, imports of medical and pharmaceutical products contributed 5.1% to total imports of goods.

3.6 Drug turnover and consumption

The latest information on the consumption and marketing of medicines is that published by HALMED for 2017, pursuant to the Medicines Act (Official Gazette, Nos. 76/13, 90/14) and the Ordinance on the type of data and method of preparation of reports on consumption of medicines (Official Gazette, No. 122/14).

In the HALMED database for the monitoring of drug consumption, the drugs are classified into 14 groups of the World Health Organization (WHO) Anatomic Therapeutic-Chemical (ATC) classification system of drugs according to ATK and International Non-proprietary Name (INN). The basis for the preparation of the Report shall be a list of medicinal products authorized in the Republic of Croatia and a list of medicinal products that have been marketed in the Republic of Croatia which are not authorized for marketing under Article 129. Of the Medicinal Products Act (Official Gazette 76/13, 90/14) (the so-called "emergency import procedure").

Data on the number of original packs of medicines dispensed at pharmacies, hospital pharmacies, specialized retail stores and wholesalers were calculated defined daily doses per 1000 inhabitants per day (DDD / 1000 / day), and the turnover for each drug was expressed financially, totaling in HRK.

The report covers all data submitted to HALMED by legal and natural persons operating on the retail market of medicinal products, in accordance with the obligation in the Ordinance on the type of data and the manner of preparing the report on the consumption of medicinal products (Official Gazette, No. 122/14). 99.84% of all legal and natural persons involved in retail trade of medicinal products in the territory of the Republic of Croatia were provided to HALMED. As the data collected represent 99.84% of all possible data, they were increased by 0.16% by the extrapolation method, which gives the assumed total value of drug consumption in the Republic of Croatia for 2017. The extrapolated results presented by all subjects express a credible result.

Number	ATC code	ATC names	DDD/1000/day
1	C	Cardiovascular system	386.38
2	A	Alimentary tract and metabolism	177.15
3	N	Nervous system	172.51

4	B	Blood and blood forming organs	100.43
5	M	Muscular and skeletal system	65.83
6	R	Respiratory system	62.56
7	G	Genito-urinary system and sex hormones	28.94
8	H	Hormonal preparations	28.76
9	J	Anti-infectives	25.14
10	L	Antineoplastic and immunomodulatory agents	8.38
11	S	Sensory organs	3.63
12	P	Antiparasitic products	0.78
13	D	Dermatologicals	0.37
14	V	Various	0.27
TOTAL			1,061.11

Table 5. Total drug consumption in 2017 according to DDD / 1000 population / day by major ATK classification, according to HALMED data

Out-of-hospital consumption of medicines in the Republic of Croatia in 2017 amounted to 1,027.88 DDD / 1000 / day (97% of total consumption), which is an increase of 1.3% compared to 2016, while, financially, it amounted to HRK 3,784,476,557.00 (62% of the total) consumption), an increase of 4% over 2016. Hospital consumption of medicines in 2017 amounted to 33.23 DDD / 1000 / day (3% of total consumption), like, financially, a total of HRK 2,347,150,918.00 (38% of total consumption). The increase in hospital spending in DDD / 1000 / day was 2.1% and in HRK 9.6% compared to 2016. The percentages expressed in outpatient and hospital spending are the same or very similar over the period 2005 to 2017. The differences between spending per DDD / 1000 / day and financial spending in kuna (3% and 38%) can be attributed to the fact that extremely expensive medicines are predominantly prescribed in hospitals and that many of them do not have DDD allocated.

Similarly, the overall consumption of medicines in the Republic of Croatia can be viewed by the type of medication dispensed, that is, whether a prescription drug (R) is issued or belongs to a group of over-the-counter (OTC) medicines (BR, BRX). According to the reported data, in 2017 the consumption of prescription drugs amounted to 967.11 DDD / 1000 / day (91%), i.e., financially, a total of HRK 5,587,581,833.00 (91%). Consumption of over-the-counter medicines (BR, BRX) was 94 DDD / 1000 / day (9%), or financially, a total of HRK

571,135,525 (9%). Considering the ratio of consumption of medicines to prescription (R) and non-prescription (BR, BRX) consumption over the period 2005 to 2017, we can conclude that the ratio of consumption distribution is very similar (HALMED, 2017).

Number	INN names	DDD/1000/day
1	acetylsalicylic acid	49,858,521
2	paracetamol	40,538,804
3	ibuprofen	38,703,699
4	paracetamol, combination with psychiatric drugs	38,328,193
5	oxymetazoline	15,952,685
6	antiseptics oral, various	15,892,637
7	electrolytes	15,041,624
8	xylometazoline	14,043,824
9	diclofenac	14,040,983
10	acetylsalicylic acid, combination without psychiatric drugs	11,701,332
11	paracetamol, combination without psychiatric drugs	10,786,457
12	organisms that create milk acid	9,937,229
13	<i>Sabal palma</i> extract	9,908,870
14	bisacodyl	9,522,936

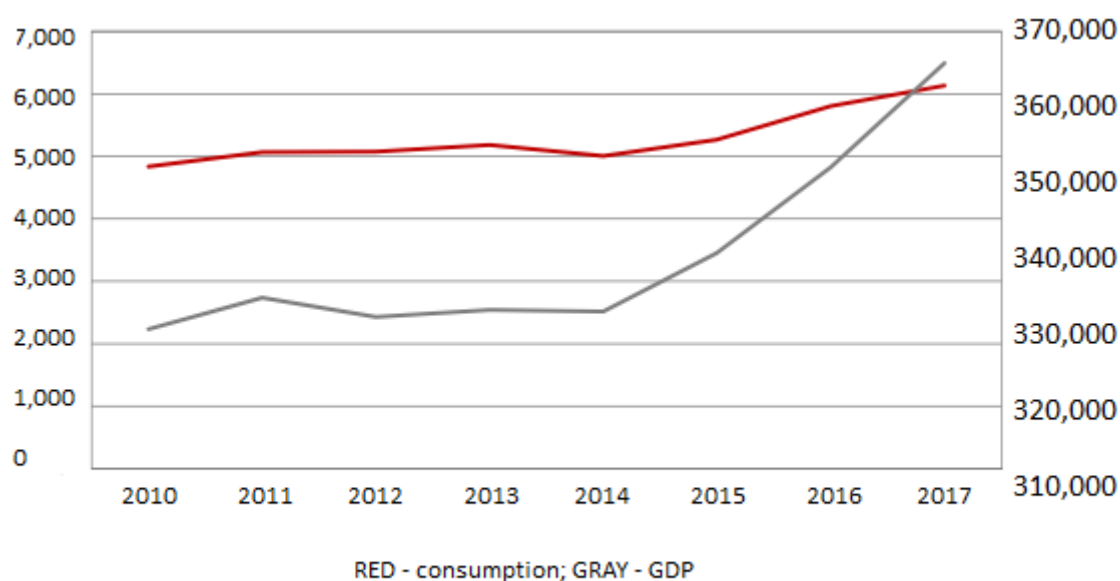
Table 6. Best selling drugs in Croatia, that are not on the fund of the Croatian Health Insurance Fund (Croatian: Hrvatski zavod za zdravstveno osiguranje, HZZO) in 2017, in HRK

Consumption of medicines is growing, reaching HRK 6 billion in 2017. Large increase in drug consumption by 1 billion from 2014 to 2017 is also related to GDP growth. Also, we can relate that growth to rising debts in the field of distribution of medicines from pharmaceutical companies to hospitals and pharmacies. The Croatian government has a long history of mounting debts to drug wholesalers. The debt has increased from 2012 to this day, when it reaches 2.6 billion HRK (Reuters, 2019). Wholesalers claim they would sue those hospitals with the longest payment delays, adding that the hospitals' debt to them is rising by some 150 million HRK a month. Croatia's hospitals, five of which delay payments by more than 800 days, settle their debts on average in 590 days. At the end of 2017 the overall hospital debt to wholesalers amounted to 1.6 billion HRK with an average payment delay of 360 days. The

legal payment deadline is 60 days. The Croatian Ministry of Health has made a promise once again that the Croatian government will try to find the best solution in dealing with this financial crisis (Reuters, 2019).

Let's look at the consumption of medicines measured by the number of defined daily doses / 1000 inhabitants / day (DDD / TSD), which in 2016 was 1,045.88 DDD / TSD. Almost every Croatian citizen consumed an average of one dose per day (HALMED, 2017). From 2012 to 2018, there is a noticeable upward trend in drug consumption in DDD / TSD. In 2010, there were some changes in DDD in some ATK groups, which resulted in lower values of the overall results. The reason for this decrease is the change in DDD units for individual drugs. For example, DDDs for the C10 drug group doubled and the calculations were halved. There is also a clear increase in the consumption of medicines per capita - every resident of Croatia spends on average HRK 1,257 a year, and every day a thousand people spend one defined daily dose of medication.

Figure 7. Total drug consumption (left scale) and GDP (right scale) in Croatia from 2010 to 2017 (in million of HRK)

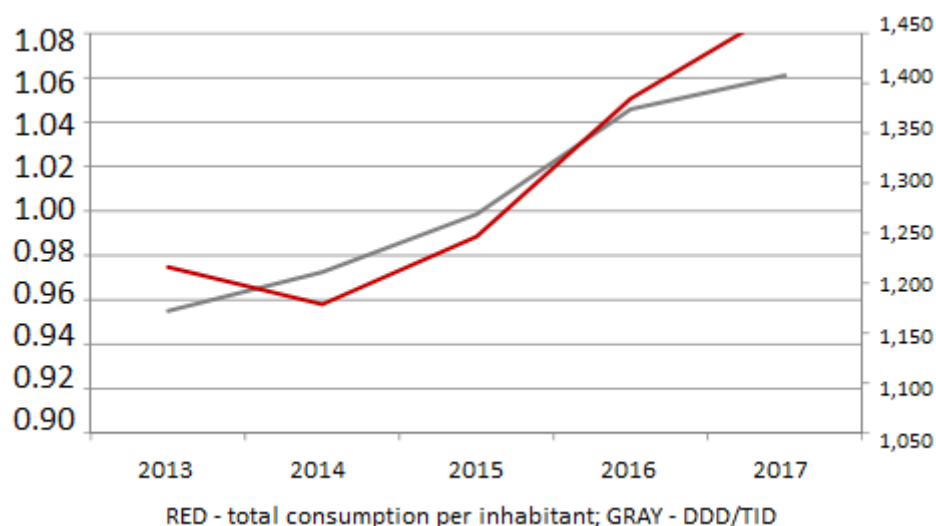


Source: HALMED, 2017

The Croatian pharmaceutical industry is mainly focused on the production of generic pharmaceuticals, which are losing market position, because despite the increase in sales of generic pharmaceuticals, the revenue is falling due to lower prices. Generic medicines

accounted for 42% of the total revenue of the Croatian pharmaceutical industry in 2015 (Barbić, 2019).

Figure 8. Total consumption of medicines per capita (left scale) and in defined daily doses per thousand inhabitants per day (right scale) in Croatia from 2013 to 2017



Source: HALMED, 2017

Between 2013 and 2017, drug consumption was seen to increase, but pharmaceutical companies' revenues grew even more, averaging 1.5 billion HRK on total consumption.

Year	Sales income	Total costs	Difference
2013	6,369	5,183	1,186
2014	6,668	5,006	1,662
2015	7,010	5,267	1,743
2016	7,671	5,803	1,868
2017	8,007	6,132	1,875
2013-2017	35,725	27,391	8,334

Table 7. Total drug consumption and total sales revenue of ten pharmaceutical companies in Croatia from 2013 to 2017 (in HRK million), source HALMED and FINA

4 PHARMACEUTICAL COMPANIES IN CROATIA

According to HALMED data, a manufacturing license for manufacturing medicines is held by 23 legal entities in the Republic of Croatia. These legal entities are considered the pharmaceutical industry of Croatia in the narrow sense of the word. These are the following pharmaceutical companies:

- Belupo lijekovi i kozmetika, d.d. (Belupo)
- FIDIFARM d.o.o.
- Genera d.d.
- Hospira Zagreb d.o.o.
- Hrvatski zavod za transfuzijsku medicinu (HZTM)
- Imunološki zavod
- JADRAN-GALENSKI LABORATORIJI (JGL d.d.)
- KRKA-FARMA d.o.o.
- MEDICAL INTERTRADE d.o.o.
- MEDIKA d.d. za trgovinu lijekovima i sanitetskim materijalom (MEDIKA d.d.)
- MEDOKA d.o.o.
- MESSER CROATIA PLIN d.o.o.
- OKTAL PHARMA d.o.o.
- PharmaS d.o.o.
- PHOENIX Farmacija društvo s ograničenom odgovornošću za promet lijekovima i opremom na veliko (PHOENIX Farmacija d.o.o.)
- PLIVA HRVATSKA d.o.o. za razvoj, proizvodnju i prodaju lijekova i farmaceutskih proizvoda (PLIVA HRVATSKA d.o.o.)
- ROCHE društvo s ograničenom odgovornošću za trgovinu i usluge
- Ruđer Medikol Ciklotron d.o.o.
- TREŠNJEVKA LABORATORIJ d.o.o.
- UTP d.o.o.
- XELLIA d.o.o.
- YASENKA d.o.o.

Although more than 30 companies operate in the domestic pharmaceutical industry, the ten largest Croatian pharmaceutical manufacturers in 2017 generate almost 99 percent of total

sector revenue and employ almost 97 percent of total sector employees. All ten leading companies are classified in the pharmaceutical manufacturing industry, with PLIVA, Belupo and JGL standing out. Below, we will review the profile of these companies as well as the latest information available about their businesses.

4.1 PLIVA CROATIA Ltd.

PLIVA CROATIA Ltd. for the development, production and sale of pharmaceuticals and pharmaceuticals (PLIVA CROATIA Ltd. or simply PLIVA), is the largest and oldest Croatian pharmaceutical company founded in 1921 in the small town of Kaštel, near Karlovac. This small town was also credited with the original name of PLIVA, which until 1941 operated under the name Kaštel. In 1927, the company's headquarters were relocated to Zagreb, at which time the company employed 60 workers, 10 of whom were university graduates (Povijest Plive).

In 1952, a research institute was established at PLIVA, and mass production of all kinds of preparations in the field of pharmaceutical, medical and cosmetic products began. In 1980, a panel of experts from the company's scientific institute, led by Dr. Slobodan Đokić, Gorjana Radoboj-Lazarevski, Zrinka Tamburašev and Gabrijela Kobrehel, discovered the formula of the chemical compound azithromycin, an active substance in the world-famous antibiotic Sumamed, one of the best-selling antibiotics. In 1981, PLIVA patented worldwide, including in the United States. The patent expired in 2005.

PLIVA is today the largest pharmaceutical company in Croatia and one of the leading companies in the region of Southeast Europe, thanks to a large number of experts, innovative technology and continuous investment in the production system. In addition to being one of the largest economic operators in Croatia, PLIVA is also one of the leading exporters: more than 80% of its products are exported, with the largest markets being the USA, Russia and EU countries.

Figure 9. Headquarters of PLIVA in Zagreb, Croatia



Source: PLIVA webpage, https://hr.wikipedia.org/wiki/Datoteka:Pliva_Upravna_zgrada.jpg

PLIVA's product portfolio includes a large number of finished drug forms for almost all therapeutic groups and active pharmaceutical substances. Focused on the development of generics and medicines with limited market competition, PLIVA has the widest range of generic medicines in Central and Eastern Europe.

Thanks to approvals from the US Food and Drug Administration (FDA), the British Medicines and Medical Devices Agency (MHRA) and other relevant European agencies, PLIVA is ranked among the manufacturers meeting the world quality standards required for the global market.

On October 25, 2006, Pliva was sold to US-based Barr Pharmaceuticals, Inc., which acquired 92% of PLIVA's shares under the terms of its \$ 2.5 billion closing bid. Together with Pliva's treasury shares, Barr now owns or controls more than 95% of PLIVA's voting rights. On December 23, 2008, Teva acquired Barr Pharmaceuticals for \$ 7.5 billion, making Barr and Pliva part of the Teva Group (Teva Completes Acquisition of Barr).

PLIVA's current success and current status is largely due to its own research and development of drugs and active pharmaceutical substances, making Zagreb one of the leading R&D centers in the Teva Group today.

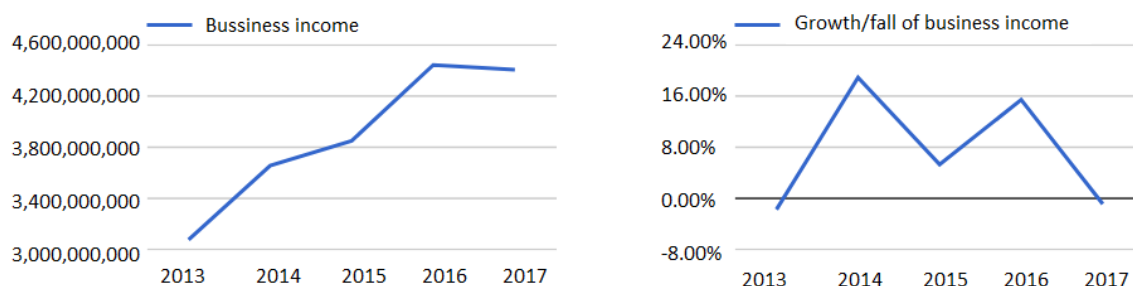
In addition to Croatia, PLIVA is successfully operating in the markets of the countries of Southern and Eastern Europe, like in Bosnia and Herzegovina, Slovenia, Serbia, Macedonia and Montenegro.

Indices	Value (HRK)
Total income	4,023,562,000.00
Total expenditure	3,701,589,000.00
Net income	113,778,000.00
Total property value	6,417,335,000.00
Total investments	211,500,000.00
Number of employees	2,338

Table 8. Key performance indicators for PLIVA for 2018, collected on the basis of available financial reports (Pliva Annual Financial Report for 2018)

In the available financial statements of PLIVA it can be seen that in 2018 the performance indicator decreased, that is, the total revenue of PLIVA decreased by 7.9% and the production decrease by 8.7%. Closely related to the indicators that they are employees, where they recorded a decrease in the number of employees in PLIVA by 2.7% compared to 2017, when that number was 2,402. The trends in operating revenues, that is, the growth and decline of PLIVA's revenues, are shown in Figure 10.

Figure 10. Operating income, and growth and decline in revenue from 2013 to 2017 in HRK



Source: Fininfo, <https://www.fininfo.hr/Poduzece/Pregled/pliva-hrvatska/Detaljno/45711>

4.2 Belupo

Belupo drugs and cosmetics, JSC Belupo is the second largest pharmaceutical company in Croatia. Belupo is now part of the Podravka Group dd, a food company based in Koprivnica. Belupo's history begins in 1970, when Podravka began preparing for pharmaceutical and chemical production, that is, creating preconditions for entering a new strategic business area. Already next year, a new drug factory was completed, and production started. 1981 was marked by the construction of a new drug factory and office building, and in 1999 another solid drug factory was built. In 2000, the company expanded to business areas across Europe, in Moscow, Prague and Belgrade, and in 2002 a daughter company was established with headquarters in Ljubljana, Slovenia. A new project to build a semi-solid and liquid drug factory was completed in 2004. Belupo is expanding its business network to pharmacy chains, and the pharmacy establishment of *Deltis Pharm Pharmacy* is established, which today has 9 pharmacy establishments. In 2008, Belupo becomes the majority owner of the B&H firm FARMAVITA Ltd., expanding Belupo's influence in Bosnia and Herzegovina. Later, representative offices were established in Poland, Ukraine and Kazakhstan, and Farmavita established representative offices in Priština, Kosovo. Belupo has received numerous awards and recognitions such as *Zlatna Kuna* for Business Excellence, Belupo's *Lupocet* wins Best Buy Health Award for 2014/2015, *Neofen* wins Trusted Brand 2011 Award, *Zlatni Ključ* Award for Best Croatian Exporter in B&H, etc.

Belupo group today is made of:

- Belupo d.o.o., Slovenia (ownership 100% Belupo JSC)
- Belupo s.r.o., Slovakia (100% Belupo JSC)
- Belupo d.o.o.el, Makedonija (100% Belupo JSC)
- Pharmacies Deltis Pharm, Hrvatska (100% Belupo JSC)
- Farmavita d.o.o. Bosna i Hercegovina (65% Belupo JSC)

In 2018, the Belupo Group realized sales of its products in both domestic and international markets. Through its organizational units, Belupo is present in the markets of Russia, Ukraine, Kazakhstan, Slovakia, Slovenia, Czech Republic, Poland, Bosnia and Herzegovina, Montenegro, Kosovo and Macedonia.

The Belupo product line is based on prescription drugs (specialty foods) and over-the-counter products:

- Herbal remedies
- Food supplements
- Cosmetics
- Over-the-counter (OTC) medicines
- Excipients

The most notable brands of the Belupo pharmaceutical company include the herbal drug *Ginkgo FORTE*, cream *BELODERM*, drugs *Neofen* and *Lupocet*.

Figure 11. Headquarters of Belupo in Koprivnica, Croatia



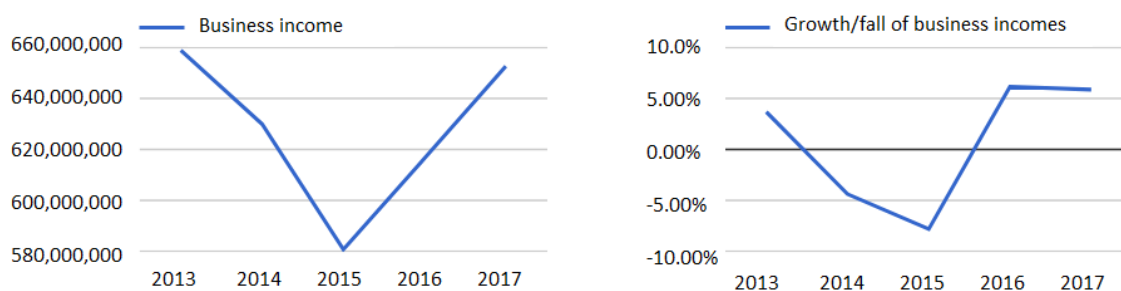
Source: Belupo webpage, <https://www.belupo.hr/hr/>

Business reports for 2018 show positive business trends for this company. As stated in the Annual Financial Report of Belupo (2018): “(...) *Pharmaceuticals generated HRK 896.9 million in sales, which is an increase of 3.4% or HRK 29.4 million compared to the previous year, while without the effect of foreign exchange differences, revenues would be estimated to be 6.4% higher. Pharmaceuticals brands grew by 2.5%, mainly due to the continuing trend of demand growth in the Russian market and the expansion of distribution in the markets of the Central Europe region. The most significant category of Prescription Drugs saw an increase in sales of 2.1%, while the OTC program recorded a 5.4% increase in sales.* ”

Indices	Value (HRK)
Total income	898,775,000.00
Total expenditure	823,658,813.96
Net income	45,117,196.04
Total property value	1,579,686,000.00
Total investments	89,023,220.51
Number of employees	1465

Table 9. Key performance indicators for Belupo for 2018, collected on the basis of available financial reports (Belupo Annual Financial Report for 2018)

Figure 12. Operating income, and growth and decline in revenue from 2013 to 2017 in HRK



Source: Fininfo, <https://www.fininfo.hr/Poduzece/Pregled/belupo/Detaljno/62870>

An insight into the financial statements of the Belupo Group and Company reveals optimistic figures that indicate business growth. The Belupo Group's revenue grew more than 3% year-on-year, and the Belupo Group's nearly 2%. Although the company's net profit declined by almost 30% annually, Belupo Group's net profit grew by more than 21%. The situation is similar with the number of Belupo Group employees. The number of employees has been growing steadily since 2008, and Belupo is one of the few in Croatia where the global recession crisis has not had a significant impact on staff reductions. This is also the case with 2017, as there was a 4% increase in staff in 2018.

4.3 JGL

JADRAN-GALENSKI LABORATORII (JGL JSC) or simply JGL is a Croatian pharmaceutical company based in Rijeka. It was founded in 1991 by Ivo Usmiani on the foundations of the Laboratory of Jadran Pharmacy in Rijeka. JGL is Croatia's first fully privately-owned pharmaceutical company. It has gradually grown into the third pharmaceutical company in Croatia to operate in the markets of Southeastern Europe and other parts of the world, and is constantly developing new products, especially sensation drugs (nose and eye drops), primarily based on seawater. In July 2015, a new Pharma Valley manufacturing facility was opened in Svilno, near Rijeka. In 1991, the first medical product was developed by JGL, *Carbo medicinalis*. In 1992, 1997 and 1998, representative offices were opened in Slovenia, Bosnia & Herzegovina and Russia. One of the most famous JGL medical brands *Aqua Maris* was released in 1998. New offices started opening in Serbia & Montenegro, Kazakhstan, Ukraine, Kosovo and North America. In 2005, JGL opened its own pharmacy chain called *Ljekarne Pablo* (Pablo Pharmacies) (JGL, Lenta vremena).

Figure 13. The *Pharma Valley* complex of JGL in Svilno, Croatia



Source: Rozić architects webpage, <http://www.rozicarhitekti.com/project/jgl-pharma-valley/>

JGL received numerous awards including certificates, like the *Zlatni ključ* award for the best exporter to Russia, Charter of the Republic of Croatia, the *Lider Invest* award for the largest production investment and the *Zlatna kuna* award.

With the opening of the new complex of Pharma Valley on 99,000 m² which was a 361,000,000.00 HRK investment, a new era began for JGL. There brands today make a big portion of the Croatian pharmaceutical market. It is notable to also mention *Lactogyn*, *Meralys* and *VizolS*.

Today, JGL is a multinational company with 160 brands, 460 products, 1,360 variations and 6,000 items. JGL invests a lot in the research and development area. R&D develops and perfects products from different categories:

- Prescription drugs (Rx)
- Over-the-counter drugs (OTC)
- Medical devices (MD)
- Nutritional supplements

JGL laboratories are equipped for:

- Preformulation testing
- Packaging development
- Formulation development and technological process optimization
- Development and validation of analytical methods

With experts from other business units, the R&D department is involved in technology transfers, clinical studies, BE and other studies conducted during the development of a new product to achieve and validate its quality, efficiency and safety.

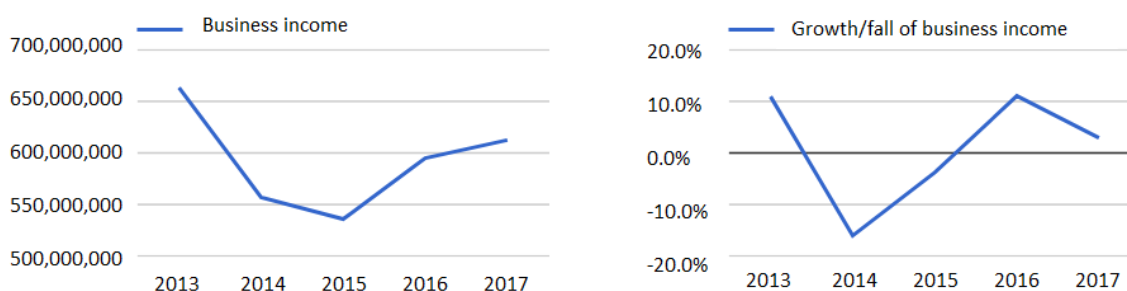
Indices	Value (HRK)
Total income	458,322,389.54
Total expenditure	441,026,294.83
Net income	18,815,160.07
Total property value	1,053,186,000.00
Total investments	43,018,000.00
Number of employees	546

Table 10. Key performance indicators for JGL for 2018, collected on the basis of available financial reports (JGL Annual Financial Report for 2018)

As the second largest pharmaceutical company in Croatia, JGL is a significant contributor to significant revenue and net profit and employs a large number of highly qualified employees (Table 10). However, the year 2018, for both PLIVA and JGL, represents a decrease in revenue and net profit over the previous year. Specifically, compared to 2017, there was a 27.7%, 73.4% and 20.5% decrease in total revenues, net profit, and number of employees of the pharmaceutical company. These figures can be partly explained by the redistribution within the company itself, that is, the large changes within the company and the sale of part of the company operating in Russia, and the redistribution in Bosnia and Herzegovina (JGL Annual Financial Report, 2018).

This information can also be seen from Figure 14, which shows business trends in JGL over the years.

Figure 14. Operating income, and growth and decline in revenue from 2013 to 2017 in HRK



Source: Fininfo, <https://www.fininfo.hr/Poduzece/Pregled/jgl/Detaljno/60561>

5 CONCLUSION

The pharmaceutical industry is one of the most profitable and fastest growing industries in the world, and we can consider it a very significant branch of the economy. It has an ancient tradition, and we can see the roots of the modern pharmaceutical industry in the 19th century. On the soil of the Republic of Croatia, one can see the deep history of pharmacy, which is evident in the opening of the first pharmacies in this region, to the first drug factories. The current legal framework has well defined the field of activity of the pharmaceutical industry, and regulatory bodies are present to carry out the work of supervising professional work in this industry. Although not very large in terms of staff, its impact can be found in the financial sector. Also, there is an increase in the number of employees in the pharmaceutical industry sector, so that sector is a significant factor whose work should be encouraged. Apart from the number of employees, in recent years there has been an increase in both net and gross wages in this sector, with the sector in which wages are mostly above the average of the Republic of Croatia. The main economic indicators also give mostly optimistic results, as most economic indicators have grown. According to the measurements of regulatory bodies, the turnover and consumption of medicines in the Republic of Croatia is steadily increasing, so this is another indicator of positive business performance and investment opportunities in the pharmaceutical industry in the Republic of Croatia. The Republic of Croatia has 23 registered legal entities which can be considered as pharmaceutical manufacturers in the narrow sense of the word, since these companies manufacture medicines in the Republic of Croatia. Of these pharmaceutical companies, the 3 largest pharmaceutical companies stand out; PLIVA CROATIA Ltd, Belupo JSC and JGL JSC. These pharmaceutical companies have a long tradition of business and have developed various brands from their product range. They are present not only on the market of the Republic of Croatia, but also on foreign, European and world markets. They have received numerous awards. Although the economic indicators of the entire pharmaceutical sector in the Republic of Croatia are constantly improving, of the 3 companies listed, only 1 company shows positive business results and an increase in the number of employees year-on-year. However, this information can be explained by the different business relocations within the companies themselves. The pharmaceutical industry in Croatia is generally showing positive business trends and is proving to be an industry-worthy investment.

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