Open University of Cyprus

Faculty of Economics and Management

Postgraduate (Master's) Programme of Study

Business Administration (MBA)

Postgraduate (Master's) Dissertation

The Pharmaceutical market in Greece-Case of Pfizer Inc.

Vaia Tasiopoulou

Supervisor

Sotiris Karkalakos

June 2020

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The present Postgraduate (Master's) Dissertation was submitted in partial fulfilment of the requirements for the postgraduate degree in Business Administration Faculty of Economics and Management of the Open University of Cyprus.

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Summary

The aim of this study is to provide a detailed overview of the pharmaceutical industry and the economy in Greece. This postgraduate dissertation is a critical and systematic review of the literature. The criteria for selecting statistical data were the time frame for their implementation (within 15 years), the completeness of the statistical data for the years under review, the relevance of the data and the reliability. The data were selected by EFPIA, AESGP, ELSTAT, OECD and EUROSTAT. In addition, the case study of Pfizer Inc., one of the world's leading biopharmaceutical companies, is presented. The case study focuses on the company's history, mergers and acquisition strategies and R&D investments.

Keywords: pharmaceutical market, pharmaceutical economy, healthcare expenditure, Pfizer

Περίληψη

Ο στόχος αυτής της μελέτης είναι να παρέχει μια λεπτομερή επισκόπηση της φαρμακευτικής βιομηχανίας και της οικονομίας στην Ελλάδα. Αυτή η μεταπτυχιακή διατριβή είναι μια κριτική και συστηματική ανασκόπηση της βιβλιογραφίας. Τα κριτήρια επιλογής στατιστικών δεδομένων ήταν το χρονικό πλαίσιο για την εφαρμογή τους (εντός 15 ετών), η πληρότητα των στατιστικών δεδομένων για τα υπό εξέταση έτη, η συνάφεια των δεδομένων και η αξιοπιστία. Τα δεδομένα επιλέχθηκαν από EFPIA, AESGP, ELSTAT, OECD, EUROSTAT. Επιπλέον, παρουσιάζεται η μελέτη περίπτωσης της Pfizer Inc., μιας από τις κορυφαίες εταιρείες βιοφαρμακευτικών προϊόντων στον κόσμο. Η μελέτη περίπτωσης επικεντρώνεται στην ιστορία της εταιρείας, στις συγχωνεύσεις και στις στρατηγικές εξαγοράς και στις επενδύσεις Ε & Α.

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Chapter 1

Introduction

1.1 Pharmaceutical industry

The pharmaceutical industry, discovers, develops, produces, and markets drugs or pharmaceutical drugs for use as medications to be administered to patients, with the aim to cure them, vaccinate them, or alleviate the symptoms. The modern era of the pharmaceutical industry is considered to have begun in the 19th century, thousands of years after intuition and trial and error led humans to believe that plants, animals, and minerals contained medicinal properties. The unification of research in the 20th century in fields such as chemistry, biochemistry, biology and physiology increased the understanding of basic drug-discovery processes. Identifying new drug targets, attaining regulatory approval from government agencies, and refining techniques in drug discovery and development are among the challenges that face the pharmaceutical industry today. The continual evolution and advancement of the pharmaceutical industry is fundamental in the control and elimination of disease around the world[1].

The following sections provide a detailed explanation of the progression of drug discovery and development, the approval process of drug development in the modern pharmaceutical industry, and the procedures that are followed to ensure the production of safe drugs.

1.2 Research and Development

Drug discovery is the process by which potential drugs are discovered or designed. In the past, most drugs have been discovered either by isolating the active ingredient from traditional remedies or by serendipitous discovery. Modern biotechnology often focuses on understanding the metabolic pathways related to a disease state or pathogen, and manipulating these pathways using molecular biology or biochemistry. A great deal of early-stage drug discovery has traditionally been carried out by universities and research institutions. As part of this process, scientists at many publicly funded institutions carry out basic research in subjects such as chemistry, biochemistry, microbiology, and pharmacology. Basic research is almost always directed at developing new understanding of natural substances or physiological processes rather than being directed specifically at development of a product or invention. This enables scientists at public institutions and in private industry to apply new knowledge to the development of new products. The results of their studies are published in scientific and medical journals. These results facilitate the identification of potential new targets for drug discovery. Once a target is identified, the bulk of the remaining work involved in discovery and development of a drug is carried out or directed by pharmaceutical companies.

Drug development refers to activities undertaken after a compound is identified as a potential drug in order to establish its suitability as a medication. Objectives of drug development are to determine appropriate formulation and dosing, as well as to establish safety. The current state of the chemical and biological sciences required for pharmaceutical development dictates that 5,000–10,000 compounds must undergo laboratory screening for each new drug approved for use in humans. Of the 5,000–10,000 compounds that are screened, approximately 250 will enter preclinical testing, and 5 will enter clinical testing. The overall process from discovery to marketing of a drug can take 10 to 15 years.

Drug discovery and development are very expensive. From all compounds investigated for use in humans only a small fraction is eventually approved in most nations by government-appointed medical institutions or boards, who must approve new drugs before they can be marketed in those countries. In 2019, the FDA's Center for Drug Evaluation and Research (CDER) approved 48 novel drugs. Although this approval count falls short of CDER's record 59 approvals of 2018, it still comes in as the third biggest approval class in the past 25 years[2]. This approval comes only after heavy investment in pre-clinical development and clinical trials, as well as a commitment to ongoing safety monitoring. Drugs which fail part-way through this process often incur large costs, while generating no revenue in return. A study by The Tufts University Center reported that the cost for discovering, developing and launching a new drug (along with the prospective drugs that fail) was $2.6 billion, informal studies have set the level as high as $6 billion in 2019 growing at 8.5% annually[3].

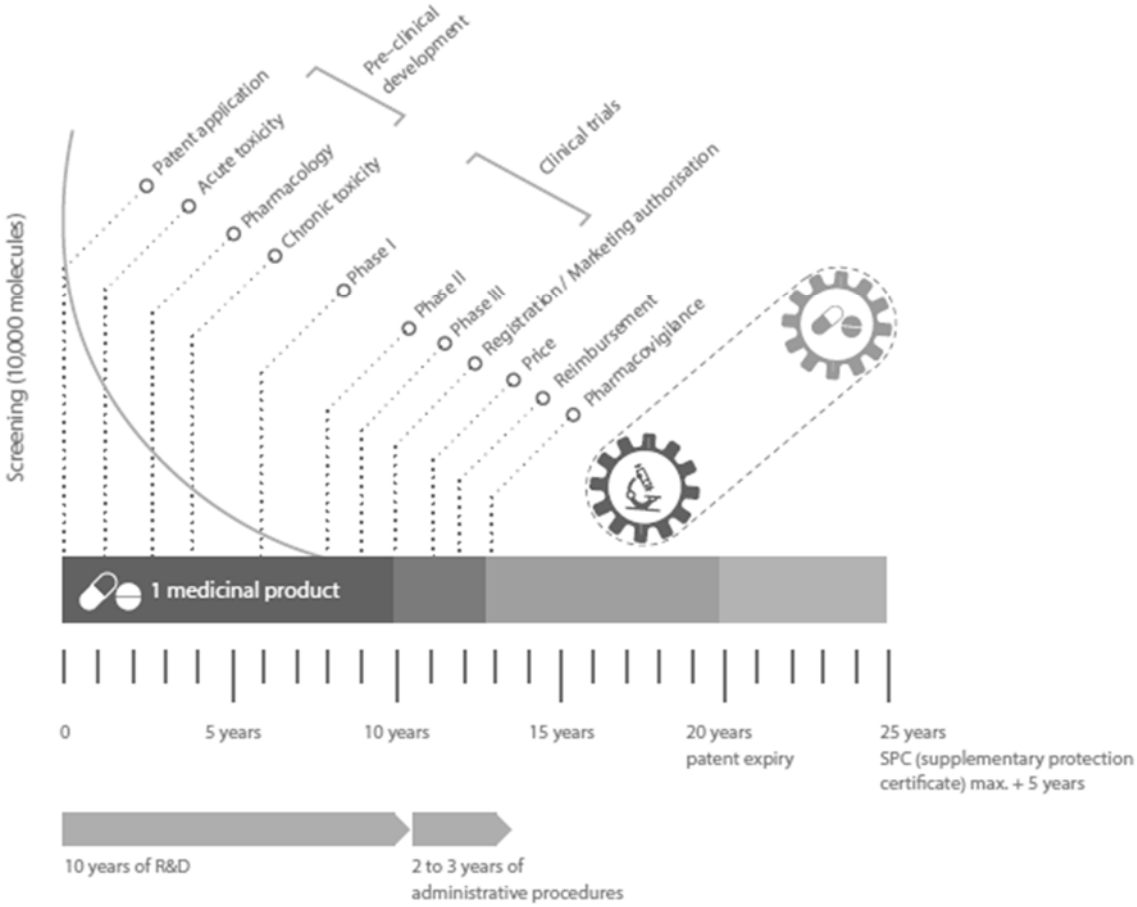


Figure 1. Phases of the research and development process

1.3 Drug Approval Process

In the United States, new pharmaceutical products must be approved by the Food and Drug Administration (FDA) as being both safe and effective[4]. This process generally involves submission of an Investigational New Drug (IND) filing with sufficient pre-clinical data to support proceeding with human trials. Following IND approval, three phases of progressively larger human clinical trials may be conducted. Phase I generally studies toxicity using healthy volunteers. Phase II can include pharmacokinetics and dosing in patients, and Phase III is a very large study of efficacy in the intended patient population. Following the successful completion of phase III testing, a New Drug Application is submitted to the FDA. The FDA reviews the data and if the product is seen as having a positive benefit-risk assessment, approval to market the product in the US is granted. The following sections describe in general terms the steps required for regulatory approval of drugs in the United States. Although the descriptions are based on the Food and Drug Administration (FDA) regulations and guidelines, these requirements are similar to those in many other countries. In Europe, the European Medicines Agency (EMA) is equivalent to the U.S. Food and Drug Administration. EMA, is an agency of the European Union (EU) in charge of the evaluation and supervision of medicinal products.

1.3.1. Discovery and Development

Typically, researchers discover new drugs through:

- New insights into a disease process that allow researchers to design a product to stop or reverse the effects of the disease.
- Many tests of molecular compounds to find possible beneficial effects against any of many diseases.
- Existing treatments that have unanticipated effects.
- New technologies, such as those that provide new ways to target medical products to specific sites within the body or to manipulate genetic material.

At this stage in the process, thousands of compounds may be potential candidates for development as a medical treatment. After early testing, however, only a small number of compounds look promising and call for further study.

Once researchers identify a promising compound for development, they conduct experiments to gather information on:

- How it is absorbed, distributed, metabolized, and excreted.
- Its potential benefits and mechanisms of action.
- The best dosage.
- The best way to give the drug (such as by mouth or injection).
- Side effects or adverse events that can often be referred to as toxicity.
- How it affects different groups of people (such as by gender, race, or ethnicity) differently.
- How it interacts with other drugs and treatments.
- Its effectiveness as compared with similar drugs.

1.3.2. Preclinical Research

Before testing a drug in people, researchers must find out whether it has the potential to cause serious harm, also called toxicity. The two types of preclinical research are:

- In vitro: studies are performed with microorganisms, cells, or biological molecules outside their normal biological context. Colloquially called "test-tube experiments".
- In vivo: studies are those in which the effects of various biological entities are tested on whole, living organisms or cells, usually animals, including humans, and plants, as opposed to a tissue extract or dead organism.

Usually, preclinical studies are not very large. However, these studies must provide detailed information on dosing and toxicity levels. After preclinical testing, researchers review their findings and decide whether the drug should be tested in people.

1.3.3. Clinical Research

Clinical research" refers to studies, or trials, that are done in people. As the developers design the clinical study, they will consider what they want to accomplish for each of the different Clinical Research Phases and begin the Investigational New Drug Process (IND), a process they must go through before clinical research begins. Researchers design clinical trials to answer specific research questions related to a medical product. These trials follow a specific study plan, called a protocol, that is developed by the researcher or manufacturer. Before a clinical trial begins, researchers review prior information about the drug to develop research questions and objectives. Then, they decide:

- Who qualifies to participate (selection criteria)
- How many people will be part of the study
- How long the study will last
- Whether there will be a control group and other ways to limit research bias
- How the drug will be given to patients and at what dosage
- What assessments will be conducted, when, and what data will be collected
- How the data will be reviewed and analyzed

Clinical trials follow a typical series from early, small-scale, Phase 1 studies to late-stage, large scale, Phase 3 studies.

Phase 1

During Phase 1 studies, researchers test a new drug in normal volunteers (healthy people). In most cases, 20 to 80 healthy volunteers or people with the disease/condition participate in Phase 1. However, if a new drug is intended for use in cancer patients, researchers conduct Phase 1 studies in patients with that type of cancer. Phase 1 studies are closely monitored and gather information about how a drug interacts with the human body. Researchers adjust dosing schemes based on animal data to find out how much of a drug the body can

tolerate and what its acute side effects are. As a Phase 1 trial continues, researchers answer research questions related to how it works in the body, the side effects associated with increased dosage, and early information about how effective it is to determine how best to administer the drug to limit risks and maximize possible benefits. This is important to the design of Phase 2 studies.

Phase 2

In Phase 2 studies, researchers administer the drug to a group of patients with the disease or condition for which the drug is being developed. Typically involving a few hundred patients, these studies aren't large enough to show whether the drug will be beneficial. Instead, Phase 2 studies provide researchers with additional safety data. Researchers use these data to refine research questions, develop research methods, and design new Phase 3 research protocols.

Phase 3

Researchers design Phase 3 studies to demonstrate whether a product offers a treatment benefit to a specific population. Sometimes known as pivotal studies, these studies involve 300 to 3,000 participants. Phase 3 studies provide most of the safety data. In previous studies, it is possible that less common side effects might have gone undetected. Because these studies are larger and longer in duration, the results are more likely to show long-term or rare side effects

Phase 4

A Phase 4 trial is also known as post marketing surveillance (PMS) trial, or informally as a confirmatory trial. Phase 4 trials involve the safety surveillance (pharmacovigilance) and ongoing technical support of a drug after it receives permission to be sold. Phase 4 studies may be required by regulatory authorities or may be undertaken by the sponsoring company for competitive (finding a new market for the drug) or other reasons (for example, the drug may not have been tested for interactions with other drugs, or on certain population groups such as pregnant women, who are unlikely to subject themselves to trials). The safety surveillance is designed to detect any rare or long-term adverse effects over a

much larger patient population and longer time period than was possible during the Phase 1-3 clinical trials.

1.3.4 FDA Drug Review

If a drug developer has evidence from its early tests and preclinical and clinical research that a drug is safe and effective for its intended use, the company can file an application to market the drug. The FDA review team thoroughly examines all submitted data on the drug and decides to approve or not to approve it.

1.3.5 FDA Post-Market Drug Safety Monitoring

Even though clinical trials provide important information on a drug's efficacy and safety, it is impossible to have complete information about the safety of a drug at the time of approval. Despite the rigorous steps in the process of drug development, limitations exist. Therefore, the true picture of a product's safety evolves over the months and even years that make up a product's lifetime in the marketplace. FDA reviews reports of problems with prescription and over the counter drugs and can decide to add cautions to the dosage or usage information, as well as other measures for more serious issues.

1.4. Patents and generics

A patent is a property right to a product and in the case of pharmaceutical companies is usually in the form of a chemical formula that may not be duplicated by any rival company. Patent protection enables the owner of the patent to recover the costs of research and development through high-profit margins for the branded drug. When the patent protection for the drug expires, a generic drug is usually developed and sold by a competing company[5]. The cost of developing a generic version of a drug for market is significantly less than the cost of developing the patented drug since many of the studies required for first regulatory approval of a drug are not required for marketing approval for subsequent generic versions. Essentially, the only requirement is to demonstrate that the new version is biologically equivalent to the already approved drug.

Bioequivalent drug products have the same rate and extent of absorption and produce the same blood concentration of drug when the two drugs are given in the same dose and in the same dosage form. Often the owner of the branded drug will introduce a generic version before the patent expires in order to get a head start in the generic market.

1.5. Prescriptions Drugs

A prescription drug (also prescription medication) is a pharmaceutical drug that legally requires a medical prescription to be dispensed. In contrast, over-the-counter drugs (OTC) can be obtained without a prescription. The reason for this difference in substance control is the potential scope of misuse, from drug abuse to practicing medicine without a license and without enough education. Different jurisdictions have different definitions of what constitutes a prescription drug.

In the worldwide, prescription drug sales for 2019 were €753 billion from this amount € 118 billion are for Orphan drugs and €71 billion for generics[6].

Chapter 2

Economic Environment

2.1 Microeconomic Fluctuations

Gross domestic product (GDP) is the sum of final consumption, gross capital formation and net exports. Final consumption includes all the goods and services used by households or the community to satisfy their individual needs. It includes final consumption expenditure of households, general government and non-profit institutions serving households. The calculation of the annual growth rate of GDP volume is intended to allow comparisons of the dynamics of economic development both over time and between economies of different sizes.

Gross Domestic Product (GDP) of the Greek economy amounted to €194 billion in 2019, increased by 1.5% compared to 2018, this rate is the same than the previous year[7]. The GDP per capita of Greece in 2019 was €17,904, in 2018, it was €18,590. To view the evolution of the GDP per capita, it is interesting to look back a few years and compare these data with those of 2009 when the GDP per capita in Greece was €27,594. Unfortunately, Greece's economy this year is expected to be hit severely by the Covid-19 pandemic and the counter measures taken to limit its spread, according to the European Commission's Spring 2020 Economic Forecast released on Wednesday. The forecast gives a discouraging picture for Greece in 2020, as it says the country's GDP is expected to contract by 9.7 percent this year – the highest out of all EU countries However, the Commission says a rebound should be expected in 2021.

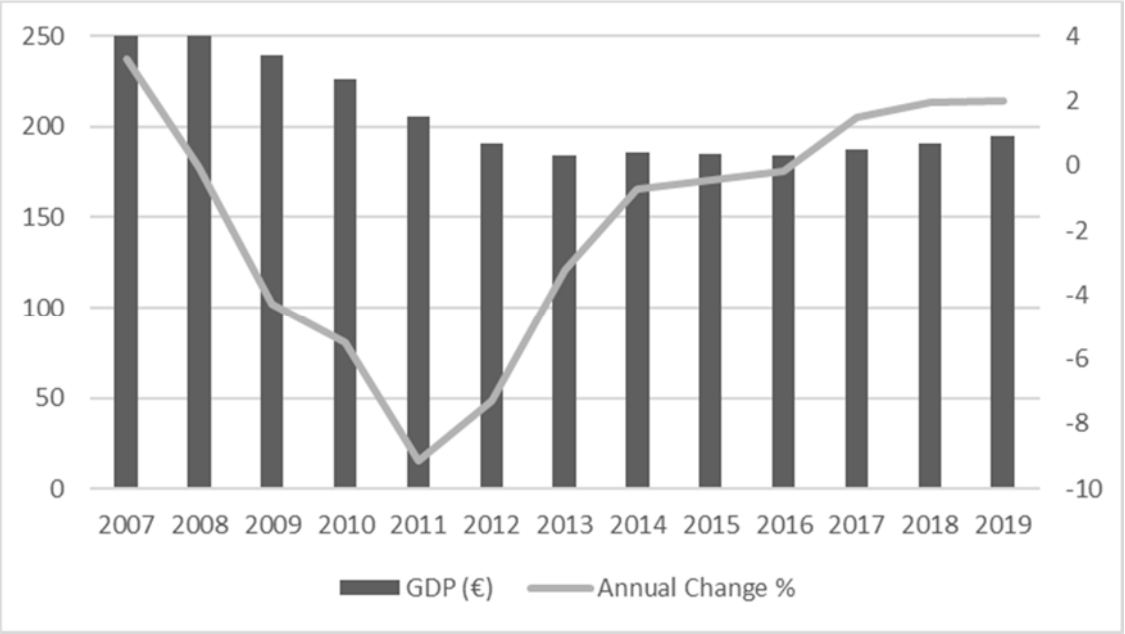


Figure 2. GDP (€) and annual change (%) – Greece

Year	Gross Domestic Product (€)	Annual Change (%)
2007	250.718	3.274
2008	249.878	-0,035
2009	239.132	-4.301
2010	226.031	-5.478
2011	205.389	-9.132
2012	190.395	-7.300
2013	184.223	-3.242
2014	185.586	-0,74
2015	184.774	-0,438
2016	184.422	-0,191
2017	187.197	1.505
2018	190.818	1.934
2019	194.597	1.981

Table 2. GDP (€) and annual change (%) – Greece from 2007 until 2020

Greece experienced an unexpected financial crisis that completely reversed the economic models and expectations of Greek citizens, started in late 2009. After experiencing an average annual GDP growth rate in Greece of 4 % per annum from 2000 through 2008, when it was around 2 % in the EU-28, GDP was –4.3 %

in 2009. A year later, in 2010, it was –5.5 %. In 2011 initial expectations were busted and the recession worsened, with GDP shrinking by –9.1 %, the worst recorded in EU history. This decrease is attributable to consumer demand of negative 7.1%, of public consumption of negative 9.1% and a –20.7% fall in investments. The first sight recovery from the recession was observed with a GDP decrease of –7.3% in 2012 and 3.2 % in 2013. Despite expectations for a recovery, the recession continues. Until 2016. Table 1 portrays the "depth" and the "duration" of the "Greek tragedy". The greatest crisis "depth" was in 2011. Regarding the duration, it lasted six years and is the longest crisis for any European country. In 2017, increased by 1.5% compared to 2016, for 2018, growth rate was 1.9 %[8].The GDP of the Greek economy had a cumulative loss of -26.4% in the period 2007-2016, while in the Southern countries, losses in the same period were down to -4.0%, while in EU 28, increased by 6.0%. It is noted that in the period 2017-2020, if the estimates are verified and projections, Greece will show a cumulative increase in the GDP by 8.2%, versus 7.7% in the EU28 and 6.3% in the Southern countries.

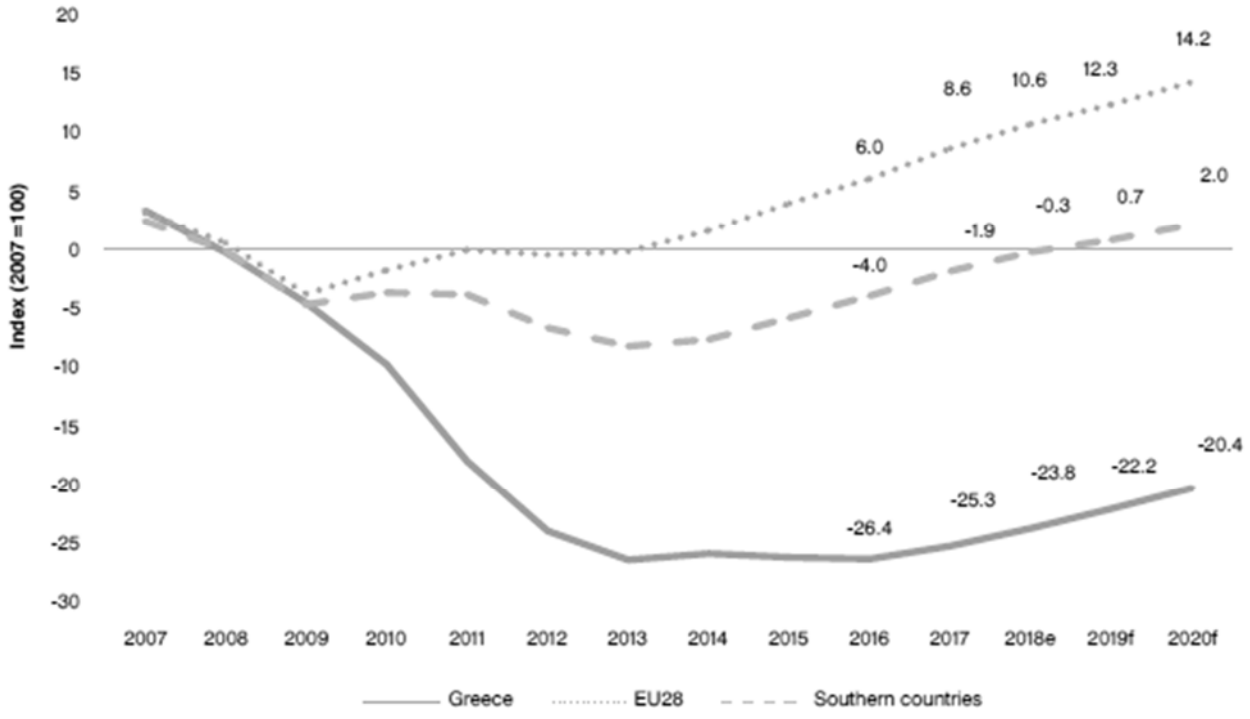


Figure 3. Index of cumulative GDP change (%) Greece-EU28-Southern countries

2.2 Total healthcare expenditure

Health financing is a critical component of health systems. Total health expenditure is defined as the sum of public and private health spending and it covers both the preventive and curative services along with emergency and rehabilitative health services for the entire population. Ministry of Finance of a country allocates the budget for health expenditure in a fiscal year[9].
Health expenditures fell or slowed in many OECD countries as a result of the global economic recession that began in 2008, after years of continuous growth[10]. The drop-in expenditures were due to the increase in the volume and prices of health care services, changes of demographic and consumer habits, rapid progress of technology as well as to the oversupply of doctors and their supplier-induced demand. European countries were forced to contain the cost of health care services after the economic recession. Given that public funds account for around three-quarters of total health expenditures on average across the European countries, governments have adopted various measure to increase the efficiency of health systems such as (a) adjusting the level of financial resources, (b) regulating the demand for services and (c) controlling the cost of care.

In Greece, total health expenditures recorded the highest value €23 million in 2008 relative to €13 million in 2002. During the economic recession, total health expenditures decreased to €17 million in 2012 of which €11,3 million referred to public health spending and €5,7 million to private sector spending. The health expenditures of the general government and the private sector decreased significantly after 2009 and 2008, respectively, keeping pace with the total health expenditures trend. This reduction resulted both from the restructuring of health spending due to structural reforms introduced after the implementation of the Economic Adjustment Program in May 2010 and the shrinkage of disposable income.

In 2017, total health expenditure in Greece amounted to €14.5 billion, out of which €8.8 billion composes public health expenditure and €5.6 million private health expenditure[11].

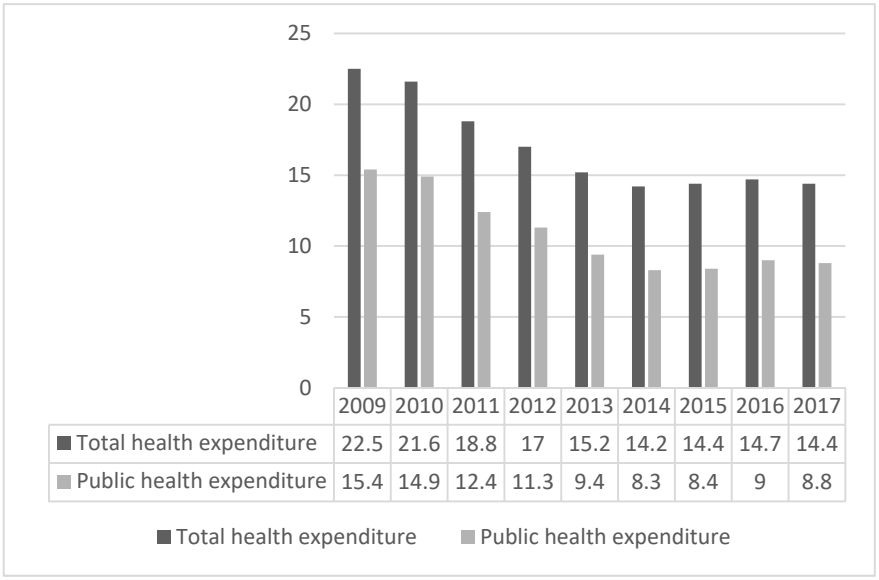


Figure 4. Total and public health expenditure (billion €)

In Greece, total health expenditure as a percentage of GDP accounted to 9.5% in 2009 and decreased at 8.4% in 2017, indicative of a faster reduction in health expenditure compared to GDP reduction during the same period.

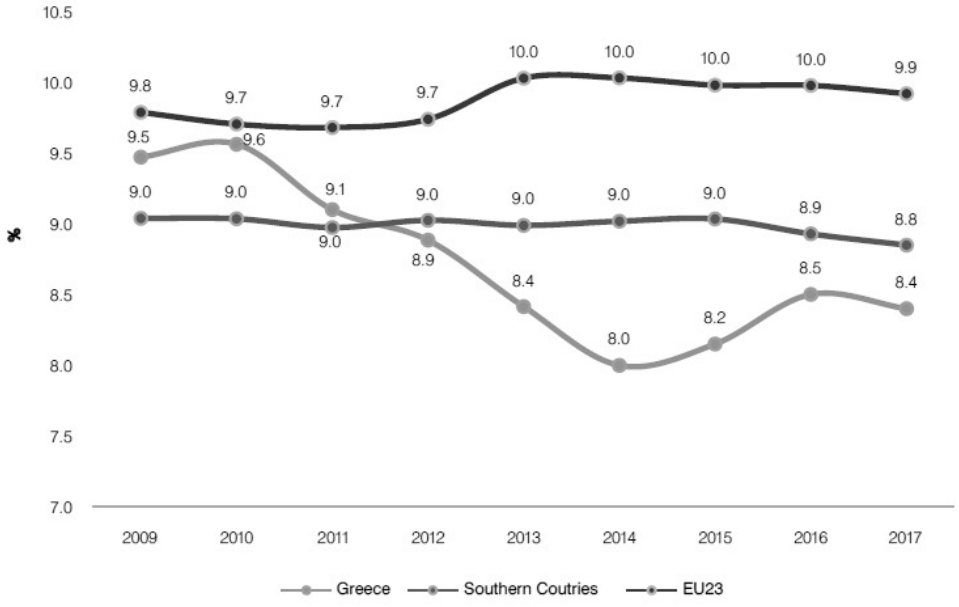


Figure 5. Total health expenditure (% GDP) Greece-EU23-Southern countries[13,14]

Public health expenditure as a percentage of GDP in Greece amounted to 5.1% in 2017 compared to 6.5% in 2009. This evolution shaped the rate of public health expenditure in Greece below EU23 average (7.9%), which remains almost stable during 2009-2017. In Southern countries that implemented economic adjustment programs, the percentage was at 6.4% for 2017.

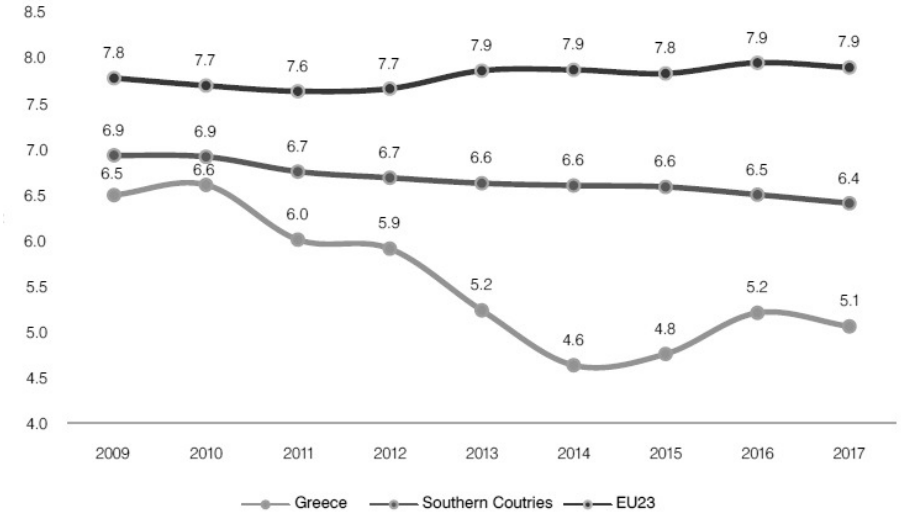


Figure 6. Public health expenditure (% GDP) Greece-EU23-Southern countries[13,14].

Total health expenditure per capita in Greece amounted to €1,381 in 2017 compared to €2,027 in 2009, that is €944 less than the average of Southern countries. Public health expenditure per capita declined in Greece by -39.1% between 2009 and 2017 and amounted to €845 compared to an increase of +22.0% in EU23 and a slower decline in Southern countries of -0.5% during the same period. Over the period 2009-2013, the per capita health expenditure in Greece declined by -8.7%, the largest among OECD countries, with an increase of 0.7% in the period 2013-2017[14].

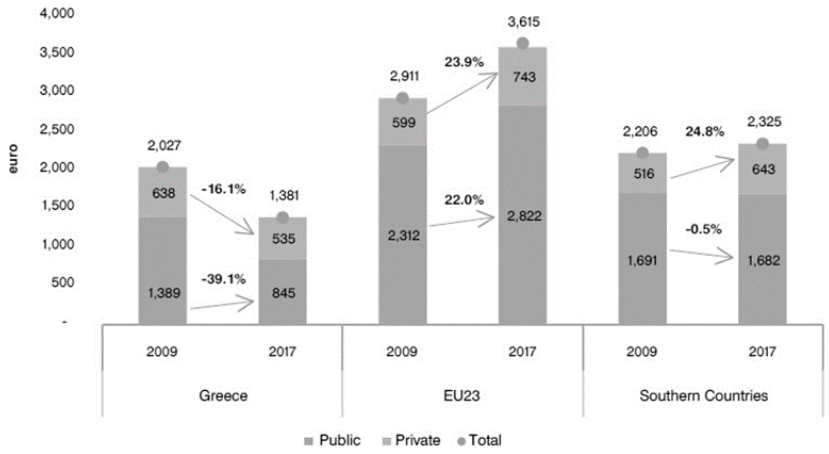


Figure 7. Total per capita health expenditure Greece-EU23-Southern countries.

Households' monthly health expenditure was contracted by -23% during 2009-2017, when it reached €103.3, which accounted for 7.3% of total household expenditure (6.5% in 2009), indicating households reduced purchasing power and increased participation in health expenditure. During the economic crisis period, there was a shift of household expenditure mainly towards pharmaceutical and hospital care. Specifically, from €103 monthly health expenditure per household, 34.2% refers to pharmaceuticals and 31.5% to hospital services, 13.6% to dental services and 11.4% to other medical services.

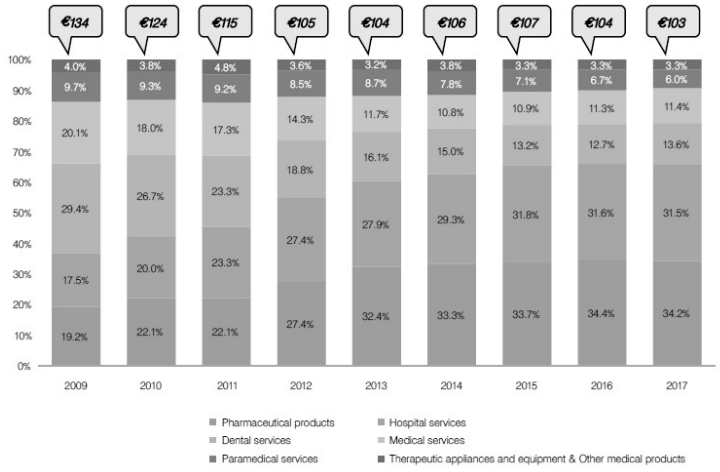


Figure 8. Breakdown of household health expenditure (%) per month – Greece[15].

2.3 Pharmaceutical Expenditure

Total expenditure for pharmaceuticals and other medical non-durable goods accounted for €3.9 billion in 2016, recording a decrease of -37.5% compared to 2009. Correspondingly, public expenditure for pharmaceuticals and other medical non-durable goods from € 4.8 billion in 2009 amounted to €2.0 billion in 2015, recording a further decline of -58.7%, while private expenditure for pharmaceuticals and other medical non-durable goods increased from €1.3 billion in 2009 to €1.8 billion 2016[13,14].

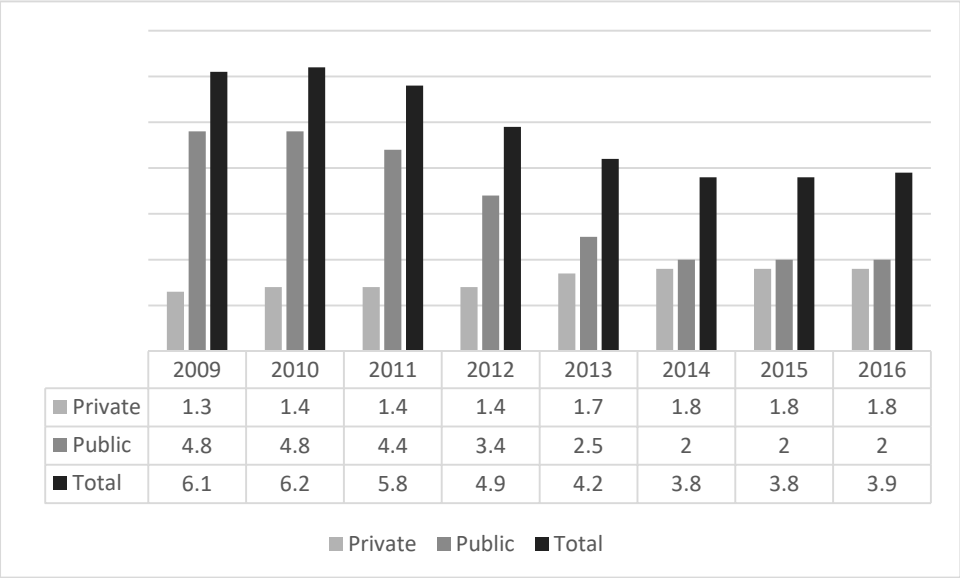


Figure 9. Total expenditure for pharmaceuticals and other medical non-durable goods (billion €) Greece [13,14].

Similarly, a downward trend was observed in public per capita expenditure for pharmaceuticals and other medical non-durable goods, from €430 in 2009 to €188 in 2016. Public per capita expenditure for pharmaceuticals and other medical non-durable goods in EU22 increased from €288 in 2009 to €303 in 2015 approximately €15 higher than Greece, while in Southern countries was €246. More specifically, the higher public per capita expenditure in 2016 for pharmaceuticals and other medical non-durable goods was recorded in Germany, Ireland and France, while Greece (€188) is below the average of EU22

(€303). On the contrary, private per capita expenditure for pharmaceuticals and other medical non-durable goods in Greece (€171) is higher than the average of EU22 (€135), ranking 5th among EU countries[8].Public expenditure for pharmaceuticals and other medical non-durable goods as a percentage of GDP in Greece is estimated at 1.1% of GDP in 2016 compared to 2% in 2009, close to EU22 and Southern countries. Public outpatient pharmaceutical expenditure amounted to €1,945 billion in 2018 (and 2019) compared to €5.1 billion in 2009, resulting in an overall decrease by -61.9%. Accordingly, there was a significant increase in the contribution of pharmaceutical industry through mandatory returns and discounts (clawback and rebates). Specifically, in 2018 industry's contribution was €990 million recording an increase of 11% in comparison to previous year. Total outpatient pharmaceutical expenditure (including estimated patients' contribution) amounted to ~€.6 billion in 2018. However, the significant decline in public outpatient pharmaceutical expenditure by 61% during 2009-2017 resulted in a 263% increase on industry's contribution over the same period. Public hospital pharmaceutical expenditure was set at €530 million for 2018, decreased by -31% compared to 2015 (€764 million), before introducing closed budget. The reduction of public hospital pharmaceutical expenditure resulted in a shift towards industry (through clawback and rebates), estimated at €436 million for 2018.

2.4. PATIENTS' CONTRIBUTION

Public pharmaceutical expenditure includes the expenditure of all the social security funds for prescribed medicines, i.e. medicines that are reimbursed by Social Security Funds (SSF). Net public pharmaceutical expenditure is the final amount paid by the SSFs after deduction of rebates & claw back.
Private pharmaceutical expenditure includes co-payment rates of insured persons for reimbursed medicines (statutory participation & the additional charge incurred when the patient selects a medicine with a higher Retail Price than the Reimbursement Price), the private costs of consumers (patients) for non-reimbursed pharmaceuticals and related products but also for those

medicines they pay or choose to pay in full, as well as the reimbursement of part of the expenditure by private insurance companies.

Patient co-payment in reimbursed medicines is distinguished in:

- Statutory co-payment: 0% or 10% or 25% of the reimbursement price
- Charge resulting from the difference between Retail Price and Reimbursement Price when the patient selects a medicine with Retail Price Higher that the Reimbursement Price

Other private payments for a medicine contain:

- either non-prescription medicines (OTC)
- either prescribed medicines which are not reimbursed (Negative List)
- either prescribed medicines of the reimbursement list, but the patient chose not to use his insurance right and chose to pay them entirely out of his pocket.

Chapter 3

Demographic Environment and Health Status of population

3.1. Social Environment

Unemployment is also a major social and health factor[16]. In Greece, the unemployment rate of the general population climbed to a historically high level of 27.5% in 2013, with a gradual improvement to 21.5% in 2017 and further de-escalation in 2018 to 19.3%, still very high for a European country[17]. It should be noted that, during the crisis the number of unemployed increased by 1,000 to 1,200 individuals per week.

Year	Unemployment Rate (%)	EU-28
2008	7,8	9
2009	9,6	9
2010	12,7	9,6
2011	17,9	9,7
2012	24,5	10,5
2013	**27,5**	**10,9**
2014	26,5	10,2
2015	24,9	9,4
2016	23,6	8,6
2017	**21,5**	**7,6**
2018	19,3	6,8
2019	17,3	6,4

Table3. Unemployment Rate of general population from 2008 to 2020 in Greece and EE-28

Unemployment among young people aged 15-24, remains very high in Greece, at 47.3% in 2017, compared with 39.6% in the South countries and 18.7% in the EU 28. Also, unemployment rates of the population aged 25-64 by educational attainment level remains high, at 23.7 % in 2017 compared with 13.7 % in the EU 28[18].

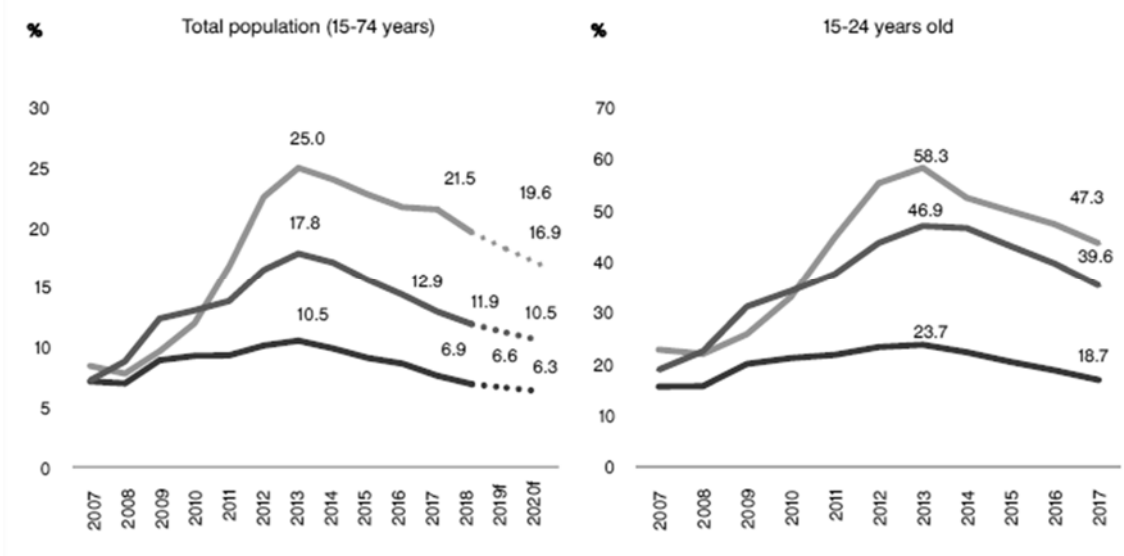


Figure 10. Unemployment rates of the population aged 25-64 by educational attainment level

At the same time, in 2017 a high rate of long-term unemployment is recorded at 72.8% of the total unemployed, that is 747 thousand people remain out of the labor market for more than 12 months. The highest unemployment rate is found among young people aged 15-24, while in absolute numbers the largest number of unemployed comes from ages 25-49, the most productive age group, with about 686 thousand people unemployed[19].

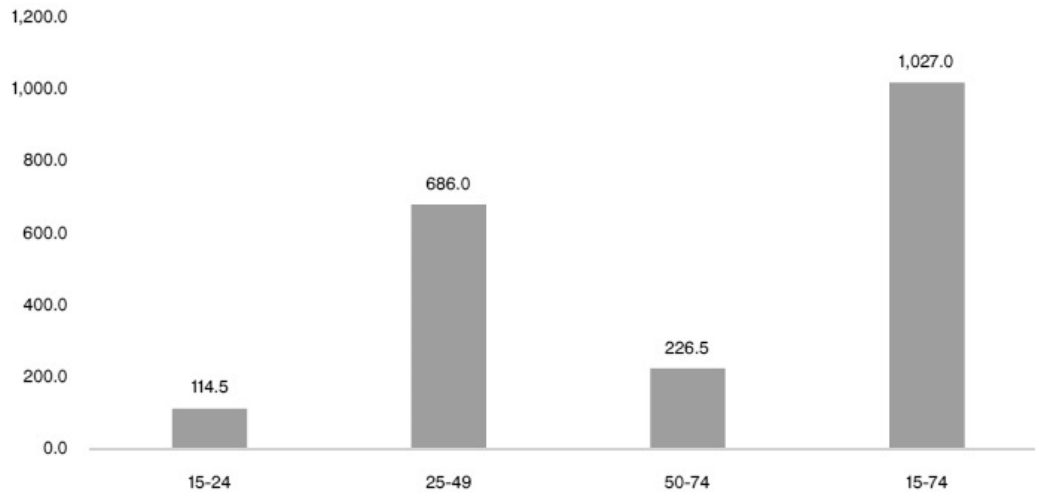


Figure 11. Number of unemployed (thousand people) by age group - Greece (2017)

Considering the long-term growth potential of Greek GDP, the long-term prospects of reducing Greek unemployment rates are not promising[20]. The weighted average GDP growth for the 2013 to 2060 period is projected to fluctuate around 0.7 percent. Such small growth in GDP is not particularly conducive to employment. Therefore, unemployment is expected to remain high until 2025 (from 28 percent in 2013 to 22.1 percent in 2020 and 17.2 percent in 2025). An easing in unemployment rates is expected after 2030, with a gradual decline that will reach 7.5 percent in 2060.

3.2 Natural Population Change

The number of births in Greece amounted to 89 thousand people in 2017 recording a 4.7% decrease from previous year, while the number of deaths recorded an increase of 4.8%, amounting to 125 thousand people. As such, the natural population change (difference births - deaths) was negatively affected in 2017, resulting in an overall reduction of -36 thousand people in the national population[21].

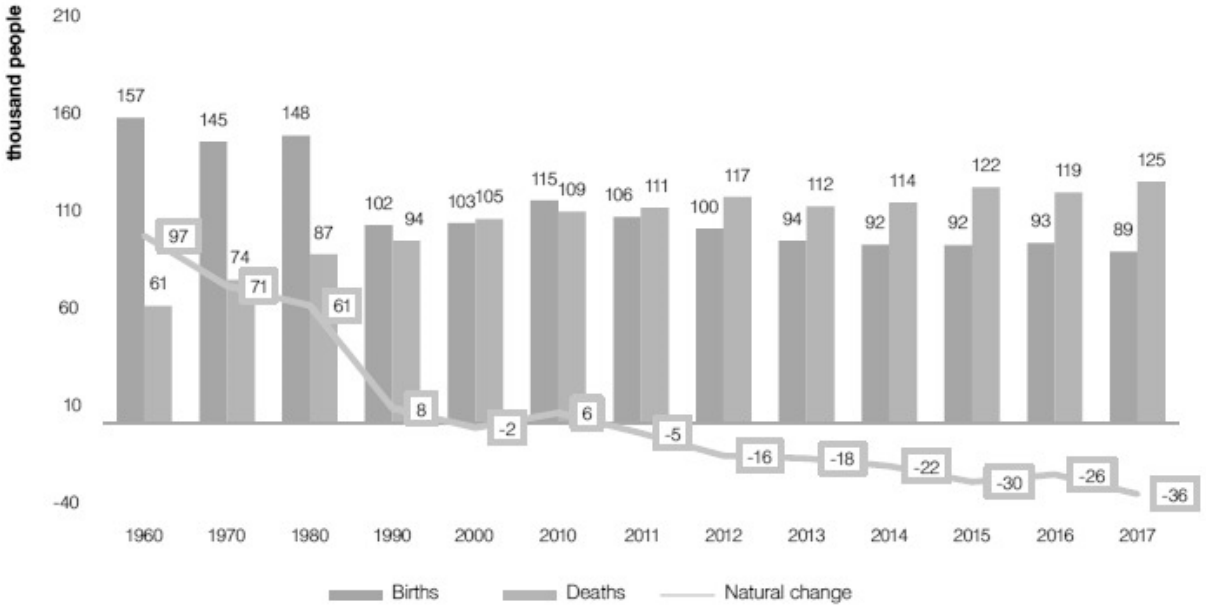


Figure 12. Natural change of population (thousand people)-Greece

3.3 Life expectancy

Life expectancy at birth in Greece reached 81.4 years in 2017, half a year more than the EU average. Since 2000, when it stood among the highest in the EU, it has increased by 2.8 years, and at a slower pace than observed in the EU as a whole. Life expectancy has increased slightly more rapidly for men while stagnating for women over the past few years, leading to a gender gap of about five years, which is similar to the EU average. Beyond the gender gap, inequalities in life expectancy also exist by socioeconomic status. In 2016, the gap in life expectancy at age 30 between people with the lowest level of education and tertiary education was 6 years for men and 2.4 years for women, although this is less than the averages in the EU (7.6 and 4.1 for men and women, respectively). The difference can be explained, at least partly, by varying levels of exposure to risk factors and lifestyles (such as higher smoking rates among men with a lower level of education)[22].

3.4 Dependency Ratio

The demographic changes directly affect population's dependency ratio. In Greece, nearly half of the population is dependent on the other half, and this proportion is expected to grow, signaling deterioration and increased pressure on the social security system, following the general trend of the developed countries. In 2018, Greece's dependency ratio reaches 53%, meaning that for every 2 active people there is 1 inactive, close to EU28 average (55%) and close to the average of Southern countries (55%). According to the United Nations, the dependency ratio in Greece is estimated to reach 91% by 2050.

3.5 Causes of death-chronic diseases prevention

Over time, a significant increase in the deaths due to circulatory system diseases is recorded, responsible for 38.3% of total deaths, despite the decline in recent years, while increase in neoplasms is recorded, accounting for 25.0% of total deaths. Interestingly, the increase in the share of diseases of the respiratory system after 2009, after a stabilization period, and finally the violent deaths and infectious and parasitic diseases compose a small part of the total deaths[22].

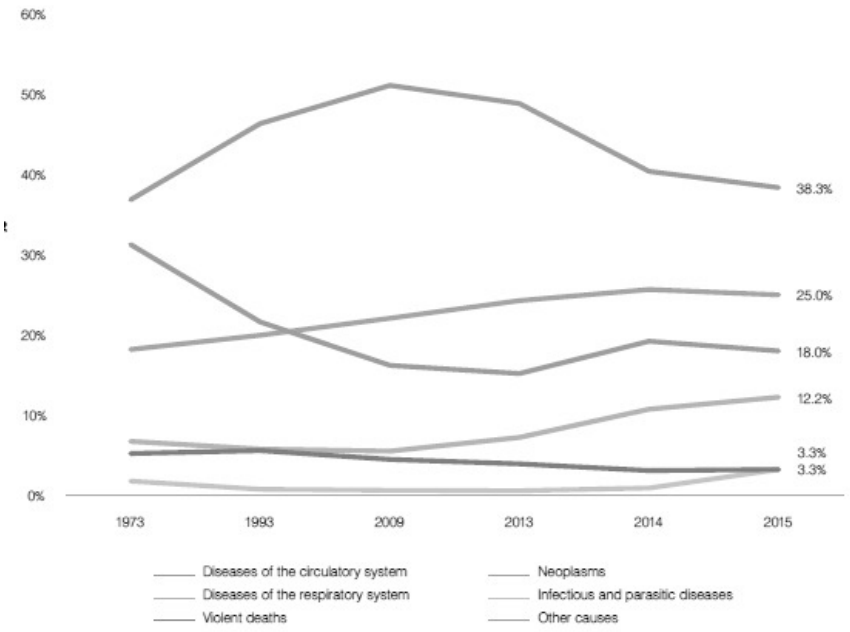


Figure 13. Causes of death (% of total deaths) – Greece

Chapter 4

Pharmaceutical Industry and economy

4.1 Supply chain for pharmaceutical products in Greece

The production and distribution of pharmaceuticals is one of the most dynamic sectors in the Greek industry. Supply chain for pharmaceutical products is comprised of pharmaceutical companies (both manufacturers and importers), wholesalers (both storage and distribution) and pharmacies. More specifically, all pharmaceutical products, except products for hospital use only which are provided through sales to hospitals, are distributed through wholesalers to pharmacies, follow the path: pharmaceutical company - wholesalers – pharmacy[23,24].

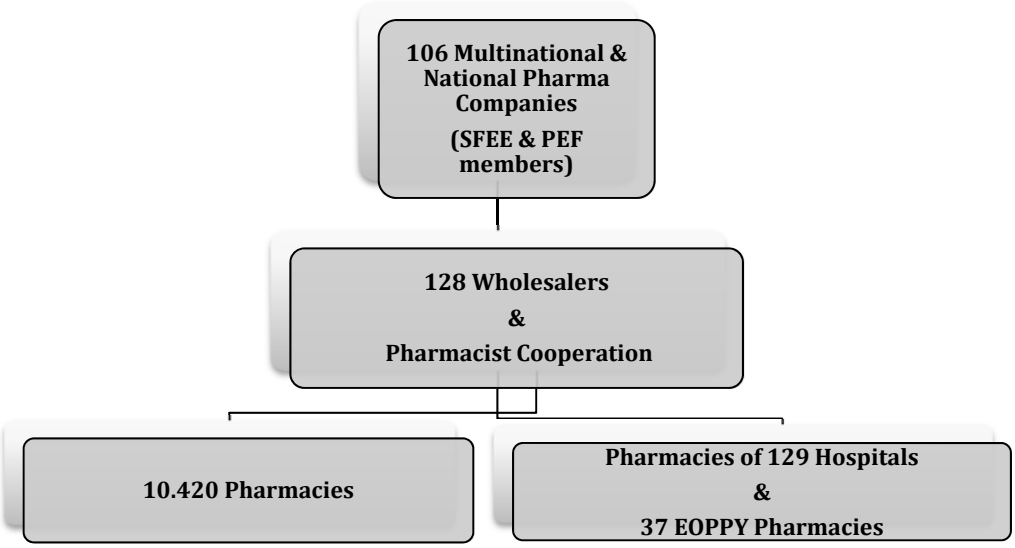


Figure 14. Supply chain of pharmaceutical products in Greece

With a pharmacy density of 97 pharmacies per 100,000 inhabitants. Greece comes first among the EU-28 average of 31 pharmacies per 100,000 inhabitants. In 2017, 10,420 pharmacies operated in Greece, out of which 3,739 pharmacies (36%) were located in the Region of Attica. The number of wholesalers in 2016 amounted to 128 in 2016 compared to 120 in 2016.

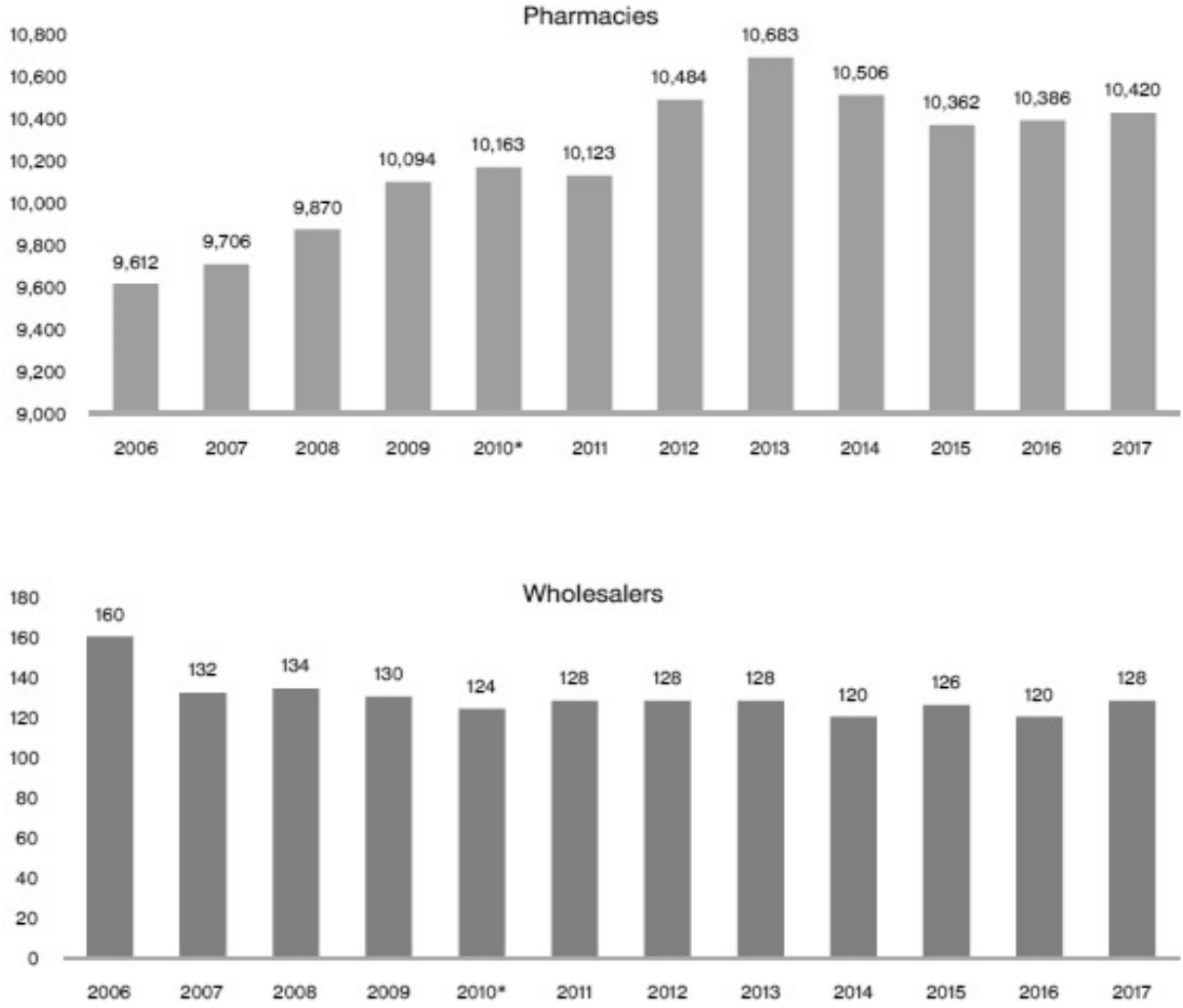


Figure 15. Pharmacies and wholesalers- Greece

EOPYY Pharmacies, EOPYY initially operated 5 pharmacies in Attica region and 1 in Thessaloniki, supplying high cost medicines without copayment and without the confirmation of the prescription by the relevant social security fund (except 2 month). Currently, 37 pharmacies of EOPYY are in operation. In other parts of the country, insured citizens can obtain high cost medicines for the treatment of

serious diseases (Law 3816/2010) from EOPYY's local health units, after placing an order.

4.2 Research and Development (R&D)

Greece invests in R&D much lower compared to other countries. In 2016 Greece spent only 5.7% compared to Italy and 8.8% compared to Spain. The investments in R&D are expected to rise, as the latest R&D tax incentive included explicitly clinical trials 1, 2 and 3. However the rise will be moderate, as long as the intensity and the simplicity of the incentives provided by the Greek state do not match the available incentives in the other countries[25].

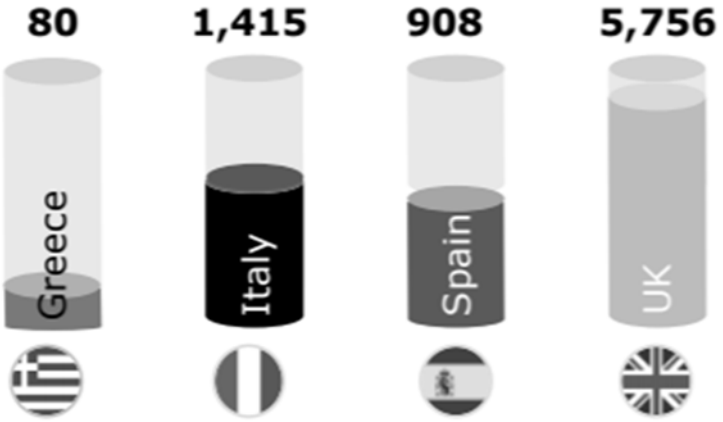


Figure 16. Pharmaceutical R&D among European countries (million €)

Greece ranked in the last places among EU countries with regards to the R&D investment, spending €80 million according to EOF estimations. With respect to the number of clinical studies conducted in 2016, irrespective of phase, it was found that 2.028 clinical studies were conducted in Greece[26].

4.3 Production

According to Eurostat database in terms of value, pharmaceutical production in Greece was estimated at €954 million in 2017, approximately 6.6% higher than in 2016[27].

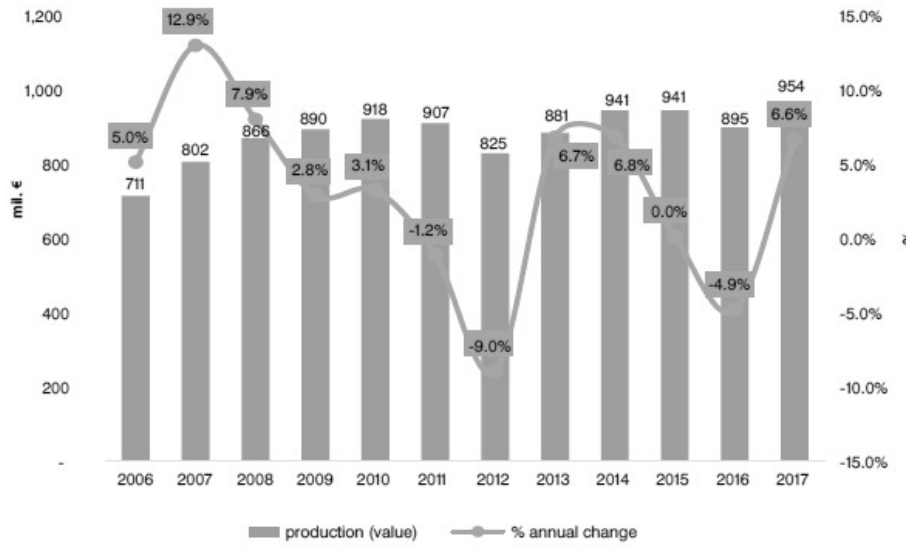


Figure 17. Production of pharmaceutical products (million €)

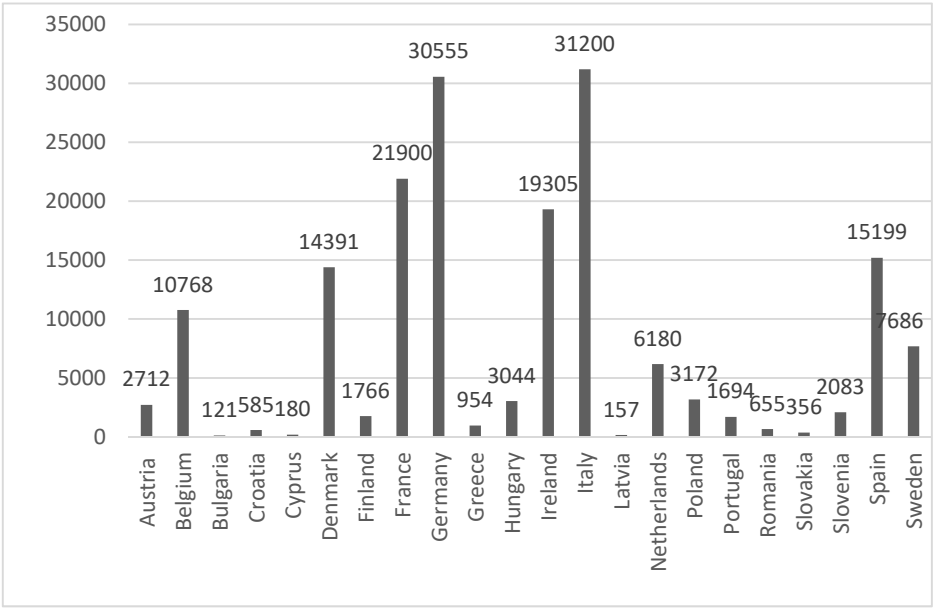


Figure 18. Production of pharmaceutical products (million €) in EU-28.

The industrial index of domestic pharmaceutical production, recorded a significant increase in 2017 and 2018, indicating that the value of domestic

Figure. Industrial index of domestic pharmaceutical production (2015=100)

pharmaceutical production for 2018 will be at higher levels[28].

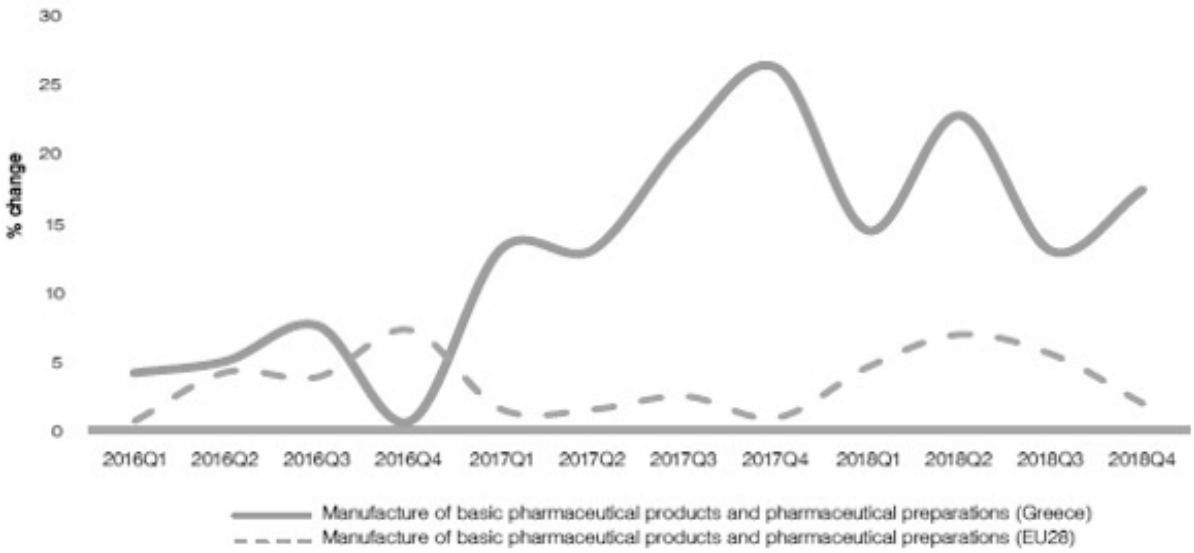


Figure 19. Industrial index of domestic pharmaceutical production (2015=100)

The gross Value Added (GVA) of domestic pharmaceutical production is estimated at €668 million In 2017, higher by 9.7% compared to 2016, and amounted with a share of 3.0% in total manufacturing sector.

Figure 20. Gross Value Added of pharmaceutical production and share in manufacturing (%)

4.4 Employment

According to Eurostat, 14.4 thousand people were employed in pharmaceutical production in Greece in 2017, demonstrating a decrease of -14.3% compared to 2016[29].

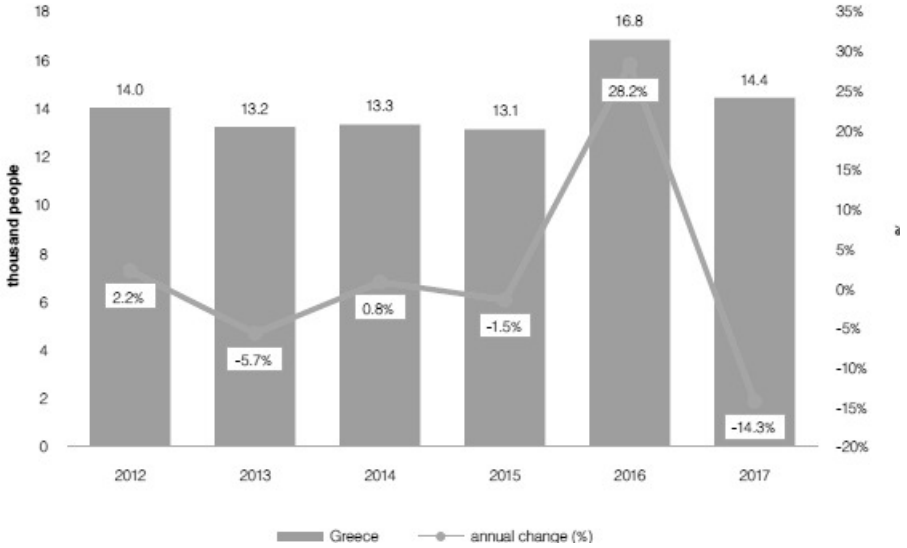


Figure 21. Employment in pharmaceutical production (thousand people)

At the same time, according to the International Standard Classification of Education (ISCED) for 2017, the educational background of people working in the pharmaceutical industry was very high, with 60,5% of total employees in pharmaceutical production with university education compared to 35,7 % in the manufacturing and 22.0%, in the total economy, indicating the high educational training of the employees in the pharmaceutical industry. This difference shows the importance of domestic pharmaceutical production as a preventive sector in the brain drain[30].

Industry	2011	2012	2013	2014	2015	2016	2017
Pharmaceutical	49,30%	48,60%	50,30%	66,40%	71,60%	64%	**60,50%**
Manufacturing	16,20%	17,80%	18,20%	18,20%	20,10%	22,70%	**22,00%**
Total Economy	30,20%	32,10%	33,40%	33,50%	33,80%	35%	**35,70%**

Table 4. Number of employees with tertiary education in pharmaceutical production (%)

The research-based pharmaceutical industry in Europe also, is one of major high-technology industrial employers. Recent studies in some countries showed that the research-based pharmaceutical industry generates about four times more employment than it other's industries. Furthermore, a significant proportion of these are valuable also skilled jobs, for instance in the fields of academia or clinical science, which can help maintain a high-level knowledge base and prevent a European "brain drain".

Country	Number of Employees	Country	Number of Employees2
Austria	14.860	Italy	65.400
Belgium	35.711	Latvia	2.154
Bulgaria	11.500	Lithuania	1.120
Croatia	5.474	Malta	1.120
Cyprus	1.140	Netherlands	17.900
Czech Rep.	10.083	Poland	29.873
Denmark	26.963	Portugal	7.700
Estonia	380	Romania	30.000
Finland	4.722	Slovakia	2.287
France	98.786	Slovenia	9.954
Germany	117.013	Spain	42.687
Greece	19.700	Sweden	11.012
Hungary	29.400	Switzerland	46.503
Ireland	29.766	U.K.	63.250

Table 5. Number of employees at research-based pharmaceutical industry in Europe.

A one other important measurement for employed people is the recording time in Full Time Equivalent (FTE), by calculating total employment assuming that all workers are employed full-time. According to the available data, pharmaceutical industry recorded a decline of employment in FTEs by -7.2% during 2010-2017 compared to total manufacturing (-23.2%), indicating that employment in pharmaceutical sector shows inflexibility. Simultaneously, total wage cost decreased by -12.3% compared to much larger decline in manufacturing (-34.3%). At the same time, the average hourly wage stood at €10.3 for

pharmaceutical industry compared to €6.7 in total manufacturing and €5.3 for the total economy[30].

Industry	Employement % change (FTE)	Compensation of Employees	Average hourly wage (2017)
Pharmaceutical	**-7,20%**	**-12,30%**	**10,30 €**
Manufacturing	-23,20%	-34,30%	6,70 €
Total Economy	-10,80%	-29,70%	5,30 €

Table 6. Change in employment and wages 2010-2017

4.5 Sales

Sales of pharmaceutical products to pharmacies & wholesalers (in values) amounted to €4.0 billion. In 2017, showing a reduction of -1.8% compared to 2016. On the contrary, sales to hospitals & EOPYY pharmacies amounted to €1.8 billion in 2017 presenting an increase of +1.9% compared to previous year. Approximately, 68.8% of total sales were supplied to wholesalers and private pharmacies, while the remaining 31.2% to hospitals and EOPYY pharmacies[31].

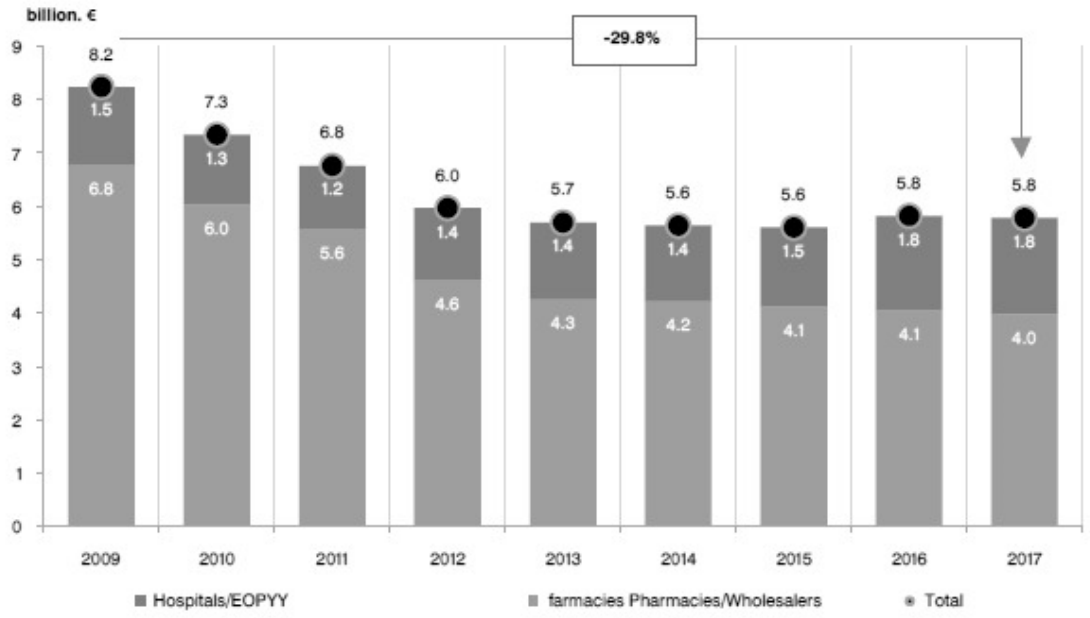


Figure 22. Sales of pharmaceutical products in values (billion €)-Greece

Regarding the number of units (packages), an increase of +2.7% was recorded in 2017 compared to 2016 (562.1 million packages) with an increase of +2.9% in pharmacies/wholesalers and an increase of 1.7% in hospitals/EOPYY pharmacies was depicted[32].

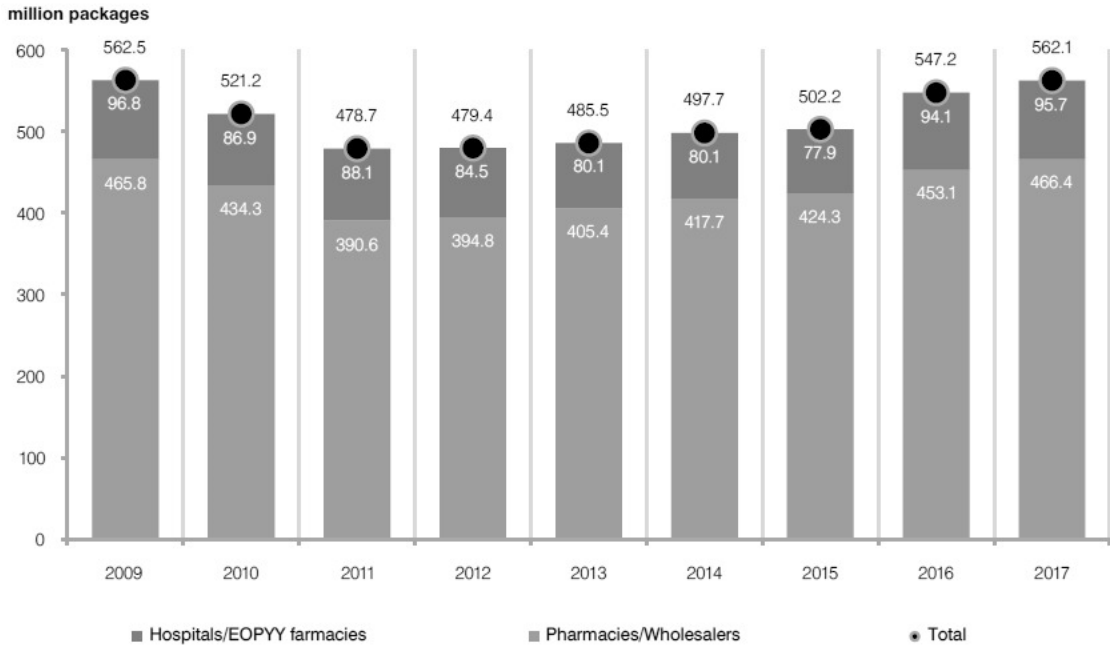


Figure 23. Sales of pharmaceutical products in units (million packages) – Greece[34]

Pharmaceutical products can be classified according to their patent protection status. According to IQVIA, the penetration rate of patent protected medicinal products, on patent (the drug is covered under patent protection, which means that only the pharmaceutical company that holds the patent is allowed to manufacture, market the drug and eventually make profit from it) in terms of volume account for 9.3% of the market, which is higher than the average of EU18 (6.18%) which can be partly justified by their significantly lower prices in Greece compared to EU18 countries (€0.91 per unit on average compared to €2.05). Respectively, the market share of non-protected pharmaceutical products, off patent and generics (generic drug is a pharmaceutical drug that contains the same chemical substance as a drug that was originally protected by chemical patents. Generic drugs are allowed for sale after the patents on the original drugs expire) amounted to 67.9% .It is worth noting that the penetration rate of off-patent is higher than the average of EU18 (19.8%), while penetration rate of generics is much lower than the average of EU18 (61.0%).

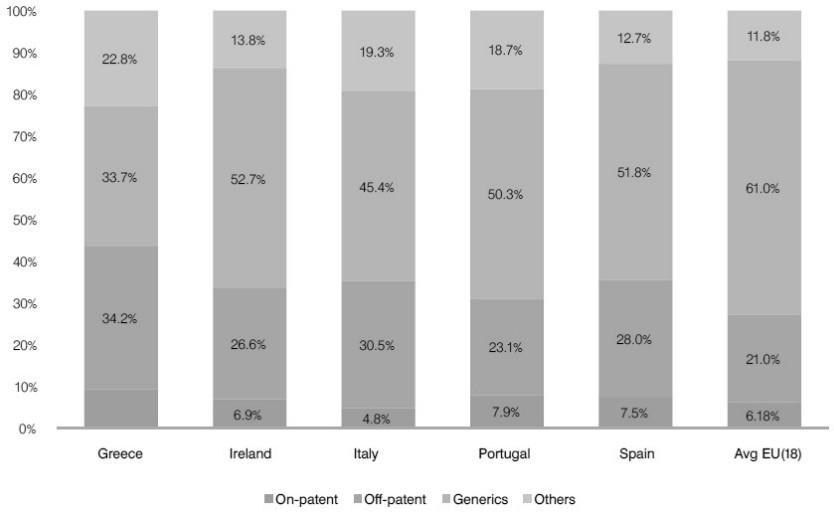
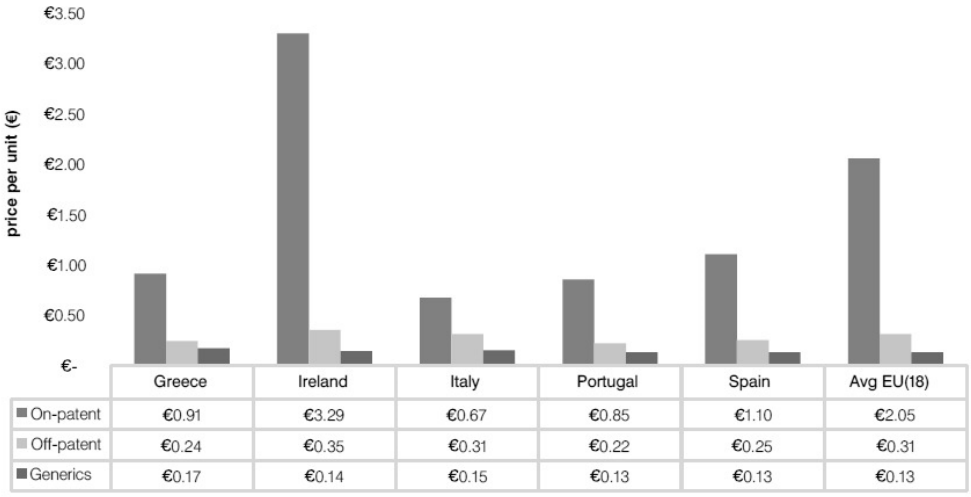


Figure 24. Penetration of pharmaceuticals in EU18, 2018 (in volume) based on patent status**. Source:** IQVIA, 08/2018

According to IQVIA, penetration rate in volume for off patent and generic products is partly justified by significantly lower prices for off patent products in Greece compared to the average of EU18 (€ 0.24 per unit compared to €0.31) and by slightly higher prices for generic products in Greece compared to the average of EU18 (€0.17 per unit compared to €0.13).



	Greece	Ireland	Italy	Portugal	Spain	Avg EU(18)
On-patent	€0.91	€3.29	€0.67	€0.85	€1.10	€2.05
Off-patent	€0.24	€0.35	€0.31	€0.22	€0.25	€0.31
Generics	€0.17	€0.14	€0.15	€0.13	€0.13	€0.13

Figure 25. Pricing of pharmaceuticals in EU18, 2018 (price per unit. €) based on patent status. **Source:** IQVIA, 08/2018

OTC (over the counter) drugs are medicines sold directly to a consumer without a prescription from a healthcare professional, as opposed to prescription drugs, which may be sold only to consumers possessing a valid prescription. The market of OTC followed an upward trend from 2013 onwards from €122 million in 2013 to €165 million in 2017, an increase of 35.2%[33].

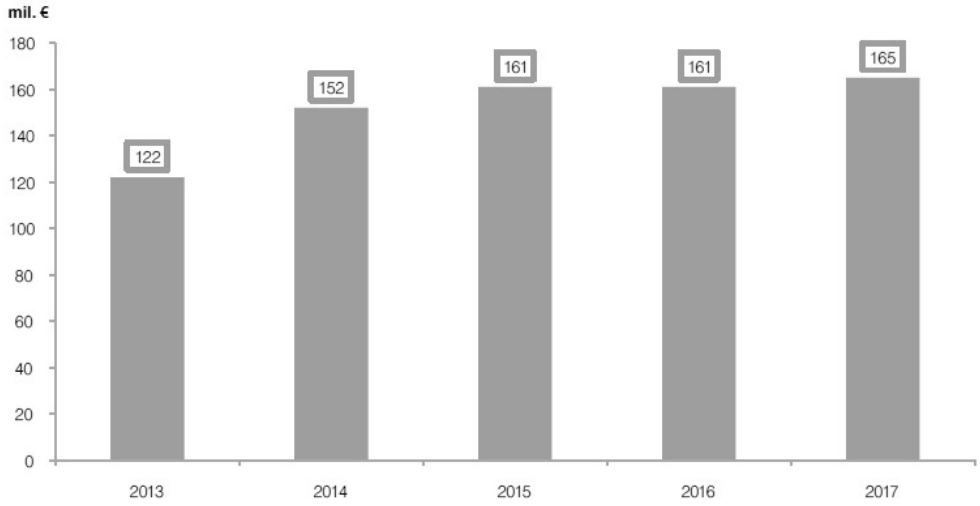


Figure 26. OTC sales in value 2013-2017 (in million €)

The general Distribution Medicines (GEDIFA), a subset of OTC (216 of the total 1.582 OTC), are available outside pharmacies and concern analgesics, antipyretics, antipruritic, topical medications, laxatives (to treat constipation) and mouthwashes. Of the self-medication products, analgesics, cough and cold products, digestive products, dermatological products and vitamins recorded the largest sales.

Category	2013	2014	2015	2016	2017	%17/17
Analgesics	60	65	64	65	71	9.2%
Cough & Cold	67	69	66	65	75	13.9%
Digestives & Intestinal	23	24	25	28	32	12.7%
Skin Treatment	33	32	32	32	30	5.1%
Vitamins & Minerals	62	70	68	67	72	7.2%
Rest categories	81	64	24	83	89	7.7%

Table7. Sales self-medication products (million €)

4.5.1 Market Share of Top Competitors

In 2016, the market appears to be quite fragmented, with 90 companies sharing 59% of the total pie and the top 10 players sharing the remaining 41%. The list of top 10 players in the market consists of 7 multinational and 3 Greek companies[34].

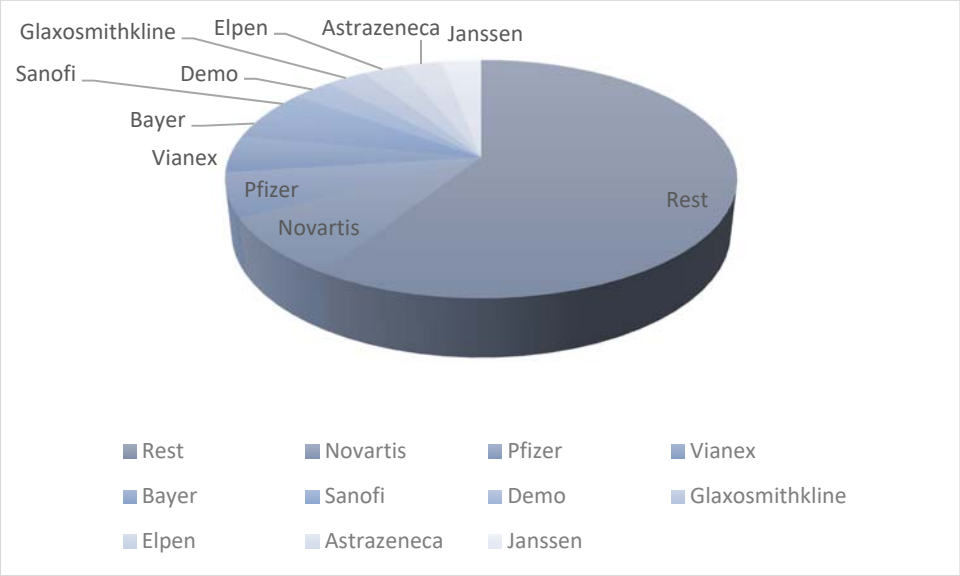


Figure 27. Market Share of top 10 Pharma Companies in Greece 2016

4.6 External Trade

Imports and exports of pharmaceutical products amounted to €2.8 billion and €1.4 billion in 2018 respectively, increased by 1.3%, and 24%, resulting on a deficit of -€1.3 billion. Pharmaceuticals exports accounted for 4.3% of total Greek exports in 2018. In comparison to 4.0% in 2017. Correspondingly, imports account for 5.0% of the total exports of the country, with downward trend over the last three years. Overall, the evolution of external trade indicates in general terms that there is a boost in exports from 2011 onwards and in parallel a decline in imports[35].

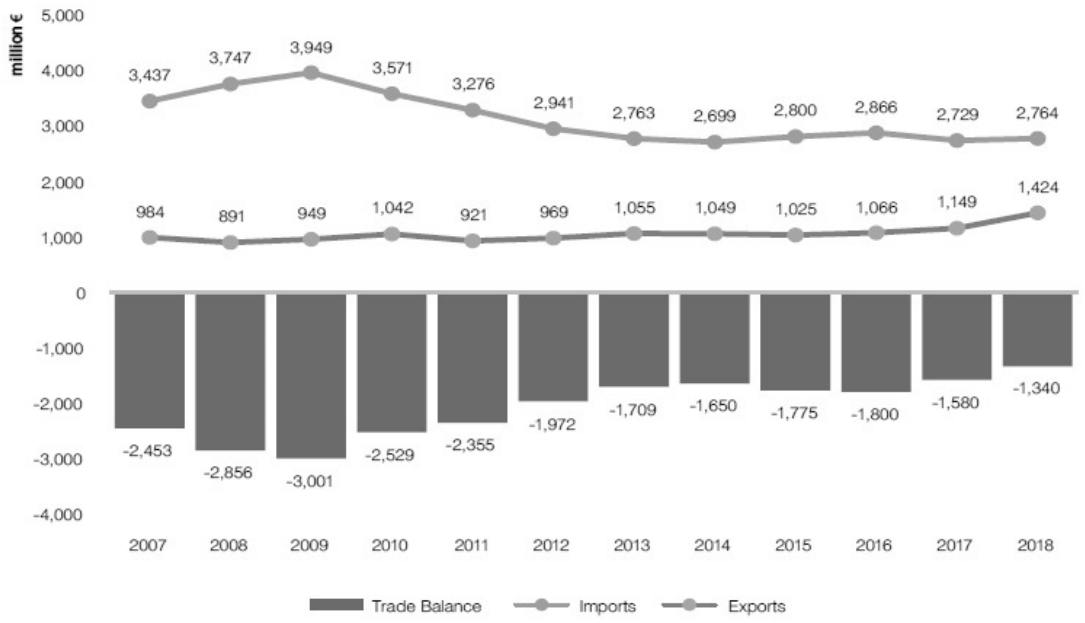


Figure 28. Evolution of pharmaceutical trade balance (million €)

Regarding the most important trading partners in the category of pharmaceuticals, on the side of imports is Germany (27%), France (10.7%) and Switzerland (10%), while on the side of exports is again Germany (18.8%), United Kingdom (14.8%) and Cyprus (7.9%). It should be noted that the Greek pharmaceutical industry imports from 61 countries and exports to 141 countries.

Chapter 5

Pfizer Inc.

5.1 Introduction

Pfizer Inc. is an American multinational pharmaceutical corporation headquartered in New York City. Operates in more than 125 countries across the world. It also has 42 manufacturing sites worldwide. It is one of the world's largest pharmaceutical companies. The research-based company has a varied portfolio that spans many therapy areas, including inflammation and immunology, internal medicine, oncology, rare diseases, vaccines and hospital (anti-infectives). Key products of Pfizer are Lipitor, Viagra, Xanax, Lyrica, Zoloft, Prevenar 13, Eliquis and Zavicefta. In 2019, the company's total revenue was about 51.8 billion U.S. dollars. and has 8 blockbusters products with sales greater than $1 billion. Pfizer has more than 95 projects in Clinical Research & Development and 88,300 employees around the world.

5.2 History

Pfizer Inc. was founded in 1849 by two recent German immigrants to the USA, Charles Pfizer and Charles Erhart. With $2,500 borrowed from Charles Pfizer's father, open Charles Pfizer & Company as a fine chemicals business[36]. A modest red brick building in the Williamsburg section of Brooklyn, New York, serves as office, laboratory, factory, and warehouse. The company's first product is a palatable form of santonin — an antiparasitic used to treat intestinal worms, a common affliction in mid-19th century America. Combining their skills, Pfizer, a chemist, and Erhart, a confectioner, blend santonin with almond-toffee flavoring

and shape it into a candy cone. The "new" santonin is an immediate success and the company is launched.

In 1862 the first domestic production of tartaric acid and cream of tartar, products vital to the food and chemical industries, is launched by Pfizer. As demand for painkillers, preservatives, and disinfectants soars during the Civil War, Pfizer expands production of tartaric acid (used as a laxative and skin coolant) and cream of tartar (effective as both a diuretic and cleansing agent) as well as other vital drugs to help meet the needs of the Union Army. Among these are iodine, morphine, chloroform, camphor, and mercurials, which, in addition to medicinal applications, are used in the emerging field of photography, the new medium photographer Mathew Brady employs to chronicle the Civil War. The expansion propelled by the Civil War continues and Pfizer's revenues double. The company now has a substantially increased product line and 150 new employees. To accommodate this growth, it buys and renovates a post-Revolutionary-era building at 81 Maiden Lane in Manhattan and moves its headquarters there. The site carries the Pfizer name for nearly a century.

In 1880 Using imported concentrates of lemon and lime, Pfizer begins manufacturing citric acid. Pfizer soon becomes America's leading producer of citric acid. As new drinks like Coca-Cola™, Dr. Pepper™, and Pepsi-Cola™ gain popularity, demand for citric acid soars. It becomes Pfizer's main product and the launching pad of its growth in the decades to follow.

On December 27, cofounder Charles Erhart dies and leaves a partnership worth $250,000 to his son William. However, the agreement stipulates that Charles Pfizer can buy William Erhart's share at half its inventory value — an option Charles Pfizer quickly exercises, consolidating ownership of the company in his hands.

A leader in the American chemical business, Pfizer in 1989 marks its 50th anniversary. Its portfolio includes a wide array of industrial and pharmacological products, anchored by citric acid, camphor, cream of tartar, borax, and iodine. The company has offices in New York and Chicago, and its contacts in the import-export business crisscross the world.

In 1905 Emile Pfizer, Charles Pfizer's youngest son, is appointed President at a special board. He serves as President from 1906 to 1941 and briefly as Chairman in 1941. He is the last member of the Pfizer/Erhart family to be actively involved with the company. At the age of 82, Charles Pfizer dies while vacationing at his Newport, Rhode Island estate. A tribute to Pfizer in The New York Tribune notes that "by bringing to his task a thorough German technical education, great industry, and determination, he successfully met all difficulties and each year expanded his business." In 1906 Company sales exceed $3 million.

Antibiotics marked the transition to the modern Pfizer. Their follow-up to penicillin, Terramycin, first marketed in 1950, was both their first proprietary drug, and the first for which the company used sales reps, them soon to be formidable force of salesmen starting with just eight members.

Pfizer initiated its first major internationalization at this stage, moving into nine new countries in 1951. It was at this time they set their site at Sandwich in the UK, initially just to finish processing compounds imported from America, but due to tariffs on imported products the company rapidly expanded the plant to accommodate producing medicines from scratch. Pfizer's international expansion put great trust in their local staff compared to other organizations, recruiting nationals and giving them a great deal of autonomy.

The areas that Pfizer directed its research into expanded in these years as well. In 1952, it established its Agricultural Division, beginning its foray into animal health, and in 1953 acquired Roerig, a nutritional supplement specialist, which became incorporated as a division in its own right. By the 1960s, Pfizer were at their "most diversified point in [its] history" – in its own words, its interests "stretched from pills to perfume, and petrochemicals to pet products".

Throughout the 60s and 70s the company continued to bring out new drugs, such as the broad spectrum antibiotic Vibramycin, and broadening its research base, reorganizing its R&D operations in 1971 into a Central Research Division, and increasing spend on this area of the company from 5% to 15% of revenue. This attention to innovation began to pay off in the 1980s, with a series of blockbusters, the first of which, the COX inhibitor Feldene, arrived in 1980

rapidly becoming one of the biggest-selling anti-inflammatories in the world. Others rapidly followed, including Glucotrol, aimed at diabetics, and Procardia, an anti-hypertensive. The 1990s and 2000s would soon take this blockbuster-based success to new levels.

The statin Lipitor, approved in 1997 for Warner-Lambert before their merger with Pfizer, became the biggest-selling prescription medicine ever, earning Pfizer $US12 billion a year in 2007, one quarter of its total sales. It almost hadn't made it through clinical development, facing problems with ineffective chiral isomers and limited efficacy in animal testing, but showed such impact in human trials that it blew the competition away. Other big sellers in recent years have included Lyrica for neuropathic pain, Celebrex

But Pfizer's almost Hollywood-level blockbuster of the 1990s was the little blue pill of Viagra, which achieved such levels of public recognition that we're all receiving the spam emails about it over ten years later. Formulated initially at the Sandwich site in the UK as an anti-hypertensive, it was found have "unexpected" side effects that made the company rapidly change the indication to erectile dysfunction. But despite the cultural ubiquity, Viagra has recently faced the inevitable threat from competition and generics, dropping from 92% of the ED market in 2000 to around 50% in 2007, with vigorous competition from drugs such as Cialis and Levitra.

Since the turn of the millennium, Pfizer has embarked on a series of mega-mergers, gobbling up Warner-Lambert in 2000, Pharmacia, Upjohn in 2002, Wyeth in 2009.

And in conclusion, Pfizer it will have the power to shape the pharmaceutical industry well into the 21st century. With fingers in every pie, ranging from small molecules to biologics in every clinical area, to stem cells and consumer goods, Pfizer will surely celebrate its 200th anniversary in as strong a position as it spent the last 170 years.

5.3. S.W.O.T. Analysis

Strengths	Weakness
• One of the world's largest pharmaceutical companies, more than 125 countries in which Pfizer sells products and 42 manufacturing sites across the world. • One of the main strengths of Pfizer is the company's' experience in 170 years Research & Development providing a broad therapeutic coverage. Pfizer's product pipeline currently consists of 95 projects. • Excellent (R&D) creating innovative products that change people live. Pfizer has more than 180 new R&D Collaborations in 2018. • Strong brand name and extensive portfolio with several best-selling drugs. • Pfizer possesses a strong market position with high sales and a solid marketing infrastructure. • 8 blockbuster products with sale greater than $1 billion in 2018. • Has 88,300 employees around the world. • Market leader: $ 51.8 billion in revenue in 2019	• Expiring Patents: The loss of exclusivity has an important impact on all of Pfizer's products, but especially on their blockbusters due to in its strong reliance on the blockbuster portfolio that generates almost a half of the overall sales. For example, for the blockbuster product Lipitor, when its patent expired in 2011, revenues decreased from US$ 9.6 billion in 2011 to US$2.3 billion in 2013. Another example is Lyrica which expiration date was June 30, 2019. The company expected to face new generic competition this year. • Negative image brand due to involvement in largest healthcare fraud settlement. In 2009, Pfizer pleaded guilty to the illegal marketing of the arthritis drug Bextra for uses unapproved by the U.S. Food and Drug Administration (FDA), and agreed to a $2.3 billion settlement, the largest criminal fine of healthcare any kind ever.
Opportunities	**Threats**
• Strategic mergers and acquisitions with other pharmaceutical companies and organizations to boost its research in Oncology category. For example, on June 2019 Pfizer announced the successful completion of its acquisition of Array BioPharma Inc., advancing breakthrough science for the discovery, development and commercialization of targeted small molecule medicines to treat cancer. • Maintain aggressive R&D and spend more of company's annual revenue. • New uses of medicinal dugs to its already existing portfolio	• Pfizer is highly dependent on external environment such as government control and healthcare regulations • Risk of unsuccessful new products, each new drug can cost as much as $1 billion to develop, with no guarantee of success. • Regulatory environment is becoming more & more stringent • Economic slowdown in European markets • Though competition from generic drug makers (i.e. Viagra high cost leading to cheaper substitutes)

5.4 Mergers and Acquisitions Strategy

Pfizer has grown by megamergers and acquisitions. In the year 2000, Pfizer acquired Warner–Lambert for $111.8 billion to gain control of Lipitor. Pfizer acquired Pharmacia to acquire full rights to the product Celebrex. Pharmacia was itself formed by the series of mergers which included Upjohn, Searle, and Monsanto. On January 26, 2009, after more than a year of talks between the two companies, Pfizer agreed to buy pharmaceuticals rival Wyeth for a combined US$68 billion. Pfizer acquired Hospira Inc. to create a leading provider of global sterile injectable portfolios. The combined company had a strong portfolio of drugs with revenues of over one billion. As it well known oncology has become one of the most profitable areas for drug companies. Thus, Pfizer acquired Medivation in 2016 and Array BioPharma 2019 in order to build a leading oncology portfolio. The addition of Medivetion and Array BioPharma will strength its pipeline of oncology drugs and accelerate its pathway to a leadership position in oncology, In late July 2019, the company announced that it would spin off and merge its off-patent medicine division, Upjohn, with Mylan, forming a brand new pharmaceutical business with sales of around $20 billion

Year	Target Company	Value in billion ($)
2000	Warner Lambert	111.8
2002	Pharmacia	60
2009	Wyeth	68
2015	Hospira	15.2
2016	Medivation	14
2019	Array BioPharma	11.4

Table 8. Mergers and acquisitions undertaken by Pfizer.

5.4.1.1. Acquisition of Warner–Lambert

In the year 2000, Pfizer acquired Warner–Lambert which was one of the fastest-growing pharma companies in the world. The acquisition added to the global strengths of Pfizer group[37]. As a result of the acquisition,
Pfizer gained product lines such as Parke–Davis branded pharmaceuticals, Listerine mouthwash. Both Pfizer and Warner–Lambert traced its history back to the mid-1800s. In 1886 drug manufacturing company William R. Warner & Co was established. During the time period, Lambert Pharmacal company was established whose main product was Listerine (antiseptic). In the year 1955, Warner and Lambert combined to form Warner– Lambert (Reuters,1993). Over the years, the company expanded through many mergers and acquisitions to become an international competitor in several businesses. In 1976, Warner–Lambert acquired Parke–Davis which was one of the largest drug makers. With this acquisition, Warner–Lambert refocused on three main businesses: prescription pharmaceuticals, consumer healthcare products, and gums and mints. In 1996, Warner–Lambert entered into a co-marketing agreement with Pfizer on Lipitor which belonged to the statin class of lipid-lowering agents. Lipitor introduced by Parke–Davis was one of the largest selling pharmaceutical products in the world. In 1999, Warner–Lambert acquired Agouron which was a leader in protein-based drug design and marketer of the protease inhibitor, Viracept (nelfinavir mesylate). In the year before merger, Warner–Lambert had net earnings of $1.7 billion on sales of $12.9 billion, and Pfizer had net earnings of $3.4 billion on sales of $16.2 billion in sales. In January 2000. Warner–Lambert was considered as a prize within the industry for its blockbuster products which included the cholesterol-fighting drug Lipitor marketed jointly with Pfizer.

5.4.1.2. Strategic Perspective of the Deal

The $90-billion merger deal in which Pfizer acquired Warner–Lambert resulted in the creation of the second largest pharmaceutical company in the world[38]. The combined firm called Pfizer Inc. had annual revenues of $28 billion and market capitalization in excess of $230 billion. Under the terms of the deal, Warner–

Lambert stockholders received 2.75 Pfizer shares for each Warner–Lambert share which was valued at $98.31 per share. On merger completion, Pfizer shareholders owned approximately 61% of the new company, while Warner–Lambert shareholders owned 39% of the company. On the basis of Pfizer's closing share price of $35.75, the value of the deal for Warner–Lambert was estimated at $90.27 billion.

Pfizer's acquisition of Warner–Lambert resulted in the combined group having eight products with greater than $1 billion in global sales and R&D budget which amounted to $4.7 billion. The deal was aimed at increasing sales, reducing costs, and sustaining growth. The combined firm was positioned for global leadership in the discovery of new medicines. The combined company was expected to have compounded 3-year annual earnings growth of 25% and achieve annual cost savings of $1.6 billion by the year 2002. The merged company was expected to spend $4.7 billion on research and development. The combination gave leadership position to Pfizer in the areas of cardiovascular, lipid control drugs, central nervous system, and infectious disease pharmaceutical segments. During the merger period, about 138 products were under development. The acquisition added a host of consumer brands like Halls cough drops, antihistamine Benadryl, the decongestant Sudafed, and Listerine mouthwash to the Pfizer portfolio. As a result of the acquisition, Pfizer increased its sales representative force by 2500 in addition to the existing force of 5000 workers. The combined company also had a research staff of 12,000 which was the largest at the same of acquisition. In the year before merger, the fastest-growing segments of Pfizer's revenue were accounted from the sales of Lipitor which was made by Warner–Lambert and from Celebrex, an arthritis drug which was made by Monsanto. One of the prime reasons why Pfizer launched a hostile bid on Warner was on account of Pfizer's co-marketing agreement with Warner– Lambert. Under the terms of agreement, Pfizer got approximately half of the profits of the drug. In the year 1999, this amount amounted to $5 billion. But when Warner– Lambert announced its plan to buy the American Products Corporation, Pfizer expected that it may lose its agreement on Lipitor. The two companies had a total workforce of 87,000 workers. The combined company had 6.3% market share. The companies had

little overlap, and antitrust issues were not expected to be a factor in completing the deal. Pfizer was best known for its Viagra impotency drug and Zoloft antidepressant at the time of acquisition. Pfizer had a more diverse therapeutic focus than Warner–Lambert. Pfizer was active in six therapy areas, while Warner–Lambert was active in three areas. The merged company held strong position within the CNS and anti-infective therapy areas mainly on account of two of Pfizer's leading products, the antidepressant Zoloft and an antibacterial Zithromax (azithromycin). Both companies also marketed treatments for diabetics. Warner–Lambert's second highest selling drug Rezulin was a diabetes drug, while Pfizer's leading diabetes drug was Glucotrol XL. The merger was expected to result in a strong cardiovascular portfolio which contains two blockbuster drugs. The combined firm was also strong in the areas of CNS and anti-infectives. Pfizer's main therapy areas – cardiovascular and CNS – were supported by the company's R&D pipeline. The acquisition also strengthened Pfizer's phase II pipeline in the therapy areas of cancer, endocrine and gastrointestinal. Scope for synergy existed between Warner–Lambert's and Pfizer's endocrine therapy areas where Warner–Lambert focused on two products for diabetes neuropathy. Pfizer was also involved in the development of a new inhaled version of insulin which complemented Pfizer's and Warner–Lambert's existing diabetes products [39]. The merger was expected to result in a number of synergies with respect to therapy area focus particularly in the area of cardiovascular products. Both companies also complemented each other with respect to their R&D pipelines.

5.4.2.1. Merger with Pharmacia

The merger between Pfizer Inc. and Pharmacia Corporation was completed in the year 2003. The combined new company became the leading research-based pharmaceutical company in the world. Pharmacia AB was established by the combination of Farmitalia Carlo Erba, Kabi Pharmacia, and Pharmacia Aktiebolaget in the year 1911. In the year 1995, Pharmacia and Upjohn merged together. The combined company became the leading pharmaceutical company focusing on human healthcare products, animal health products, diagnostics, and

specialty products. In April 2000, Pharmacia merged with Monsanto and Searle to create innovative medicines. In 2002, Pharmacia spun off its agricultural subsidiary, Monsanto Company. Pharmacia Corporation had the full rights to one of the blockbuster arthritis drugs Celebrex. Pfizer the largest drug maker bought Pharmacia for $60 billion.

5.4.2.2. Strategic Perspective of the deal

The merger deal gave Pfizer the arthritis drugs Celebrex and Bextra which both Pfizer and Pharmacia co-promoted. Pfizer also added heart disease drugs like eplerenone to its cardiac market portfolio[40]. Pfizer was already the dominant player in the cardiac market with Lipitor and Norvasc which were the leading drugs for Cholesterol and hypertension. Pfizer and Pharmacia did not face serious competition for many of their drugs. The merger was expected to enhance their earnings growth. The merger created a drug company with $46 billion in annual sales and added portfolio of leading drugs for impotence, high cholesterol, arthritis, glaucoma, and depression. The merger consolidated Pfizer's position as the number one drug maker in terms of annual sales. As a result of the union, Pfizer with a market capitalization of $256 billion became the third largest company behind General Electric and Microsoft. It had one of the largest researches and development budgets of $7 billion. The merged company held 11% of the world's market for prescription drugs. Through the merger with Pharmacia, Pfizer obtained drugs like Rogaine for hair loss, Nicorette the gum for quitting smoking habits, Xalatan the drug for glaucoma treatment, Xanax for treatment of anxiety, and Detral the overactive bladder treatment drug[41]. Pfizer also got control of Camptosar the drug for treatment of colorectal cancer and the arthritis drug Celebrex. The merger positioned the new Pfizer to deliver a stream of innovative new products and cost-effective health solution. The combined companies manufacture products in different segments like cardiology, endocrinology, neuroscience, rheumatology, urology, ophthalmology, and oncology. The merged pharmaceutical company had 12 products with annual revenues greater than $1 billion. The combination of Pfizer and Pharmacia had an R&D pipeline of nearly 120 new chemical entities in development and more

than 80 additional projects for product enhancements. This merger was relevant in the context of the patent expiry of billion-dollar blockbusters wherein large companies were increasingly finding ways to meet the impending shortfall in revenues due to the generic invasion.

5.4.3.1. Merger with Wyeth

Wyeth is one of the world's largest research-driven pharmaceutical and healthcare product companies in the world. It was a leader in the discovery, development, manufacturing, and marketing of pharmaceuticals, vaccines, biotechnology products, nutritionals, and non-prescription medicines that improve the quality of life for people worldwide. The company's major divisions include Wyeth Pharmaceuticals, Wyeth Consumer Healthcare, and Fort Dodge Animal Health. On January 26, 2009, Pfizer and Wyeth entered into a definitive agreement under which it was proposed that Pfizer will acquire Wyeth in a cash-and-stock transaction. The deal was valued at $68 billion. The combination was aimed at creating one of the most diversified companies in the global healthcare industry. The combined company had strong product offerings in different therapeutic areas, strong product pipeline, and manufacturing capabilities. The combined company armed with broad and diversified product portfolio and reduced dependence on small molecules was expected to provide stable top line and EPS growth. It was expected that no drug of the combined firm will account for more than 10% of the total revenues by 2012.

5.4.3.2. Strategic Perspective of the deal

The combination of Pfizer and Wyeth created the world's premier biopharmaceutical company with diversification and scale position. The combined company became an industry leader in human, animal, and consumer health sectors[42]. It became one of the leading players in primary and specialty care and small and large-molecule sectors. Wyeth had leadership position in attractive growth areas such as vaccines, nutritionals, and biologicals. Wyeth developed the first pneumococcal vaccine for infants. Wyeth had immense

strength in biotechnology sector with products like Enbrel which is the number one biotechnology product in the world. Pfizer and Wyeth have highly complementary businesses. The combination was aimed at enhancing the in-line and pipeline patent-protected portfolio in key invest to win disease areas such as Alzheimer's disease, inflammation, oncology, pain, and psychosis. The consolidation was also expected to make Pfizer a top-tier player in biotherapeutics and vaccines. The new company could accelerate growth in emerging markets, create new opportunities for established products, and create a lower and flexible cost base. The combined company had top-tier portfolios in key therapeutic areas like cardiovascular, oncology, women's central nervous system, and infectious diseases. The new combined company had a diverse product portfolio with 17 products with more than $1 billion each in annual revenue. With the acquisition of Wyeth, Pfizer became the world's second largest specialty care provider with products like leading biologic Enbrel, Prevnar the world's largest selling vaccine, Sutent drug for cancer, Geodon for schizophrenia, and Zyvox for infection. Pfizer had global leadership position in animal health sector with strong product lines for companion animals, biologics, and anti-infectives. The new company has one of the best resources to invest in research and development. The consolidated company had access to all leading scientific technology platforms which included vaccines, small and large molecules, nutritionals, and consumer products. The merger also brought together a robust pipeline of biopharmaceutical research and development projects which included programs in diabetes, inflammation/immunology, oncology, and pain. Significant opportunities also exist with respect to Wyeth's Alzheimer's disease pipeline which had a number of compounds in development phase which included biotech compound bapineuzumab. The merged company also achieved an enhanced ability to innovate as each business unit was given responsibility to oversee product development from clinical trials to commercialization. In geographic terms the combination would enhance Pfizer's and Wyeth's portfolios in important growth areas. The combined company will be number one in terms of biopharmaceutical revenues in the United States with approximately 12% market share. In Europe the combined company had a market share of approximately 10%. The combined Pfizer–Wyeth had significant

growth opportunities in emerging markets such as Latin America, the Middle East, and China. The merger was completed on October 15, 2009, with the receipt of regulatory approval from all government authorities as required by the merger agreement and approval by Wyeth shareholders. The acquisition which was termed as the third largest in the drug industry since 1998 was expected to help Pfizer company to shorten the major gap in revenue in the year 2011 when its blockbuster Lipitor cholesterol drug started facing generic competition.

5.4.4. Acquisition of Hospira

In February 2015, Pfizer and Hospira agreed that Pfizer would acquire Hospira for $15.2 billion. Including debt, the deal is valued at around $17 billion owned. In a deal designed to enhance the buyer's established drug business and global reach with the potential for growth in injectable drugs and infusion technologies, as well as biosimilars, the companies said today[43].Hospira was an American global pharmaceutical and medical device company with headquarters in Lake Forest, Illinois. Was the world's largest producer injectable drugs and infusion technologies and a global leader in biosimilars. In buying Hospira, Pfizer is seeking to add revenue growth in order to recoup expected losses as many of its top-selling drugs face patent-cliff expirations of exclusivity. That opportunity for revenue growth, Pfizer reasons, can be found in generic sterile injectables—a market the pharma giant said is projected to reach $70 billion by 2020—as well as biosimilars, which by the same year is expected to expand into an approximately $20 billion segment of the global biopharma industry.

5.4.5. Acquisition of Medivation

On August 22, 2016 Pfizer announced that they have entered into a definitive merger agreement under which Pfizer will acquire Medivation, a biopharmaceutical company focused on developing and commercializing small molecules for oncology, for $81.50 a share in cash for a total enterprise value of approximately $14 billion to boost its oncology portfolio[44].

Medivation is an American biopharmaceutical company focused on rapid development of novel therapies to treat serious diseases for which there are limited treatment options. Medivation's portfolio includes XTANDI (enzalutamide), an androgen receptor inhibitor that blocks multiple steps in the androgen receptor signaling pathway within the tumor cell. XTANDI is the leading novel hormone therapy in the United States today and generated approximately $2.2 billion in worldwide net sales over the past four quarters, as recorded by Astellas Pharma Inc., with whom Medivation entered an agreement in 2009 to develop XTANDI globally and commercialize jointly in the U.S. Since its approval for advanced metastatic prostate cancer by the U.S. Food and Drug Administration in 2012, XTANDI has treated 64,000 men to date in the U.S. alone. Medivation and Astellas have built a robust development program for XTANDI, including two Phase 3 studies in non-metastatic prostate cancer and another Phase 3 study in hormone-sensitive prostate cancer. It is also being further developed in Phase 2 studies for the potential treatment of advanced breast cancer and hepatocellular carcinoma. In addition, Medivation has a promising, wholly owned, late-stage oncology pipeline, which includes two development-stage oncology assets, talazoparib and pidilizumab. Talazoparib, currently in a Phase 3 study for the treatment of BRCA-mutated breast cancer, has the potential to be a highly potent PARP inhibitor and could be efficacious across several additional tumors. Pidilizumab is an immuno-oncology (IO) asset being developed for diffuse large B-cell lymphoma and other hematologic malignancies and has the potential to be combined with IO therapies in Pfizer's portfolio.
The addition of Medivation will strengthen Pfizer's Innovative Health business and accelerate its pathway to a leadership position in oncology, one of their key focus areas, which they believe will drive greater growth and scale of their business over the long-term.

5.4.6 Acquisition of Array BioPharma

Pfizer Inc announced on June,17 2019 will acquire Array, a commercial stage biopharmaceutical company focused on the discovery, development and

commercialization of targeted small molecule medicines to treat cancer and other diseases of high unmet need. Pfizer has agreed to acquire Array for $48 per share in cash, for a total enterprise value of approximately $11.4 billion[45].
it would buy Array Biopharma Inc for $10.64 billion in cash, a deal it hopes will help make it a leader in colon cancer and build up its pipeline of oncology drugs. Array BioPharma is a U.S.-based, clinical stage, pharmaceutical company. Array provides an approved combination of targeted medicines, the potential to generate significant long-term growth, and a highly productive discovery engine with a proven track record. Specifically, the combination of Array's BRAFTOVI(encorafenib) and MEKTOVI (binimetinib) is approved for the treatment of advanced BRAF-mutant skin cancer. The therapy is also poised to become a potential first-in-class therapy for patients with BRAF-mutant metastatic colorectal cancer (mCRC). Metastatic colorectal cancer impacts 150,000 patients globally per year and is the second most deadly cancer in the United States. Up to 15 percent of patients with the disease have BRAF mutations. The prognosis for patients with metastatic colorectal cancer is currently very poor. This is an important moment on Pfizer journey to build a leading oncology portfolio in targeted and combination therapies. With the acquisition of Array, they have the potential to create an industry-leading franchise for colorectal cancer alongside Pfizer's existing expertise in breast and prostate cancers. Array is Pfizer's first major purchase under new Chief Executive Albert Bourla, who took on the role in January.

5.4.7. Pfizer Upjohn merger with Mylan

In 2018 Pfizer announced it would reorganize its business into three separate units: a) a higher-margin innovative medicines division b) off-patent drug division c) consumer healthcare division.

In late July 2019, the company announced that it would spin off and merge its off patent branded and generic established medicines business, Upjohn, with Mylan, creating a new global pharmaceutical company with sales of around $20 billion. Under the terms of the agreement, which is structured as an all-stock, Reverse

Morris Trust transaction, each Mylan share would be converted into one share of the new company. Pfizer shareholders would own 57% of the combined new company, and Mylan shareholders would own 43%[46]. The new company will transform and accelerate each businesses' ability to serve patients' needs and expand their capabilities across more than 165 markets by bringing together two highly complementary businesses. Mylan brings a diverse portfolio across many geographies and key therapeutic areas, such as central nervous system and anesthesia, infectious disease and cardiovascular, as well as a robust pipeline, high-quality manufacturing and supply chain excellence. Upjohn brings trusted, iconic brands, such as Lipitor (atorvastatin calcium), Celebrex (celecoxib) and Viagra (sildenafil), Lyrica (pregabalin), Zoloft (Sertraline) and proven commercialization capabilities, including leadership positions in China and other emerging markets. The transaction will allow the new company to meaningfully expand the geographic reach of Mylan's existing broad product portfolio and future pipeline – including significant investments that have been made across complex generics and biosimilars – into new growth markets where Upjohn has existing sales infrastructure and local market expertise. The combination will drive a sustainable, diverse and differentiated portfolio of prescription medicines, complex generics, over-the-counter products and biosimilars supported by commercial and regulatory expertise, established infrastructure, best-in-class R&D capabilities and high-quality manufacturing and supply chain excellence.

5.5. Research and Development Pipeline

Pfizer's priority is researching and developing medicines and vaccines that will benefit patients around the world. They are committed to addressing unmet needs across a number of important therapeutic areas including, Oncology, Inflammation & Immunology, Vaccines, Internal Medicine and Rare Disease, with the goal of delivering innovative products to patients[47]. As of January 28, 2020, the company had 95 projects in R&D. The projects range from discovery through registrations. Clinical trials follow a typical series from early, small-scale, Phase 1

studies to late-stage, large scale, Phase 3 studies. From these, 26 programs are in Phase 1 through registration. Testing is carried out on healthy volunteers for dose ranging and checking drug safety. The testing is carried out on up to several hundred people with the disease/condition in Phase 2 to check efficacy and side effects and 300 to 3,000 volunteers who have the disease or condition in Phase 3 to check efficacy and monitoring of adverse reaction. The company had 95 projects in existing R&D pipeline. From these, 37 are programs in Phase2 and 23 programs in Phase 3, 9 programs in Registration and Marketing authorization stage.

Figure 29. Pfizer's Existing Pipeline

5.5.1 Research & Development Spending

Pharmaceutical R&D is crucial for finding and creating new drug compounds and agents that have the potential to save lives or improve medical symptoms. Pharmaceutical R&D in the U.S. has become a booming industry and spending is increasing year-over-year. The number of federally registered clinical trials in the U.S. has been increasing significantly in recent years as well. Pfizer's expenditures on research and development (R&D) have been variable in recent history. A of 2019, Pfizer expended some 8.65 billion U.S. dollars on R&D efforts. This is an increase from the previous year, but a decrease from 2010 when the company spent about 9.5 billion dollars on R&D[48].

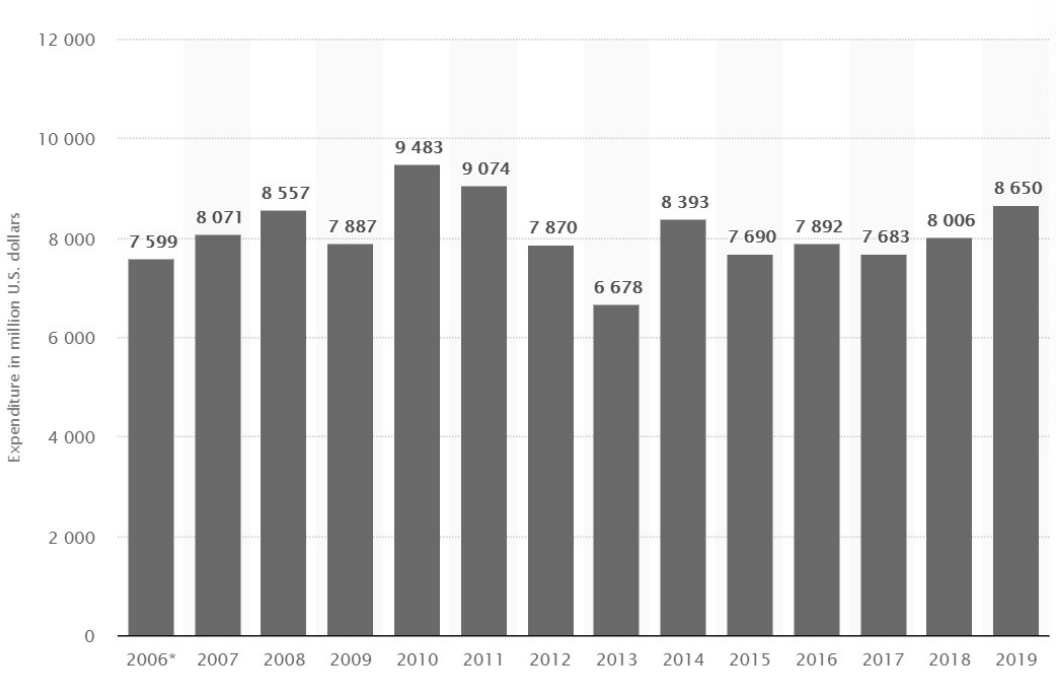


Figure 30. Pfizer's expenditure on research and development from 2006 to 2019 (in million U.S. dollars)

5.5.2. Oncology R&D Pipeline

Cancer is one of the leading causes of death worldwide. With more than 100 types and a biology that's constantly changing, it's also one of the most complex diseases known to mankind. In 2012, there were 14.1 million new cancer cases and 8.2 million cancer deaths worldwide. By 2030, the global burden is expected to grow to 21.7 million new cancer cases and 13 million cancer deaths as a result of growth and aging of the population. Pfizer Oncology is committed to discovering, investigating, and developing transformative therapies that improve the outlook for cancer patients worldwide. Through clinical cancer research they create results for oncology treatment options. Pfizer is developing treatments that are as diverse as the disease itself with a sharp focus on the most disruptive advances in science and guided by the urgency to help patients receive the next wave of life-changing cancer medicines. The key to cancer treatment is not just to understand how cancer cells behave on their own, but to learn how they evade the body's immune system and existing treatments. Pfizer's pipeline of potential

cancer medicines includes differentiated therapies with multiple mechanisms of action that target both the tumor itself and the immune system. They are investigating medicines for breast cancer, non-small cell lung cancer, gastric cancer, ovarian cancer, renal cell carcinoma, and hematologic malignancies, including leukemias and lymphomas. Their strong pipeline—one of the most robust in the industry—includes biologics, small molecules, immunotherapies, and biosimilars, and is centered on exploring a wide array of approaches across many tumor breakthroughs medicines that redefine life with cancer for patients[49].

The company had 40 projects in oncology R&D pipeline. From these, 14 programs are in Phase 1, 10 and 11 are in Phase 2 and Phase 3, respectively. Thera are 5 programs in Registration and Marketing authorization stage[50].

Figure 31. Pfizer Oncology Pipeline

5.5.3. Inflammation and Immunology R&D Pipeline

Inflammation is a critical response to potential danger signals and damage in organs in our body. But with autoimmune diseases such as rheumatoid arthritis, lupus, ulcerative colitis, Crohn's disease and many others, our own immune system turns against our organs[51]. These painful and debilitating conditions take an immense toll on people's quality of life and many of these diseases are poorly managed by existing treatments that provide only symptomatic relief. For decades, doctors relied on steroids to suppress immune response. Though an important option, steroids come with many potentially harmful side effects. Fortunately, science has continued to advance, and today Pfizer has the opportunity to transform the management of inflammatory diseases with new

classes of therapies that target other key proteins and pathways in the body. As science evolves beyond broad immunosuppression and into more selective agents, patients living with autoimmune and inflammatory disease have new hope. Pfizer scientists operate with a sense of urgency, focused on three areas with the greatest unmet need:

- **Rheumatology**: Investigating therapies for rheumatoid arthritis and lupus
- **Gastroenterology**: Looking at the next wave of medicines in ulcerative colitis, Crohn's disease and nonalcoholic steatohepatitis (NASH)
- **Medical Dermatology**: Focusing on the next generation of medicines for atopic dermatitis, psoriasis, vitiligo and alopecia areata

Pfizer's mission is to deliver medicines that make a real difference in quality of life for patients with autoimmune diseases and chronic inflammation. Scientists in their research and development (R&D) programs are committed to speeding the delivery of new treatments. They pledge to maintain the safety of patients who take part in their trials and to uphold the highest ethical standards in all of their research initiatives.

The company had 24 projects in inflammation and immunology R&D pipeline. From these, 3 programs are in Phase 1, 16 and 3 are in Phase 2 and Phase 3, respectively. Thera are 2 programs in Registration and Marketing authorization stage[52].

Figure 32. Inflammation and Immunology R&D Pipeline

5.5.4 Vaccines R&D Pipeline

Vaccines are one of the greatest public health advancements of all time, resulting in the control, elimination, or near elimination of numerous infectious diseases that were once pervasive and often fatal. Today, more people benefit from safe and efficacious vaccines to prevent infectious diseases than ever before, and vaccines provide essential health benefits at all ages, from maternal and infant populations to seniors. Today is an exciting time in vaccine research and development, as scientific discoveries, technological advancements and regulatory paradigms are paving the way for novel vaccines. While Pfizer's Vaccine Research and Development scientists continue to extend their leadership position in pneumococcal and meningococcal disease prevention, they also work on vaccines against other major infectious diseases while striving to bring the benefits of vaccines into previously unexplored areas. They are at the forefront to usher in a new era of vaccine innovation, both to prevent and treat disease, with special focus on maternal/neonatal, hospital-acquired infections (HAI), and cancer[53].

Pfizer's mission is to deliver medicines that make a real difference in quality of life for patients with vaccines-related conditions. The company had 6 projects in vaccines R&D pipeline. From these, 4 are in Phase 2 and 3 are in Phase 3[54].

Figure 33. Vaccines R&D Pipeline

5.5.5. Internal Medicine – Metabolic Disease R&D Pipeline

Cardiovascular and Metabolic Diseases (CVD) remain the number one cause of death worldwide. In recent decades there have been remarkable reductions in death from cardiovascular diseases, largely due to a decreased prevalence of smoking and modern science that has led to effective therapies for hypertension and high cholesterol. Even so, cardiovascular diseases (CVD) remain the number one cause of death worldwide. CVD continues as an epidemic, driven by a number of factors, including the rising rates of obesity and its resulting metabolic diseases, such as type 2 diabetes mellitus and the metabolic syndrome, which refers to the group of risk factors that increase an individual's risk for heart disease and other health problems. The modern lifestyle has promoted a new array of cardiovascular risk factors, but treatments for these have remained elusive. We believe that a comprehensive program is needed to address the collection of diseases of the cardiovascular system, as well as their root causes, including obesity and metabolic disease. We now understand obesity leads to diabetes, and diabetes in turn increases the risk of heart failure and other types of heart disease. In fact, more than two-thirds of people age 65 or older with diabetes die from some form of heart disease. Another significant area of unmet need that reflects the global dysmetabolic state is non-alcoholic steatohepatitis (NASH). NASH is preceded by an abnormal accumulation of lipid in the liver, a condition that is associated with obesity and insulin resistance and is estimated to impact as many as 30% of all adults in the US. Ultimately, NASH can lead to liver fibrosis, cirrhosis and eventually liver failure or cancer and has no approved treatment. With costly hospitalizations on the rise, economists project that failure to properly invest in prevention and treatment could cost as much as $47 trillion worldwide by 2036.7For more than 50 years, Pfizer has led the way in redefining the management of cardiovascular risk by bringing much-needed treatments to patients. Today, Pfizer is focused on investigating potential therapies that treat both the metabolic abnormalities that increase the likelihood of cardiovascular disease and the heart itself by trying to alter the way it responds to the abnormal metabolic state. This includes more targeted potential therapies, as well as possible therapies that are a combination of two or more

drugs, which could bring additional benefits to patients. Our early discovery efforts focus on emerging areas of CV research such as control of eating disorders, type 2 diabetes/muscle uptake of glucose and non-alcoholic fatty liver disease/non-alcoholic steatohepatitis[55].

Pfizer's mission is to deliver medicines that make a real difference in quality of life for patients with metabolic diseases and at cardiovascular risk. The company had 10 projects in internal medicine - metabolic disease R&D pipeline. From these, 5 programs are in Phase 1, 4 and 1 are in Phase 2 and Phase 3, respectively[56].

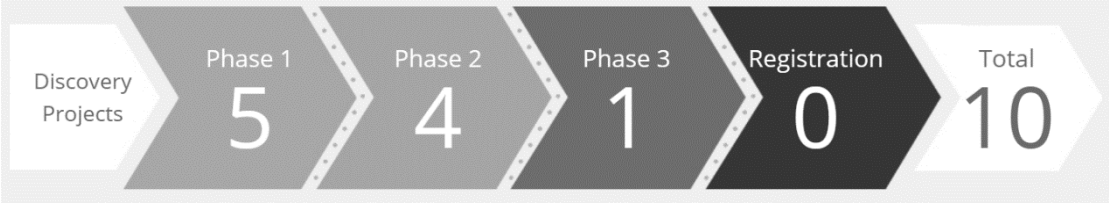


Figure 34. Internal Medicine – Metabolic Disease R&D Pipeline

5.5.6. Rare Diseases R&D Pipeline

More than 30 million people in the U.S. and 350 million globally are impacted by one of 7,000 distinct rare diseases, and the National Institutes of Health estimates that half of all people affected by rare diseases are children.
Over the past 25 years, genes responsible for approximately 50% of the monogenic diseases, diseases where a single gene is mutated, have been identified and it is estimated that the remaining disease-causing genes will be known by the year 2020. Scientific advances over the past decade have increased understanding of rare diseases and their underlying causes, even enabling the development of critical treatment options for some. But today, just 5% of rare diseases have an available therapeutic, and a significant unmet medical need remains. At Pfizer, they are making important strides in our understanding of rare diseases and there is tremendous opportunity for patients driven by recent scientific breakthroughs to enable the discovery and development of new medicines. A majority of rare diseases are caused by a single gene mutation, and thanks to genome sequencing, they now have clues that lead them in the best

direction for potential therapies. This is key for Pfizer as they focus on monogenetic diseases, partly through our gene therapy efforts. With more than 20 years of experience in rare disease research, treatments approved in 81 countries, and multiple drugs in clinical trials, Pfizer is uniquely positioned to lead advances in rare disease treatment. They are focused on two main areas of research in rare disease:

- **Hematologic Diseases**: An area where Pfizer has a long heritage in Hemophilia and where they are excited about their collaboration with Spark Therapeutics, Inc. The next frontier for Pfizer is in Sickle Cell Disease, a devastating condition with a high unmet need for new treatments. They have assets in their pipeline that have that may manage the disease, and others that may actually modify the course of the disease.
- **Neuromuscular Diseases:** These often-inherited diseases can be debilitating and cause muscle weakness, and in some cases, can even impact heart function and one's ability to breathe. They are focusing their efforts in Duchenne Muscular Dystrophy, and other neuromuscular diseases. Through their acquisition of Bamboo Therapeutics Inc., they have preclinical programs in Friedreich's Ataxia and Canavan disease, and a Phase I asset for Giant Axonal Neuropathy.

Gene therapy is an emerging area of medical research focused on developing highly specialized, one-time, transformative treatments aimed at addressing the root cause of diseases caused by genetic mutation. Gene therapy is a promising investigational technology, especially for patients with rare diseases, many of which are caused by a single genetic mutation. The technology involves introducing genetic material into the body to deliver a corrected copy of a gene to a patient's cells to compensate for a defective one. The genetic material can be delivered to the cells by a variety of means, one of which is uses a viral vector such as recombinant Adeno-Associated Virus (rAAV).To bolster their capabilities in gene therapy, Pfizer acquired Bamboo Therapeutics, Inc., a privately held biotechnology company based in Chapel Hill, N.C., focused on developing gene therapies for the potential treatment of patients with certain rare diseases

related to neuromuscular conditions and those affecting the central nervous system. This acquisition significantly expands Pfizer's expertise in gene therapy by providing Pfizer with clinical and several preclinical assets that complement the company's rare disease portfolio, an advanced rAAV vector design and production technology, and a fully functional Phase 1/2 gene therapy GMP manufacturing facility that Bamboo acquired from the University of North Carolina. Their strategy focused on accessing the most effective vector design and manufacturing scalability to ensure we are phase 1/2 ready. They are building capabilities in gene therapy while also collaborating with some of the leading experts in this field[57].

Pfizer's mission is to deliver medicines that make a real difference in quality of life for patients with rare disease. The company had 14 projects in rare disease R&D pipeline. From these, 4 programs are in Phase 1, 3 and 5 are in Phase 2 and Phase 3, respectively. Thera are 2 programs in Registration and Marketing authorization stage[58].

Figure 35. Rare Disease R&D Pipeline

Chapter 6

Conclusion

Based on the latest available data, Gross Domestic Product (GDP) of the Greek economy amounted at €194 billion in 2019, increased by 1.8% compared to 2018. For 2020, Greece's economy is expected to be hit severely by the Covid-19 pandemic and the counter measures taken to limit its spread, according to the European Commission, GDP rate is expected to contract by 9.7 percent this year. Total health expenditure decreased by -30.9% during the period 2010-2017 amounted at €14.5 billion in 2017. Public health expenditure decreased by -38.2% over the same period, amounted at € 8.8 billion in 2017 and private health expenditure amounted € 5.6. The decline in public health expenditure has resulted in a shift in health spending to the private sector, with private health expenditure reaching 39% in 2016. With regards to the pharmaceutical expenditure, which is a small part of total health expenditure ~20%, total outpatient pharmaceutical expenditure in Greece estimated at €3.6 billion in 2018. While total out-of-hospital pharmaceutical expenditure remains relatively stable over the period 2012-2018, public outpatient pharmaceutical expenditure decreased by -62% the same period. At the same time the weight shifted towards private sector, with industry's contribution, through flat mandatory returns and discounts (rebate and clawback). As far as public hospital pharmaceutical expenditure is concerned during the period 2012-2015 amounted to € 760 million. From 2016 onwards, with the introduction of closed budget, it was significantly reduced by -30%, resulting in the contribution of pharmaceutical industry with € 436 mil. in 2018. However, the needs of the population for health

care are affected, amongst others, by demographic trends: life expectancy in Greece is high (81.5 years higher than EU average 81.0 years in 2016), steady reduction of the population (births - deaths) by -36,000 people (2017), and increased ageing population (over 65) from 21.9% of the total population in 2017 rising to 36.5% in 2050. From the above, the growing demand for health care, thus for public funding on health care services and pharmaceuticals is documented, with further increase in the private expenditure considered unsustainable in an environment of long-term unemployment and significant decline of national income. Despite the significant impact of fiscal adjustment on public funding, the pharmaceutical industry remains a pillar for investment in Greece with Research and Development (R&D) expenditure close to 8% of total R&D expenditure in Greece (2015) and 2,506 clinical studies independent of phase and stage conducted until 2018 (1,434 completed). Production of pharmaceutical products in Greece was estimated at ε954 mil., with Gross Value Added (ex-factory) at € 668 million (3.0% of the manufacturing). Employment in the manufacturing of pharmaceutical products in Greece was estimated at 14.4 thousand people in 2017, with 60.5% of them with university education, compared to 35.7% of the total economy and 22.7% of the total manufacturing. Imports and exports of medicinal products amounted to € 2.8 billion and € 1.4 billion respectively in 2018. Lastly, exports accounted for 4.3% of total Greek exports in 2018.

Pfizer Inc. one of the world's premier biopharmaceutical companies, headquartered in Connecticut, USA. The Company is engaged in the discovery, development and manufacture of healthcare products. The research-based company has a varied portfolio that spans many therapy areas, including immunology, oncology, neurosciences and rare diseases.

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