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#### Tesi di laurea

L'Industria Farmaceutica Internazionale e la sua importanza per l'Italia.

The International Pharmaceutical Industry and its Importance for Italy.

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# The International Pharmaceutical Industry and its importance for Italy.

#### Abstract.

Lo scopo di questo paper è dare una panoramica del mercato dell'industria farmaceutica internazionale soffermandosi con maggiore attenzione sulla realtà europea e in particolare sul sistema Italia. Secondo la relazione n. 15-09 di Confindustria del 16/05/2015 l'industria farmaceutica italiana segna il primato di crescita dell'export (+50% dal 2010 al 2014) a traino di una produzione, che si posiziona al secondo posto in Europa. In questo lavoro si vuole ribadire l'importanza di una corretta e stabile governance politica del settore, in quanto non solo preziosa fonte di ricchezza per il Paese, ma anche elemento fondamentale per la sezione R&S soprattutto grazie agli investimenti di capitali esteri.

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#### Introduction.

The international pharmaceutical industry has a critical role in improving global healthcare. Drugs companies are responsible of medicines development, production and selling. Science and technologies cooperate in this sector, which has the highest R&D expenditure: millions of dollars, 10-15 years to develop a new medicine and eventual failure during pre-clinical and clinical trials not so remote. Because of long research time, limited drug patent life and high competitiveness of the sector, drugs portfolio management becomes strategic for the long-term prosperity of the pharmaceutical company. Big Pharma is nowadays undergoing time of significant changes: mergers and acquisitions (M&A), strategic alliances and business disinvestments are quite common. Also pharmaceutical sector is looking with more interest to developing countries, not only for new selling markets, but also for settling there their own manufactures.

As far healthcare demand is quite independent from its price, so pharmaceuticals can earn huge profits and be very close to high powers and authorities. As it emerges from sector literature, critical and controversial aspects are frequent matters for drug companies: two of the most disputed ones are information about medicines given directly by drug companies and their choice to invest in R&D only for profitable markets.

The major pharmaceutical companies headquarters are located between U.S. and Western Europe with only one Asian company – the Japanese Takeda. According to IMS Health data, in 2013 North America accounted for 41.0% of world pharmaceutical sales compared with 27.4% for Europe. 55% of sales of new medicines launched during the period 2009-2013 were on the U.S. market, compared with 23% on the European one (source: IMS Health, IMS Retail Drug Monitor, March 2014). Pharmaceutical industry is a key asset in the European economy: it is one of Europe's top performing high-technology sectors.

In 2015 Italy confirms an excellence position in EU for its pharmaceutical production: the Country is the second producer in Europe (after Germany) and it is leader in medicines and vaccines export growth. Italy has an advantage for the quality of its human resources and the efficiency of satellite activities (for instance raw materials, machines and packaging). But Italian pharmaceutical market regulation and its public funding are always in constant change, without a long term strategy by policy-makers. This is not compatible for new drugs and therapy development, which needs high investments and stable sector rules helping companies to plan their production. Stable policies are also important to attract capital

investments, considering that 60% of pharmaceutical companies in Italy are based on foreign capital.

The present paper consists in three parts. Part one contains: a general overview of international pharmaceutical industry, principal sector aspects and strategies, major players on the market and relevance for EU Countries of their drugs manufacture. Second part is dedicated to Italian pharmaceutical industry and its critical role for national economy. Part three presents the summary and the results of the entire work.

#### Part 1.

#### 1.1 General overview of the sector.

There is for sure no industry that has a longer life than one, whose purpose is to make people stay better. The pharmaceutical industry plays a critical role in improving global health care. In our times science and technology have improved life expectancy, which is steadily growing in developing countries. As a result, elderly population promises even more growth of demand for healthcare products. Also developing economies such as Asia, South America and Eastern Europe suggest an increasing financial liquidity and this attracts the attention of Big Pharma. According to the World Health Organization (WHO) the global pharmaceutical market is worth US\$ 300 billion a year and this number is going up to US\$ 400 billion in the next three years. The pharmaceutical industry is characterized by a high level of concentration and the ten largest companies control over one-third of the market. According to IMS Health, as restated in the 2004 AstraZeneca Annual Report, the United States, the European Union and Japan represent 88% of world sales - U.S. alone accounts for about 47% of world salesand this is predicted to continue through all the 21<sup>st</sup> century.

**Industry trends**. For sure the fact that there are few companies holding the whole market gives to top-companies an important advantage in competition, but this obviously cannot guarantee success. The sector is going through a time of significant changes and transformations: mergers and acquisitions, new joint-ventures and strategic alliances are very common. In this way, bigger companies can diversify their drugs portfolio, by combining resources and allowing further R&D projects in order to be more stable in the future. Another way to keep strong growing sales is to sell low-profitability or non-core businesses, as well described in Boston Consulting Group Matrix "dogs" area.

**R&D.** Research and development area is perhaps the most important section of Big Pharma companies. According to industry statistics, only about one in ten thousand chemical compounds discovered by pharmaceutical industry researchers demonstrates to be both medically effective and safe enough to become an approved medicine. Moreover about half of all new medicines fail in the late stages of clinical trials. On average it takes about 10-15 years and millions of dollars to develop a new medicine.

**Big Pharma strategies**. The main challenges for drug companies move in four areas: competition; price control; protection of patents; drugs portfolio management.

1. Competition. The sector has a high competitive environment, which is given by the competition of Big Pharma companies among themselves, with generic drug

- manufactures and with other health care industries. And this is a vital aspect of the sector. It is renown that competition compels industry to provide higher quality goods and services at lower prices. In particular in pharmaceutical manufacturing competition can motivate brand companies to create new and improved drugs and encourage generic companies to offer less expensive alternatives.
- 2. Price control. The country and the type of product are a significant variable for the regulation, in which the pharmaceutical companies operate. This is particularly true, when it comes on drug prices. In fact, if you consider the American pharmaceutical market- the most attractive one-, there is no direct drugs price control by government, but this is not true in European countries. The Old Continent keeps control on drug prices and downward pressure on prices has been increasing in the last years. Actually in the U.S. new pharmaceutical products are approved by Food and Drug Administration (FDA). In 1992 a law has been adopted, the "Prescription Drug User Fee Act": FDA is allowed to collect fees from drug manufactures to fund the drug approval process. It means, FDA is in pharmaceutical companies payrolls, in order to speed up the approval process of new drugs. However it is common sense to understand that rushing in the new molecules approval process can be very dangerous and it involves the risk of lethal or damaging drugs reaching the market and finally consumers. Indeed in ten years by the introduction of the law, thirteen dangerous drugs have been withdrawn from the market after causing hundreds of deaths.
  - Also in 2003, as well reported in "Sicko" documentary film by American filmmaker Michael Moore (2006), President G.W. Bush and members of the Congress were paid by American pharmaceutical companies to pass a law: the "Medicare Prescription Drug, Improvement, and Modernization Act". This deliberation allows pharmaceutical industry to choose the price of their products and it gives to insurance companies the role of intermediaries. And curious enough, after the emanation fourteen members of the Congress went to work for medical industry companies!
- 3. Protection of patents. This is one of the key condition necessary for further development of pharmaceutical industry. For this reason non-efficient legislation of patent protection in developing countries discourages Big Pharma to expanse their industries in those areas. A drug covered under patent protection means that only the pharmaceutical company holding the patent is allowed to manufacture, introduce on the market and make profits from the drug. The lifetime of the patent varies between different countries and also between different medicines. Once the patent expires, the

- drug can be produced and sold by other companies at different prices. At this point, the drug is referred to as a generic drug.
- 4. Drugs portfolio management. Last, but not least is for sure the careful planning of R&D projects, responsible of long-term prosperity of pharmaceutical companies. In order to understand this point it's better to consider firstly that projects started today will give only in 10-15 years their financial results to the company (always considering that only few projects are effectively realized). Secondly, as patents keep drug exclusivity only during a limited time, the major portion of revenue from any drug comes before the expiration date of its patent. As soon as a patent expires other companies start manufacturing generic drugs causing significant reduction of its sales. For this reason it's very important, that companies have new products available for the date of expiration, as a turnover of the old medicine.

**Conflicts.** Reading literature about pharmaceutical industry two major conflicts come to light: information about medicines given directly by drug companies and choice made by drug companies to invest in R&D only for profitable markets.

The first conflict is about the public need of information to select and use drugs in a conscious way. This basic need is in danger, because pharmaceutical companies are the main source of information about the effectiveness and the risks of their own products. How can they be impartial? After repeated accusations and finding that some clinical trials conducted or founded by pharmaceutical companies may report only positive results, the industry is now more deeply checked by independent groups and governmental agencies. It's not uncommon that drug researchers, not directly employed by pharmaceutical companies, look to them for grants and companies look to researchers for studies that will make their products look attractive. Sponsored researchers are rewarded by pharmaceutical companies, for example with support for their conference/symposium costs. Finally lecture, scripts and even journal articles presented by academic researchers may actually be "ghost-written" by drug companies.

The second conflict of interest is in the area of drug R&D. The private sector dominates the research & development and every year millions of dollars are spent in developing new drugs for the mass market. The pharmaceutical companies are willing to pay for producing only those drugs, whose return on company's investments is high. As a result, drugs used in the industrialized world are prioritized over ones for the South, where instead the need of medicines for survival is higher.

In his "Deadly Medicines and Organised Crime: How Big Pharma Has Corrupted Healthcare" Peter Goetzsche, Danish physician and medical researcher, who worked for pharmaceutical companies, says that Big Pharma industry can be related to criminal organizations. He says that "The main reason we take so many drugs is that drug companies don't sell drugs, they sell lies about drugs. This is what makes drugs so different from anything else in life...Virtually everything we know about drugs is what the companies have chosen to tell us and our doctors...". The author remembers the novel "The new World" by Aldous Huxley (1932), in which characters can take every day the "Soma" pill and have full control on their lives and erase bad thoughts. Commercials in the U.S. push people to the same exact thing: spot characters are sad people, who regain confidence and good mood after pills consumption. Always in the point of view of the author in the U.S. and in Europe drugs are the third most important cause of death after cardiovascular diseases and cancer. For the Danish researcher pharmaceutical and tobacco companies have a lot in common. They both have a lack of interest for human life with the difference that, if tobacco companies can anymore hide the evidence that their own products are dangerous killers, pharmaceutical industry does. Moreover both pharmaceutical and tobacco companies in the exact moment data about the product dangerousness emerge, they provide low quality researches with opposite results. Big Pharma have been accused of a various number of violations: medicine illegal promotion for unauthorized data (off-label), alteration of researches results, data cover-up on the predictable damage and fraud on the National Health Service. In comparison with any other industrial sector, pharmaceutical companies are the most important fraud charged to the Federal Government of the U.S. (starting by the federal law on False Declarations). Moreover Goetzsche is very critical to clinical trials and generic promotion. From his point of view the clinical tests are not realized to improve people health, but to maximize product selling or to fix a better marketing strategy. Tests with unwelcomed results are buried or manipulated before the publication. The author says that pharmaceutical companies show to have the same sense of responsibility for people health as fast-food companies for health eating habits. Finally the generic use is discouraged by pharmaceutical companies by saying that the effectiveness of these substances is not constant, but this is false as it has been proved by equivalence tests between drugs and their generics.

**Pharmaceutical marketing**. Digitalization represents the future of pharmaceutical marketing. Companies are now investing in new applications development, in order to have a direct relationship between patients and producers. This would help industry to have real-time feedbacks and to match with consumer's needs.

Life expectancy is increasing and so chronic diseases are growing. The per person expenditure of an over 75 is twelve times bigger than the expenditure of 25-34 years old person. However big companies are not interested only in aged people: their R&D work is also oriented to attract new age groups, intercepting health needs. The expression "disease mongering" (or commonly said "the commercialization of disease") indicates a marketing strategy, quite common nowadays, oriented to induce healthy consumer to feel sick, even if he is not, and become an ill patient in needing of a particular therapy. This is also called in literature "the Business of Disease". As reported in "La casta dei farmaci", pharmaceutical companies are now always more involved in financing "ad hoc" communication campaign to promote disease mongering. The strategy is to give information about prevention and treatment of some very "curious" pathologies. The human natural and normal routine condition – unhappiness, bone thinning, stomach aches, boredom, menopause and jet lag – is increasingly redefined as pill-treatable disease. They try to make people think, that there is a real pain, even where it's not. Pharmaceutical industries promote anxiety of illness in consumers, who are in good conditions, because they describe minor problems as important pathologies needing an immediate therapy (for instance getting fat, loosing hair, high cholesterol, osteoporosis, erectile dysfunction, ...). The book alerts on the reality: if there is a "new" disease, there are for sure million of worried and anxious citizens, ready to become new patients and to undergo a new treatment. Fear makes people weak and weak patients are easily controlled by Big Pharma (as also well showed and reported in the doc film by Michael Moore).

According to "La casta dei farmaci", companies, in order to get high returns, are now selling more diseases than drugs, i.e. they invent new diseases to match their existing drugs. To make this possible they are cooperating with psychologists in addition to researchers. The marketing process mission is to sell pills to everybody and the author is asking himself, if the most innovating thing in the pharmaceutical industry isn't perhaps marketing. It is a true fact that pharmaceutical companies are now investing more in marketing than in R&D sector.

Access to medicines and pharmaceutical social campaigns. WHO estimates that one third of developing world's people are unable to receive or purchase essential medicines on a regular basis. Of course the access to medicines is highly dependent on the availability of affordable medicines. But what "affordable" means is often unclear. It depends on who is paying and the constraints he faces. Frequently pharmaceutical companies group countries together according to aggregative measures, such as World Bank-defined income level. However many organization interested in developing countries say that pharmaceutical

companies should take account of differences between countries diseases burdens, inequality level, healthcare financing systems and the ability of different groups to pay. To mention once again Goetzsche's book, from his point of view, high drugs prices have nothing to do with R&D costs. The author says that the price is related to the value of prevention and disease treatment. It is nothing different to the reflection of what society is disposed to pay and how much pharmaceutical companies are good in taking under control the competition (for example with illegal price-fixing agreements). Goetzsche mentions a lot of real examples: zidovudina, first drug for AIDS treatment was synthesized in 1964 by "Michigan Cancer Research Foundation". The cost for Burroughs Wellcome, the company who was selling the drug, was negligible. Despite that, in 1987 one year of treatment for a patient was costing 10.000 \$. That was a situation of abuse of monopoly position by the company: desperate patients were asking for the new drug, whatever the price was. Another example is Abbott' decision of increasing of 400% the price of its AIDS drugs, rotonavir. The development of the medicine had been financed by millions of dollars paid by tax-payers: as a result, there was a boycott of Abbott drugs by hundreds of doctors. Taxol is one of the most tumour effective drugs: it comes from the bark of a tree (in specific the pacific yew). Even if Bristol-Myers Squibb had little initial costs, one year of treatment in 1993 was costing something in between 10.000 and 20.000 dollars. Once the patent expired, the company started to sue all the other pharmaceutical manufactures trying to put on market lower price generics. Twenty-nine States of U.S. reported the company for violation of anti-trust legislation: by the time it took to have a conclusion of the trial with the sentence to pay a 135 million dollars sanction, Bristol company managed to earn more than 5 billion dollars by selling of taxol. La Roche introduced its Librium and Valium drug on the Colombian market increasing sixty-five times the price in comparison to the price in use in Europe.

Some Big Pharma support health development through public-private partnerships. International corporations and foundations have supplied drugs or products free of charge to help in disease eradication. SmithKline Beecham has made a US\$ 500 million commitment to World Health Organization of its drug albendazole, used to treat lymphatic filariasis (elephantiasis). American Home Products has provided a non-toxic larvicide and the DuPont Company has contributed free cloth water filters for the eradication of guinea-worm disease (dracunculiasis). The Japanese Nippon Foundation has enabled WHO to supply blister packs containing the drugs needed for multi-drug therapy (MDT) enough to treat about 800.000 patients a year in 35 countries. The patients of course receive the treatments free of charge.

**Health Systems**. World Health Organization in 2000 carries out the first analysis about world's health systems in 191 member states. For the report are used five indicators: level of population health; health inequalities (or disparities) within the population; level of health system responsiveness (a combination of patient satisfaction and how well the system acts); distribution of responsiveness within the population (how well people of different economic status find that they are served by the health system); and the distribution of the health system's financial burden within the population (who pays the costs). The result is that France has the best health care system followed by Italy, Spain, Oman, Austria and Japan. In 1970, Oman's health care system was not performing well. The child mortality rate was high. However major government investments have proved to be successful in improving system performance. U.S. are in 37 position, even if the country spends in health care a higher portion of its GDP than other countries. The most relevant result is that there is a big performing difference in countries with very similar level of income and health expenditure. One big recommendation from the WHO report is to extent health insurance to as many people as possible. In industrial countries private health expense is in average 25 %, because of universal health coverage, but there are countries like U.S., where the percentage is 56. In the U.S., according to the United States Census Bureau, in 2012 there were 48.0 million people without health insurance (15,4% of the entire population). Also, as reported in Michael Moore's doc film, it is very difficult almost impossible for people with cancer or cardiovascular disease to get a health insurance or most sadly sick people are often dumped by insurance companies, when their costumers need too expensive therapies or they can find technicalities allowing them to step back in their care duty (for example a pre-existent pathology). In many countries without an health insurance safety net, many families hit by emergencies have to pay more than 100 percent of their income: illness forces them into debts. Universal health coverage means that everyone has free access to quality health services, when they need them without risking financial hardship from paying for them. This requires: a strong, efficient, well-run health system; access to essential medicines and technologies and well-motivated health workers. The challenge for most countries is how to expand health services to meet growing needs with limited resources.

## 1.2 Major players of international pharmaceutical industry and the importance of the sector in UE countries.

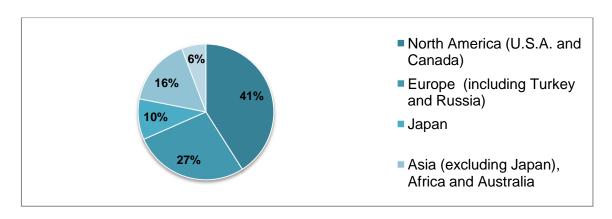
The major pharmaceutical companies headquarters are located between U.S. and Western Europe with only one Asian company – the Japanese Takeda (Table 1.1). According to IMS Health data, in 2013 North America accounted for 41.0% of world pharmaceutical sales compared with 27.4% for Europe (Figure 1.1) and 55% of sales of new medicines launched during the period 2009-2013 were on the U.S. market, compared with 23% on the European market (source: IMS Health, IMS Retail Drug Monitor, March 2014).

Table 1.1. Top 15 pharmaceutical companies on the basis of their total revenues in 2008.

2008 Chart	Company	HQ Location	Total Revenue, mln USD	
1	Pfizer	USA	67,809	
2	Novartis	Switzerland	53,324	
3	Merck & co.	USA	45,987	
4	Bayer	Germany	44,200	
5	GlaxoSmithKline	GB	42,813	
6	JohnsonandJohnson	USA	37,020	
7	Sanofi-Aventis	France	35,645	
8	Hoffmann-LaRoche	Switzerland	33,547	
9	AstraZeneca	UK	26,475	
10	Abbott	USA	22,476	
11	Bristol-Myers Squibb	USA	17,914	
12	Eli Lilly	USA	15,691	
13	Amgen	USA	14,268	
14	Boehringer Ingelheim	Germany	13,284	
15	Schering-Plough	USA	10,594	

Source: "Top 50 Pharmaceutical Companies Charts & Lists, Med Ad News, September 2007".

Figure 1.1. Breakdown of world pharmaceutical market- 2013 sales.



Source: IMS Health (MIDAS), 2013 (data relate to the 2013 audited global retail pharmaceutical market at ex-factory prices).

As explained in the report "The Pharmaceutical industry in the Global Economy" by Larry Davidson and Gennadiy Greblov, only two of the major companies have revenues from sales of pharmaceutical products that are lower than 50% of their total sales. These companies are American Johnson & Johnson, with its consumer goods and medical devices, and German Bayer. Instead only two companies, Merck & co. and Ely Lilly, concentrate their resources almost exclusively on pharmaceutical products having each about 94% of sales from this business segment. Although this approach can reward the most, because of the high returns, however the lack of diversification (especially in less risky segments) requires a careful planning of drugs production. U.S. and European pharmaceutical companies have either successful products or significant investments in R&D in the areas having a huge market and promising high rewards. It is not a surprise that they are focusing on anti-bacterial/anti-infection, anti-inflammatory/analgesics, cardiovascular diseases, neurology/psychiatric disorders and oncology (Figure 1.2).

1800 1800 1400 1200 1000 800 600 400 200 0 ontodrod neurology neurology agrithmenting agrit

Figure 1.2. Europe 2015: over 7000 medicines in development (divided in categories).

Source: Farmindustria elaboration on PhRma data.

In "The Pharmaceutical industry in the Global Economy" authors, in reporting the 2003 United Nation's Statistics Division annual report on drugs import and export value, underline various data. First the U.S. is the largest importer of pharmaceutical products followed by EU 15 (the fifteen countries that comprised the European Union before the expansion) and Switzerland. Also Japan and Canada are important destinations. China in 2003 imported less than US\$ 2 billion, but it remains an interesting destination, because of its remarkable growth and development. Second it is very interesting to mention the most growing changes in pharmaceutical imports between 1995 and 2003. Japanese imports from Asia shows huge percentage growth as China's imports from Central & South America and Africa. Switzerland is also increasing its imports from Asia. So, having good luck by selling in Japan, China and Canada, Africa is becoming a more important exporter of pharmaceutical products and also Asia with its exports to the U.S. and Switzerland.

The pharmaceutical industry is undergoing a time of radical transformation: in 2003 there was the acquisition of Pharmacia (on its own one of the largest pharmaceutical companies in the world) by the top pharmaceutical company Pfizer. But also outside the U.S. three of the major European pharmaceutical manufactures recently underwent the merging process: British GlaxoSmithKline was the result in 2000 of the merger of Glaxo Wellcome and SmithKline Beecham; British AstraZeneca in 1999 from Astra and Zeneca companies and French Sanofi-Aventis in 2004.

Today European citizens can expect to live up to 30 years longer than they did a century ago. Some major steps in biopharmaceutical research have allowed mortality reduction, for instance from HIV/AIDS-related causers and a number of cancers (Figure 1.3). European citizens can expect not only to live longer, but to live better quality lives.

5000 4000 3000 2000 1000 2000 2001 2002 2003 2004 2005 2006 2007 2008 2009 2010 2011

Figure 1.3. Total number of deaths among AIDS cases in Europe (EU-28).

Source: CISID database, annual HIV/AIDS surveillance data collected from WHO Regional office for Europe and the European centre for disease prevention and control (EcDc), April 2014.

Pharmaceutical industry is a key asset of the European economy. It is one of Europe's top performing high-technology sectors.

1 dolo 1.2. Data Salililai y oli 110 phallilaccatical iliaasii y ootwooli 2003 alia 2011	Table 1.2: Data Summar	y on EU	pharmaceutical	industry	between 2	2005 and 2011
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Variable	2005	2006	2007	2008	2009	2010	2011	11/05
Production	172,0	182,3	187,2	196,3	189,0	200,1	205,0	19,2%
Balance of	35,8	44,4	48,1	52,2	58,8	71,5	80,0	123,5%
Trade	00,0	, .	10, 1	02,2	00,0	7 1,0	00,0	120,070
R&D	21,7	24,8	26,0	26,5	27,4	27,8	27,5	26,5%
Investments	2.,,,	21,0	20,0	20,0	2,,.	21,0	27,0	20,070
Employment	634,5	643,1	636,4	633,1	640,3	663,5	660,0	4,0%
R&D	99,9	107,0	117,6	113,4	116,7	117,2	116,0	16,2%
Employment	00,0	101,0	, , , ,	1 10, 1		, _		10,270
Sales	129,5	133,4	141,3	146,5	179,2	153,4	157,3	21,5%

Source: "Perchè l'Italia non può fare a meno dell'industria farmaceutica. Stefano da Empoli e Davide Integlia. Rubbettino Editore". Authors own elaboration on EFPIA and Eurostat data.

The research-based pharmaceutical industry can play a critical role in Europe's growth and its future competitiveness in an advancing global economy. Contribution of the sector to the economy is both direct, with employment, production and R&D area, and indirect, with the

impact on satellite activities and lower costs for Health Care Services, because of the improvement of new drugs and the containment of public expenditure.

Between 2005 and 2011, as showed in Table 1.2, the fundamental variables for European pharmaceutical industry generally increased. The best result is the positive balance of trade (+123,5%) made possible by an export expansion (+59,7%). It is also relevant the increasing propensity to innovate, with + 26,5% in R&D investments. However the sector faces real challenges. Besides the additional regulatory hurdles and escalating R&D costs, the sector has been severely hit by the impact of fiscal austerity measures introduced by governments across most European Countries since 2010.

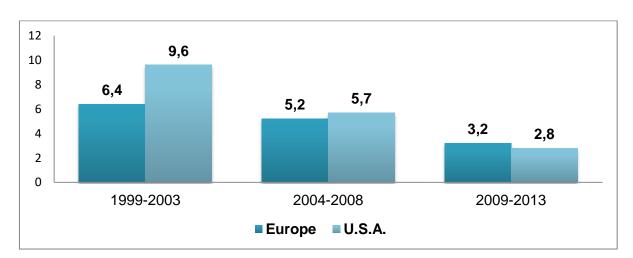


Figure 1.4. Pharmaceutical R&D expenditure – annual growth rate (%).

Source: EFPIA, PhRMA data.

Nowadays even if Europe has a pharmaceutical R&D expenditure (Figure 1.4) and a scientific production comparable in quality and quantity with the American and Japanese ones, it has lower capacity in developing new technologies and transforming them into market products. The gap is due to lacking industrial policies sustaining pharmaceutical production. This makes the difference in global competition. One possible solution of the problem would be an exemption from taxes on the money invested in R&D: direct tax reduction would support businessmen in spending more money in research. So, positive effects given by a new research policy could go even beyond national borders: more investments in research affect new industrial inventions and new licences for other modern or developing countries. Of course this would stimulate employment. According to Heinz Redwood's words in his book "Why Ration Health Care" (1993), there are two opposite, but equally pressing needs in drug production and consume. On one side there is the Countries need in limiting healthcare growing costs and on the other side the need of progress by new treatments, in order to

guarantee everybody a better healthcare outcome. They are definitely two conflicting interests: on one hand the pharmaceutical innovation and drugs price accessibility and on the other the sustainable cost for public expenditure. But they are not by definition opposites. These two problems conflict, only when policy makers don't consider them jointly, but they pay attention only to one of them. A great number of studies on the relation between price control and pharmaceutical innovation has been carried out. The results underline the existence of a significant trade off between the two events: the stricter drugs price control, the lower research outcome (typical example of pharmaceutical research outcome is the discovery of a new active ingredient). In the European Union the pharmaceutical price control doesn't take sufficient account of the aspects described above.

#### Part 2.

#### 2.1 Pharmaceutical Industry in Italy.

According to Confindustria and its own elaboration on Istat and Eurostat data, pharmaceutical industry in Italy is characterized by a wide number of manufactures and a solid production capacity. Its composition is unique in Europe, because it's represented by 60% of foreign capital companies with a strong industrial position in the Country and by 40% of Italian capital companies (Figure 2.1).

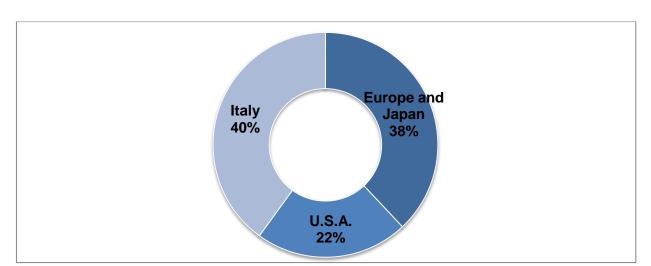


Figure 2.1. Capital Nationality of Italian pharmaceutical companies in total percentage.

Source: Farmindustria data.

There are 63.500 employees (90% graduated with 43% women) and other 66.000 people working in satellite activities along the peninsula. 6.100 employees work for Research and Development section (52% are women). 30 billion  $\in$  of production, of which 73% is for export (22 billion  $\in$ ). 2,6 billion  $\in$  in investments (of which 1,4 for R&D and 1,2 for production/infrastructure).

The data just showed demonstrate the pharmaceutical industry value for Italy, but it will be wrong to take it for granted. As for many other sectors, also for the pharmaceutical one the global scenario is deeply changing. Developing countries importance is fast growing, job organization is changing, companies profile is transforming. Although international investors are looking with great attention to the Italian Country, several conditions are for sure essential to keep the sector growing in the future.

**Production, GDP and employment**. 2015 confirms Italy excellence position in EU for its pharmaceutical production: the Country is the second producer (after Germany and before France and Great Britain) with 26% of total production and 19% of the market.

Pharmaceutical production growth in the last five years depended for its 32% by activities already realized in Italy, for its 21% by new medicines production and for its 47% by the attraction of productions previously realized in other countries (data source: Bain & Company, Prospettive per il comparto produttivo dell'industria farmaceutica in Italia, 2014). There is a high probability that, in medium term, Italy will be first producer in Europe, if some choices will be made for helping further investments. A comparison with the GDP, in the period 2010-2015, clearly shows the remarkable importance of pharmaceutical industry for Italy. In the first 4 years, when national economy suffered of recession, pharmaceutical companies managed to keep it positive and in 2015 – with a finally positive GDP- the sector kept pulling manufacturing activity. In the span considered pharmaceutical production grew of 11%. Employment numbers in 2015 confirm also an upswing after years of decrease. The number of new employees (6.000, increasing of almost 20% in comparison with the late four years) has exceeded the exits: this clearly means the increase of total employment.

**Export**. In the last years, in one of the most difficult moments for Italian industries, in every sector, companies have expressed a remarkable competing capacity on the international market. Pharmaceutical companies are an outstanding model: between 2010 and 2015 Italy has increased its medicines and vaccines export more than any other country (Figure 2.2). Not only export value has increased, but also export quantity (Table 2.1). In 2014 Italian medicine export average value was higher than in the other big UE Countries (+4%); when in 2010 this value was lower than 27%.

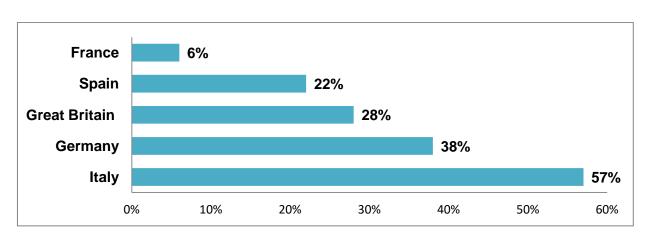


Figure 2.2. 2010-2015 pharmaceutical export growth in Europe (% of variance).

Source: Farmindustria elaboration on Istat and Eurostat data.

Table 2.1. 2010-2014 pharmaceutical export in percentage.

	Value	Quantity	Average Value
Italy	+50,2%	+15,8%	+29,7%
Germany	+21,0%	+13,5%	+6,6%
Other Big EU Countries*	+3,5%	-14,0%	+20,3%

<sup>(\*)</sup> France, Great Britain and Spain.

Source: Farmindustria elaboration on Eurostat and Fondazione Edison data.

**R&D.** Research and Development is for sure the mission of pharmaceutical industries: new ideas and projects with the effort to discover alternative therapies or to improve the already existing ones. In 2015 with 1,4 billion € invested for R&D section, pharmaceutical industries represent 7% of Italy total investments and they contribute to the research national system, in particular with 700 million € for clinical studies in National Health System structures. Pharmaceutical is third for total expenditure in R&D, after transport and mechanic, but it is first for its operators. In these years there is a reinforce of its leadership by an increase of patents (+54% in 2015) and of investments (+15% in the last 2 years). Also, a recent Bain & Co study shows that 75% of pharmaceutical companies declare to intensify in the next years their R&D expenditure in the Country and 20% to confirm it. So investments can grow more. As for the rest of the economy, Italy has a R&D intensity lower than the other principal EU Countries and this represents one of the most important challenges for the sector. Nevertheless the country is well known for its scientific production and it is the head-quarter of important excellence centres: for example for oncology, rare diseases, genetic therapies, vaccines, biotechnologies. This fields of science have made a great progress, putting Italy on the list of the Countries with more impact on the scientific community. We have to mention that the first stem cell based drug approved in Europe has been realized by researchers of an Italian company and first effective anti Ebola vaccine was born in Italy. Pharmaceutical companies represent more than 80% of the biotechnology developing more than 400 drugs and vaccines. This is very important, because in all over the world the researching making method is changing and in the future we'll have "open innovation" and network method. Innovation is not anymore depending only on the size of laboratories, but also on the network made of knowledge, public-private partnerships between small and medium companies and companies with an international vision, that together can set important research programs. In such a scenario Italy can recover the gap due to the less research expenditure than in the other principal EU countries.

Competitiveness. Italy produces more drugs than it consumes them. This is confirmed by the positive balance of trade. This means that the country is capable to intercept increasing shares of world demand. Productivity theme is strategic and for this aspect Italian pharmaceutical companies confirm brilliant results in Italian industry. They have the record both for value added per employee and for the increase in the last ten years. This result depends totally by the export, which, with the contraction of the national market, has been the only growth factor for production. It's a matter of fact that Italian companies are competitive on the international market, but they should also count on the internal market.

Competitive advantage for Italian pharmaceutical industry. Particular characteristic is the employees education: 90% of them are graduated and women have big opportunities of making career in the sector. Pharmaceutical industry has also an innovative model of industrial relations and welfare skills. Investments and human resources quality makes pharmaceutical sector an high value added one: in the industrial average pharmaceutical wages are higher than others. These are the characteristics of a modern and developed economy. As it is said above women presence in the sector is quite high (43% of the total in comparison to 25% of the rest of the national industry). Women are strategic in the companies, as showed in Table 2.4, and have important jobs in business administration (in drugs companies female chief executives are 31% in comparison with 12% in the rest of the national industry).

Table 2.2. Employment divided in gender and category (% of total).

	Pharmaceutical Industry			Total Industry			
	Women	Men	Total	Women	Men	Total	
Chief executives	30,8	69,2	100,0	12,5	87,5	100,0	
Managers	41,6	58,4	100,0	23,1	76,9	100,0	
Employees	51,2	48,8	100,0	34,5	65,5	100,0	
Intermediates	17,5	82,5	100,0	9,3	90,7	100,0	
Labourers	26,8	73,2	100,0	19,0	81,0	100,0	
Total	42,5	57,5	100,0	25,1	74,9	100,0	

Source: Farmindustria elaboration on Confindustria data.

**How is a drug born?** Chemical molecules aspiring to become new drugs undergo to a long series of tests, in laboratories and on animals first and then on humans. These researches lasting generally about seven- ten years are charged by pharmaceutical companies and are

divided in "in vitro" studies and in studies on animals (pre-clinical tests). Pre-clinical tests are important to verify how molecules behave and what is their toxic level on living organisms. Then researches are made on humans whit clinical tests. These last tests have to prove that new drugs have a sufficient effectiveness in comparison with their benefits and risks.

**Authorization to the market introduction**. After tests provided by clinical trials, before the new drug reaches pharmacy shelves, another step is requested: AIFA (Agenzia Italiana del Farmaco, the equivalent of the American Food and Drug Administration, FDA) has to grant AIC (the authorization to the market introduction). Any drug can be sold in the Italian Country without AIFA's authorization. Scientific technical commission, with the help of internal and external experts and ISS (Superior Health Institute), makes the requested evaluations (chemical- pharmaceutical, biological, pharmacotoxicological and clinical) in order absolutely sure of the effectiveness and safety of the new drug. Also pharmaceutical company test results and reports are evaluated. When AIC is released, it becomes the drug ID. It has all the fundamental information about the drug: the name, the composition, the description of the production process, the therapeutic directions, contraindications, a model of the packaging, package leaflet and so on. For this reason, after the release of the medicine AIC, every single change in the dosage and in the pharmaceutical form, in the presentation or in the consumption, needs the request of a further authorization. Now in Italy for the AIC it is requested, in addition to the national registration process, also the EU registration. AIFA regulatory activity in 2015 authorized the introduction on Italian market of 647 pharmaceutical products, mostly approved with the national procedure.

**Drug consume in Italy**. According to AIFA, in 2015 more than 16.000 medicine packs were consumed (60% reimbursed by National Health System) and the total pharmaceutical expenditure (public and private) was estimated for 28,9 billions of Euros (76,3% reimbursed by NHS). Total (private and public) territorial pharmaceutical expenditure has increased of 8,9% in relation to 2014 expenditure. Public expenditure amounts to 13.398 million Euro, that is to say 61,5% of total pharmaceutical territorial expenditure. Cardiovascular drugs drop to the third position in terms of total (public and private) pharmaceutical expenditure (4.079 million of Euro), but they maintain the first position in terms of consume. Antibiotics are now the first drug category in terms of pharmaceutical expenditure (4.402 million of Euro). Antineoplastic and immunomodulatory medicines hold the second position in the most expensive therapies list for total pharmaceutical expenditure (4.213 million Euro), as in 2014. Another important category for the expenditure of the Country is gastrointestinal tract and central nervous system drugs. The regional variability examination shows that the lowest

territorial expenditure is found in the autonomous province of Bolzano (195,7 Euro pro person), when the highest is in the Campania region (332,3 Euro pro person). In 2015 dead patent drugs (generic medicines) were 69,8% of the entire consume charged by NHS. The drug consume monitoring is highly related to the Pharmacovigilance System (RNF, Rete Nazionale di Farmacovigilanza): this system constantly watches drug security profiles after the market introduction authorization. As reported in "La casta dei farmaci" 40% of Italians, with more than 65 years, go to the pharmacy at least once a month (between 65 and 69 years at least one a week). The trusting relationship with pharmacists is often less problematic than the one with doctors and surely there are less queues. Patients/Consumers can receive advice, have the pressure measured and product discounts. The pharmacist becomes a good alternative to the doctor and even if drugs are not commodities, in pharmacies they are.

Cost control by government on pharmaceutical. Drug price in Italy is lower of 15/20% than in other principal EU Countries: drug price is nationally agreed by Agenzia Italiana del Farmaco (AIFA). All drugs to be commercialized need a price and a reimbursement class, that is to say if the drug is covered by the National Health System (A and H class medicines) or by the patients (C class medicines). The reimbursement class is disposed during the AIC procedure.

For drugs covered by patients (C class) AIFA monitors the prescription-only medicines, providing the respect of two conditions:

- Drug price can increase every two years (odd number year);
- The increase can't exceed the expected inflation.

For medicines with no prescription needed the price is chosen freely by pharmaceutical companies and for medicines reimbursed by the NHS (A and H class drugs) there is a price negotiation process between AIFA and the company owner the AIC.

Governance and pharmaceutical industry. In 2014 Italy spent for pharmaceutical products less than 30% per person of its public expenditure in comparison to the EU average, as showed in the Figure 2.3.

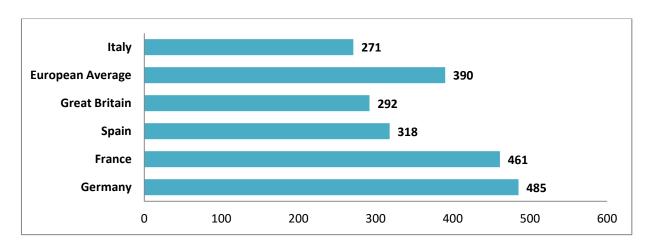


Figure 2.3. 2015 pharmaceutical public expenditure per person (in Euro).

Source: Farmindustria elaboration on Aifa, IMS, Eurostat data.

In 2011, with the international crisis, Troika indicated to the monitored countries the ratio goal of 1% for public pharmaceutical spending / GDP: this value has been reached in Italy since 2006. Between 2011 and 2014 total public spending (interests net) increased of 3,9%, while both healthcare and pharmaceutical spending decreased respectively of 1,1% and of 2,6%. Pharmaceutical companies ask for a better consideration of their role in the national welfare, considering their capacity of avoiding costs. Instead it has to give value to efficient welfare rules, considering the avoiding costs: for example expensive health services (one day of hospitalization costs almost 1.000 Euro, as four years of public pharmaceutical assistance, that is to say  $271 \in \text{per person}$ ) or prevention (one euro spent for a vaccine can avoid  $24 \in \text{for taking ill caring}$ ).

Investments go to innovation welcoming countries. For this reason Italy has to cover its gap with other countries in the access to new products caused by bureaucratic restrictions. The Country has a EU record of restrictions for the regional and national access to new drugs: more than one year is requested for the access to a new drug (Figure 2.4).

467 445 500 363 400 272 300 200 100 42 44 0 European Germany **Great Britain** France Italy Spain **Average** 

Figure 2.4. Days requested for the access to new drugs.

Source: Farmindustria elaboration on IMS and IFPIA data.

AIFA and its control system have a key role in keeping high quality production in the Country. For this reason it could be essential to reinforce the staff for a faster execution of needed tests without jeopardize the test quality.

**Drugs and Environment.** The global growth of pharmaceutical manufactures and the increase of drugs consume for human or animal use are now requiring the maximal attention on their impact on the habitat. For this reason a new science was born, Ecopharmacovigilance (EPV). According to the WHO definition, this science has to do survey, evaluation, comprehension and prevention activities. Drugs are generally water soluble and they easily turn up in the sewer. Many chemical pharmaceutical substances can't decompose, because they are intended to resist in stomach acids and they can penetrate in the environment and by the food chain get back to humans. Ecopharmacovigilance targets are: eco-green drugs manufactures, eco-friendly chemistry, biodegradable product development, minimization of industrial emissions, rational use of drugs education and a better logistic and disposal of unused or expired drugs.

#### 2.2 Elements of risk to the future of Italian pharmaceutical industry.

After the data-based demonstration of the importance and the critical role played by pharmaceutical sector in Italy, it's now important to underline the undisputed relevance of national regulation: a good one will set the basing condition for the continuous growth of the sector, but a negative will speed up processes of delocalization and reorganization. An efficient National Health Service combined with an industry capable of innovation and development of drugs more and more effective, if well ruled, can give a significant improvement in patients therapies. This obviously effects the general wealth with a positive impact on public expenditure.

However, new drugs and therapies development needs high investments in R&D section and long lasting and stable sector rules in support of companies planning programs. Stable policies are also essential to attract foreign capital investments. Nevertheless Italian pharmaceutical market regulation and its public funding is anyway in constant change without a long term strategy and by this running the risk to be contradictory. As pharmaceutical expense is one of the most fast growing part of healthcare expenditure, it is the easiest one to be adjusted and changed because of budgetary constraints. And so policy makers take time inconsistent decisions about the budget for classes of drugs, medicines prices, drugs reimbursements and patent lives. Obviously the current situation can intimidate multinational companies and it could put the base to a progressive disinvestment from the Country: this is already more than just a threat. The loss of capitals for R&D or the construction of a new production site (or its restoration), especially in non-developed areas, has an high opportunity cost.

With the V title Constitution reform and the start of healthcare federalism, Regions have voice in many drugs regulations. Pharmaceutical companies managers believe that this double authority, regional and national, confuses the regulatory system and provides ambiguous guidelines, in many cases even contradictory. Pharmaceutical managers find also difficult to start clinical tests in Italy, because of the long response time requested by ethics committees and the bureaucratic procedure for the introduction on the market.

In addition in the country there is a general expectation of low medicines prices. Because of all this problems comes out the threat of low risk option for Italian pharmaceutical market: companies could choose to invest in research programs oriented to incremental and not disruptive innovation. By this avoiding high failure risk.

The solution is simple: clear and certain rules, more plan capacity by policy makers and dialogue with the industrial world, more instruments to repay companies effort in research programs and production in the Country. This can help the sector avoiding the threat of production delocalization and the disinvestment in R&D.

#### Conclusion.

Pharmaceutical industry market is one of the most competitive in the world. As you have read, pharmaceutical companies don't compete only with themselves, but also with generic drugs producers and other healthcare industries. Because of the long time (from 10 to 15 years) requested for the drug developing and because of the threat of patent expirations and the decrease of revenues from it, drug companies have necessarily to plan in a very conscious way their production. An huge amount of money is invested to develop new products and these don't always reach the market. In order to join energies for research, pharmaceutical industries are undergoing times of mergers and acquisitions and strategic alliances.

High competitive sector pushes pharmaceutical multinational companies to look beyond the old American, European and Japanese markets. Developing countries, such as China, Thailand, Egypt, Mexico and South America Countries, represent a new sell opportunity for Big Pharma. Drug import demand is increasing in these Countries and obviously, thanks also to deregulation and lower wages-costs, new drugs companies are launching their production and Big Pharma are building their branches there.

But Italy? Can this Country do without the pharmaceutical sector? This is the main question set in "Perché l'Italia non può fare a meno dell'industria farmaceutica". The answer is no, firmly no. First of all, as reported by I-Com data, Italy without the sector would lose 1,5% of its GDP (between direct and indirect contribution) in short term, but in medium-long term it would lose without doubt much more with almost 300.000 employees and 5 billion Euro tax revenues every year. In addition to that, pharmaceutical industry makes much bigger R&D and human resouces investments than the Italian industrial average. As it has been reported, in the last five years Italian sector has climbed several position in Europe for pharmaceutical production, getting in second position after Germany: this means that further growth possibilities are high. Production has been pushed mostly by export, whose growth represents an Italian leadership. More important is the sector contribution to R&D area ( even if Italian R&D expenditure is lower than in other European Countries) and Italy couldn't have an high-tech manufacturing sector worth the name without pharmaceutical industry.

As you can notice, the position of pharmaceutical business in Italian economy is so high, that it can't be negligible, even if it has been neglected by Italian policy-makers. The lack of a careful political governance could be extremely dangerous and start a chain of disinvestments from the Country (this is already more than just an hypothetical threat). Please, notice that the capital composition of Italian drugs companies is 60% based on foreign capital. The threat

matches with international drug companies attention to developing countries with lower production costs and a general national reduction of pharmaceutical expenditure budgets. Market regulation is the key condition for attracting foreign investments.

What are the possible solutions to avert the threat?

- a. Simplifying. As reported by pharmaceutical managers, the system needs to be simplified, because it is often complex and difficult to comprehension. There is a need of reducing ethics commissions, having a better coordination between them and reducing test trials time of response.
- b. Synergic plan. Coordination of regional and national guidelines are very important: it is not uncommon that they contrast one with the other. Also drug companies should have the right to give at least their opinion, when policy-makers take big impact decision on the industrial sector.
- c. AIFA reward. Finally AIFA should give a reward to drug companies, that channel big amounts of money for R&D and production projects in the Italian Country. A rewarding system making Italy more attractive for foreign capital investments needs to be very explicit and clear for multinational companies. The rewarding system could provide tax incentives, exemption to reimbursement price review or a bonus for the company effort in the sector.

#### Bibliography.

AA. VV., Indicatori Farmaceutici 2016. Roma, Farmindustria Centro Studi, giugno 2016.

AA.VV., Nota dal CSC n. 15-9. Confindustria Centro Studi, 16 maggio 2015.

- S. Da Empoli D. Integlia, *Perché l'Italia non può fare a meno dell'industria farmaceutica*. Soveria Mannelli (CZ), Rubbettino Editore, 2012.
- L. Davidson G. Greblov, *The Pharmaceutical industry in the Global Economy*. Bloomigton, Indiana, Indiana University Kelley School of Business, 2005.
- P. C. Goetzsche, *Medicine letali e crimine organizzato*. *Come le grandi aziende farmaceutiche hanno corrotto il sistema sanitario*. Roma, Giovanni Fioriti Editore, 2015.

Jacky Law, *Big Pharma come l'industria farmaceutica controlla la nostra salute*. Torino, Giulio Einaudi Editore, 2006.

F. Maggi – A.Maio, *La casta dei farmaci*. *La prima inchiesta sul mondo delle multinazionali farmaceutiche*. *Un business senza scrupoli, tra scandali e false malattie*. Roma, Newton Compton Editori, 2011.

#### Sitography.

Site of Agenzia Italiana del Farmaco: <a href="http://www.aifa.it">http://www.aifa.it</a>

Site of Ministero della Salute: http://www.salute.gov.it

Site of World Health Organisation: <a href="http://www.who.int">http://www.who.int</a>

Site of Associazione delle imprese del farmaco: http://www.farmindustria.it

Site of Confindustria: <a href="http://www.confindustria.it">http://www.confindustria.it</a>

Site of European Federation of Pharmaceutical Industries and Associations: <a href="http://www.efpia.eu">http://www.efpia.eu</a>

#### Filmography.

Sicko, Michael Moore, U.S.A., 2006.