ITALY
AND ITS PHARMA COMPANIES
A SHARED PATH

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THE PRESIDENT'S INTRODUCTION

This year Farmindustria celebrates 40 years of activity. This is an important anniversary that we are sharing with the country. 40 years ago, the National Health Service was founded, and the Constitutional Court ruled that medicinal products could be patented. The two events constitute the foundations for our companies' growth along with our country's one.

Today, after years of dedication and investment, Italy is the now the first pharmaceutical producer in the EU.

We are immensely proud of this primacy, not as fact in itself but because it means greater job opportunities for the young and for women, investments that generate value in the territory, first rate upstream industries, cooperation with universities and clinical trials that improve the quality of healthcare treatment.

Of course, such economic prowess also means that the pharmaceutical production is higher than the overall spending but, principally, it allows them to pursue their principal objective – meeting health needs, improving the quality of life and helping the sick and their nearest and dearest.

Moreover, this mission is being performed in a phase of extraordinary enthusiasm for R&D. A record number of medicines are under development and new organisational models are emerging that by "contaminating" our companies with ICT, mathematics and IT help them to develop new and more effective therapies based on preventive and personalised medicine.

The Italian pharmaceutical companies have participated in this phase by increasing investments at a pace that far outstrips that of our European partners.

These 40 years have ushered in a high-quality pharmaceutical system: a shared asset made up of pharmaceutical companies, together with an array of institutions, workers, upstream industry, pharmacists, distribution systems, the NHS, physicians and other health workers, the academic world, scientific societies, no-profit and patients' associations.

It is doubtless true that the demographic, epidemiological, social, industrial, and scientific transformations we are experiencing today are really enormous, but they are also the expression of major innovations that, at an ever-greater speed, are characterizing not only products but also processes, organisation and necessary skills.

Pharmaceutical companies will continue to exhibit their great desire, along with their undoubted capacity, to play a proactive role in a country that has shown itself able to mobilise and capitalise upon its many public and private excellencies..

Massimo Scaccabarozzi, President of Farmindustria

ITALY AND ITS PHARMA COMPANIES A SHARED PATH

Pharmaceutical companies are part and parcel of our industrial system. They constitute a national asset based upon research, innovation, development, skills and professionalism. In terms of production, they rank first in the EU and are held to be among the first in the world, thanks to an export performance that surpasses that of their EU competitors. With rising job numbers, these companies represent an important stimulus for our economy, our territories and our communities that goes far beyond the specific confines of their own industry. The economic performance of the entire production chain generates benefits for patients, as well as providing satisfying and professionalising employment, new investments, technological innovation, new ties to the country's economy system and greater appreciation of human capital.

THE VALUE OF OUR PHARMACEUTICAL COMPANIES BRINGS BENEFITS TO ITALY: THEIR ECONOMIC PERFORMANCE

THE EUROPEAN PRIMACY. Italy is the leading producer of medicinal products in the European Union. At 31.2 billion the value of our production exceeds that of Germany and the other major EU countries. This result is entirely due to an increase in exports: in the last 10 years, Italy has registered the largest growth (a cumulative +107%) of all the big EU nations (average growth +74%).

European leadership ensures that Italian pharmaceutical companies will continue to play a growing role in the national, manufacturing system. Currently, pharmaceuticals account for 6% of total exports.

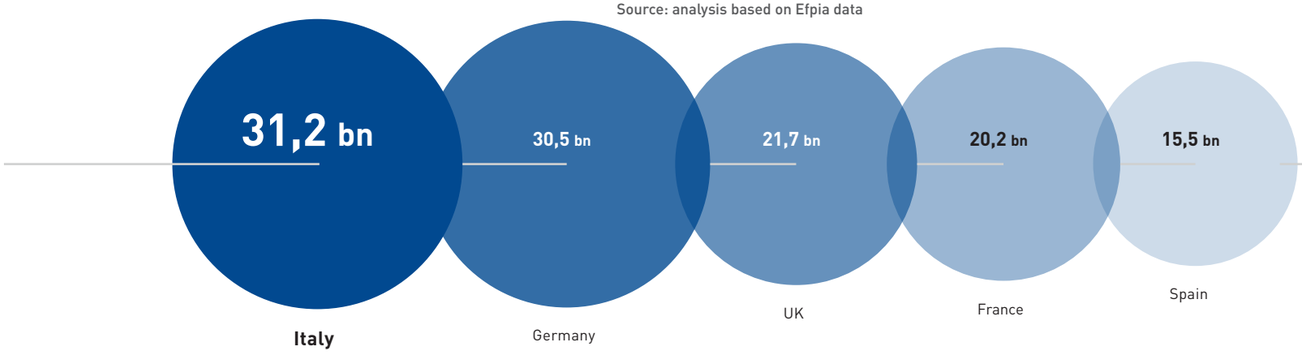
These results are reflected in the investments made in Italy, attesting to the pharmaceutical companies' enduring confidence in our country. In 2017, they invested 2.8 billion: 1.5 in R&D and 1.3 in production facilities. This value is up 3% from 2016 and up 20% from 2013.

PRODUCTION BROUGHT BACK TO ITALY. The quality of Italy's industrial pharmaceutical system has been a magnet for production activities previously carried out elsewhere in the world. If we analyse the increase in

FIRST IN THE EUROPEAN UNION FOR PRODUCTION

PHARMACEUTICAL PRODUCTION
VALUE, BILLIONS OF €, 2017 ESTIMATE

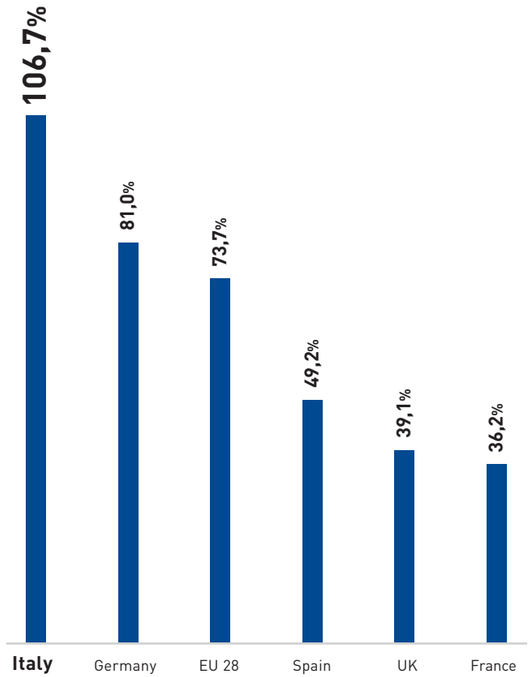
Source: analysis based on Efpia data



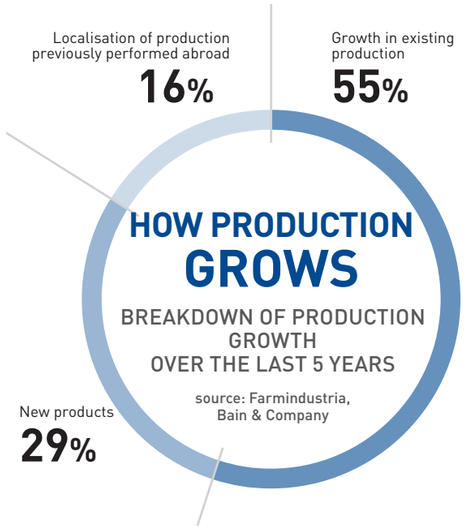
EUROPE'S MOST DYNAMIC EXPORTER

2007 - 2017 CUMULATIVE % CHANGE

source: Istat, Eurostat



Italian production over the last 5 years, we will find that about one half (55%) is linked to investments in the country's ongoing manufacturing activities, almost one third (29%) is the result of new product launches, reflecting the industry's innovative capacity, while 16% derives from the relocation of activities previously conducted outside Italy. This phenomenon is the exact opposite of delocalisation.



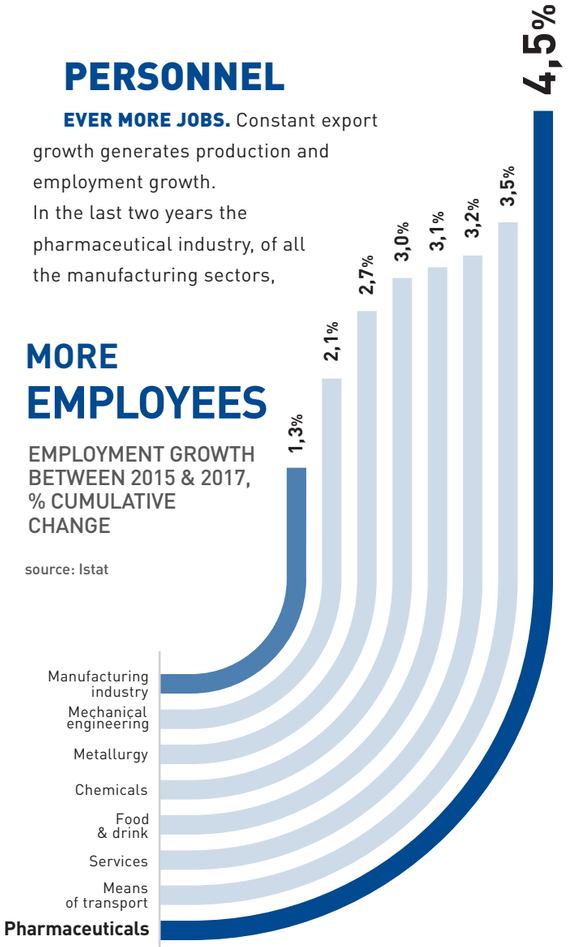
PERSONNEL

EVER MORE JOBS. Constant export growth generates production and employment growth.
In the last two years the pharmaceutical industry, of all the manufacturing sectors,

MORE EMPLOYEES

EMPLOYMENT GROWTH BETWEEN 2015 & 2017, % CUMULATIVE CHANGE

source: Istat

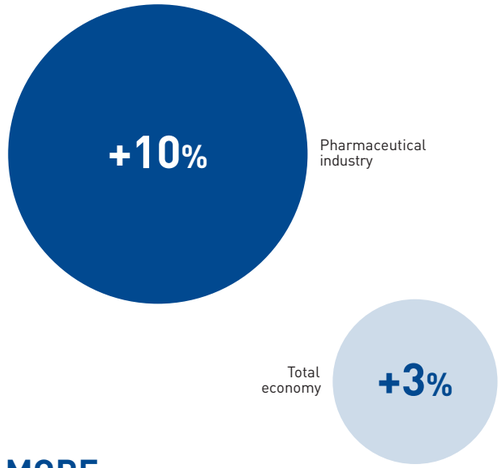


has recorded the highest growth in employment: +4.5% compared to +1.3% of the rest of industry. Thanks to over 6 thousand new jobs per year in the last three years, employment is growing again. The number of pharmaceutical employees in 2017 was 65,400; one thousand more (+1.6%) than the previous year. Furthermore, 93% of workers are on open-ended employment contracts.

INCREASINGLY BETTER QUALIFIED AND MORE PRODUCTIVE. Good corporate performance depends on the excellence of the human resources employed. 90% of the employees in the Italian pharmaceutical industry have a degree or a high-school diploma. They are also among the most productive in Italy (three times the average for the total economy) and in Europe. Whereas 20 years ago, productivity per head in our industry was lower than that in the other major European countries, now it is about 10% above the average. These results are the product of innovative, participatory and cooperative industrial relations: a major tool for competitiveness and growth.

AND INCREASINGLY YOUNGER. Youth employment is strategically important for the survival of both companies and the country itself and is clearly a major problem that Italy must resolve. From this viewpoint, the role played by pharmaceutical industry is very virtuous and forward-looking. National Pensions (INPS) data reveal that from 2014

to 2016 (the latest available figures) the number of employees aged under 35 in the pharmaceutical industry grew by 10% compared to +3% for the economy as a whole. If 100 is taken as the overall increase in employment in our sector, the under 35s constitute 55% of all employees.



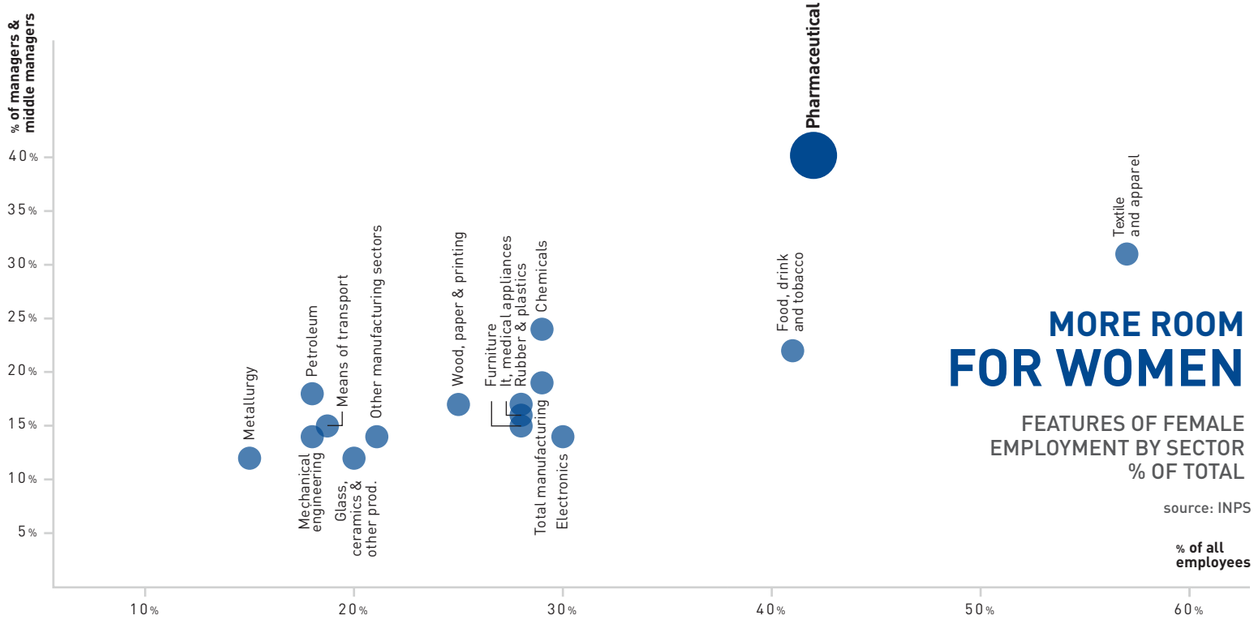
MORE YOUNG PEOPLE

UNDER 35 EMPLOYMENT GROWTH, 2014 – 16
% CHANGE

Source: analysis based on INPS data

All the data show a performance well above the national average. Employment and quality: 3 out of 4 new under-35, recruits are on open-ended employment contracts. Such job security guarantees high quality work for companies and life projects for the nation's citizens.

With our country's future in mind but also to familiarise young people with working life, Farmindustria, as the Confindustria System's leading association, is coordinating a pilot project known as School-Work Alternation "in the production chain", that brings together a number of companies, the areas of excellence in the auxiliary industries and the trade unions. The project, an initiative of the Ministry of Education, Research and the Universities, is aimed at giving students a first-hand experience of business and industry.



MORE ROOM FOR WOMEN

FEATURES OF FEMALE EMPLOYMENT BY SECTOR
% OF TOTAL

source: INPS

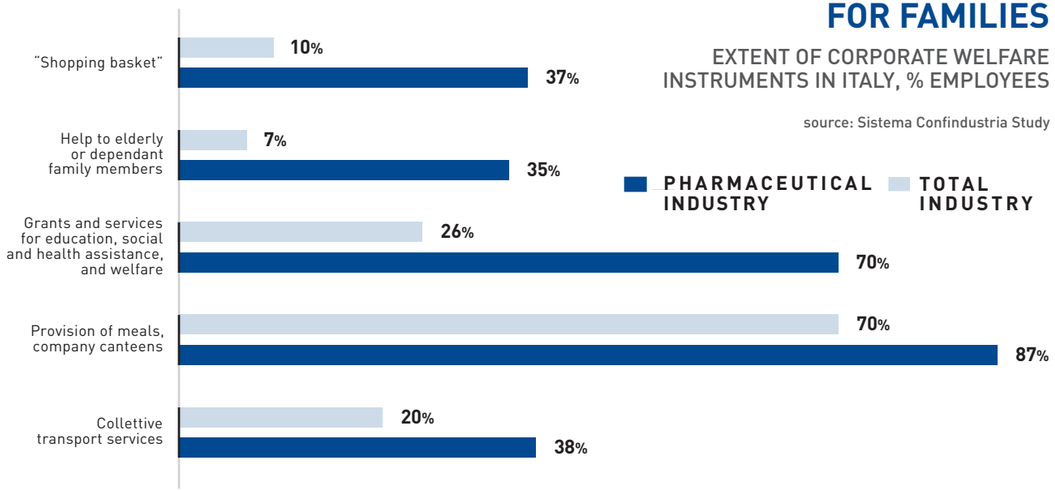
WOMEN'S ROLE. Another significant feature of the companies in the sector is that women are well represented. They account for 42% of all employees against 22% in other industrial sectors. In pharmaceutical companies they also perform important organisational functions: almost 40% of managers and middle managers are women, a much higher percentage than in other economic sectors in Italy (19%). This top and middle-management percentage, as that of female employment overall, shows that gender parity really exists in our industry. Moreover, as concerns research personnel, the percentage of women rises to 52%.

WELFARE. If productivity depends upon the quality of work, quality of work, in its turn, depends upon the quality of life. Pharmaceutical companies fully understand this and therefore guarantee their employees modern and effective corporate welfare services. Considerable attention is being given to conciliating work with the well-being of employees and their family members, as also in assisting elderly and dependant family members. To demonstrate just how far the pharmaceutical companies have taken this philosophy we can compare their welfare provisions with those offered by national industry as a whole. The differences range from basic services such as collective transport (available for 38% of pharmaceutical workers, 20% for other sectors), canteens (87% against 70%), to vouchers, educational services, social and health

WELFARE
FOR FAMILIES

EXTENT OF CORPORATE WELFARE INSTRUMENTS IN ITALY, % EMPLOYEES

source: Sistema Confindustria Study



assistance and welfare (70% vs. 26%) and help to elderly or dependant family members (35% vs. 7%). Pharmaceutical companies accept their social responsibility for the entire life of their employees. And in so doing, corporate welfare has emerged as a strategic and essential factor of production.

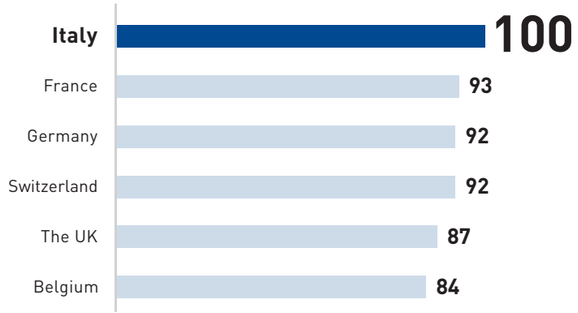
THE TERRITORY

UPSTREAM INDUSTRIES' EXCELLENCE. If Italy has become a worldwide productive hub for pharmaceuticals this is also due to the skills, flexibility and efficiency of its upstream industries, whose activities range from producers of raw materials and semi-finished goods, to mechanical engineering, packaging and services. As explained by CERM

AN ENGINE
FOR UPSTREAM INDUSTRIES

IMPACT OF PHARMACEUTICALS ON DOMESTIC USTREAM INDUSTRIES, INDEX ITALY=100

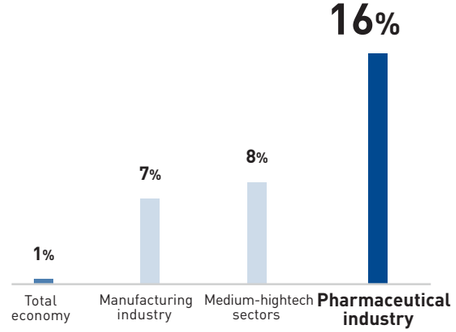
source: CERM



THE MOST CONVINCED
R&D INVESTORS

ITALY: R&D INVESTMENTS AS % OF VALUE ADDED

source: Istat



(Competitività, Regole, Mercati), Italy is again the European leader in terms of the extent to which pharmaceutical production deploys its upstream industries. In no other country is the transmission belt between pharmaceutical companies and their suppliers so strong.

REINFORCING THE RESEARCH SYSTEM. With 1.5 billion invested in 2017 (7% of the total for Italy), the pharmaceutical industry ranks third among manufacturing sectors in terms of R&D investments and first for expenditure per employee on innovation. Investments grew by 22% in the last 5-years (+ € 300 million); a much higher increase when compared to the average of the other European countries (16%). Research is always carried out in partnership with universities, centres of

THE ENVIRONMENT

excellence, SMEs, start-ups, and non-profit bodies in both the public and private spheres. This innovative research network besides guaranteeing companies the best talents on the market also ensures that an ever-greater share of investments produces advantages for subjects outside the companies, while powering the national research system for the benefit of the country as a whole.

OPERATIONS IN SOUTHERN ITALY. Pharmaceutical companies do not operate solely in the North. In the Abruzzo Region (L'Aquila and Pescara) about 2,800 persons work directly or indirectly in the pharmaceutical industry. In Campania (especially in the province of Naples and Avellino) pharmaceutical employees number 4,000. Similarly, Sicily (Catania) accounts for over 3,000 direct and indirect employees. In Puglia there are over 3,000 employees in the pharmaceutical and upstream industries. Furthermore, in Bari and Brindisi, (2 of Puglia's largest cities), pharmaceuticals represent a quarter of all manufactured exports.

The South accounts for 6% of all pharmaceutical employees and produces 13% of pharmaceutical exports. In the last 10 years, exports have more than doubled, representing a growth trend higher than the European average, and even higher than Germany's. In the last 10 years, pharmaceuticals in the South have shot up from 3.4% of all manufactured exports to the current figure of 7.3%, revealing the important role played by pharmaceuticals in the industrial life of these territories.

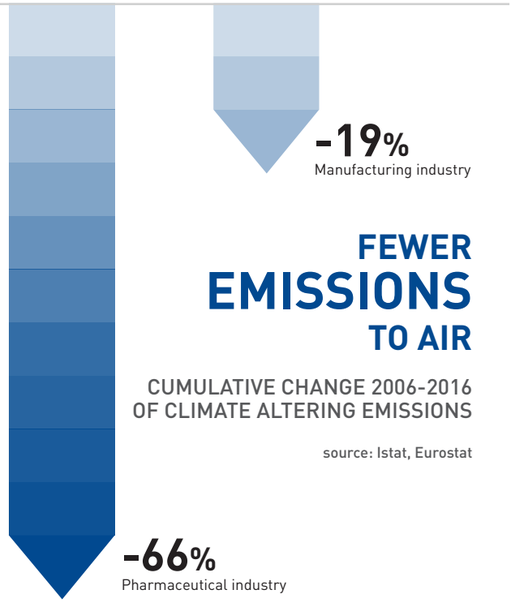
LESS ENERGY, MORE EFFICIENCY. Italian pharmaceutical companies in accepting the challenge posed by the environment have managed to turn it into an important competitive factor, commencing from energy use. At the height of the macroeconomic crisis, in the decade 2005 - 2015, the industry abated energy consumption - production output remaining equal - by about 70%. In contrast, the manufacturing industry as a whole only managed an average 18% reduction.

Climate-altering emissions have undergone a similar reduction, in line with the Paris Agreement on global warming. The gas emissions causing global warming (carbon dioxide, nitrogen dioxide, methane) produced by pharmaceutical companies in Italy have been cut back 66%, compared to 19% in manufacturing as a whole.

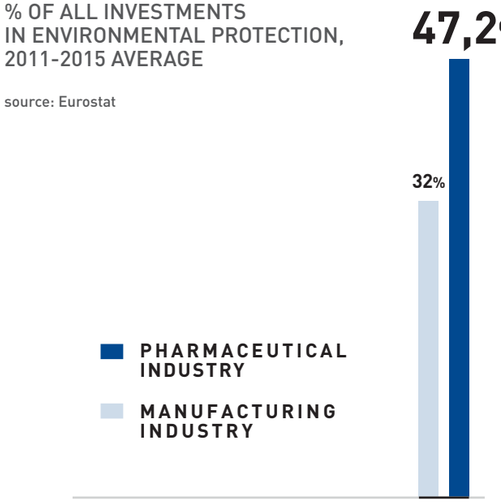
BETTER TO PREVENT. Underlying all such progress is the pharmaceutical industry's capacity to seamlessly innovate in all spheres including the environment. Here, too, differences emerge with other manufacturing sectors. While pharmaceutical companies are geared to prevention, manufacturing, considered as a whole, has mainly (68%) opted for investments in pollution abating technologies (i.e. downstream technologies to handle already generated pollution). Only one third (32%) of its investments address prevention (investments in equipment to cancel or reduce pollution at source in the production process).

The pharmaceutical industry's investments, on the contrary, are far more prevention orientated. At 47%, such investments are on a par with those for pollution abatement (52.8%).

In 2015, the pharmaceutical industry introduced the so-called Eco-Pharmaco-Stewardship (EPS), a European programme for the intelligent and sustainable management of the environmental impact of medicinal products over their entire life-cycle. Moreover, since 1980, pharmaceutical companies in Italy have been operating a centralised system, together with the entire supply chain, to ensure the correct disposal of medicines whose use by date has expired.



MORE INVESTMENT IN "CLEANER TECHNOLOGY"



THE ADVANTAGES FOR THE NHS

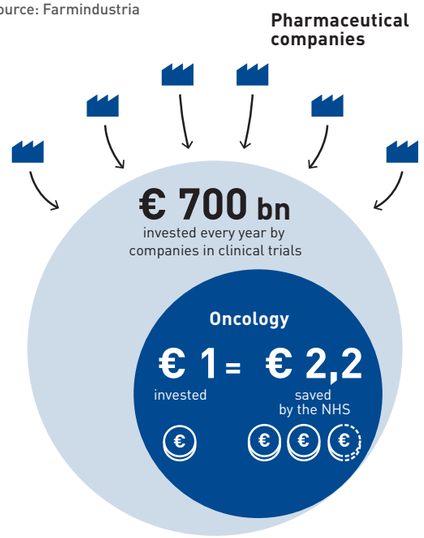
THE VALUE FOR THE ITALIAN RESEARCH SYSTEM: CLINICAL TRIALS. If Italy has become a worldwide pharmaceutical hub this is equally due to the quality of its healthcare eco-system (from hospitals to universities and private and public research centres). The next step is to further consolidate the country's position as an authoritative and recognised world centre for clinical trials in the sector. In a medicinal product's path from discovery to market access, clinical trials constitute an essential passage as this is the stage when its safety and efficacy are tested on patients. Italy plays an increasingly important role in this delicate passage. 20% of clinical studies in the EU are carried out in our country, and every year the industry invests over € 700 million in Italy for such trials: one of the highest contributions made to the national research system.

Clinical trials not only guarantee innovative therapies for patients but also the professional development of physicians and researchers, thereby enhancing the scientific competitiveness of the entire system. They also provide important resources for the National Health System: during a clinical trial, companies bear all related costs (from hospitalisation to medicines and diagnostic examinations).

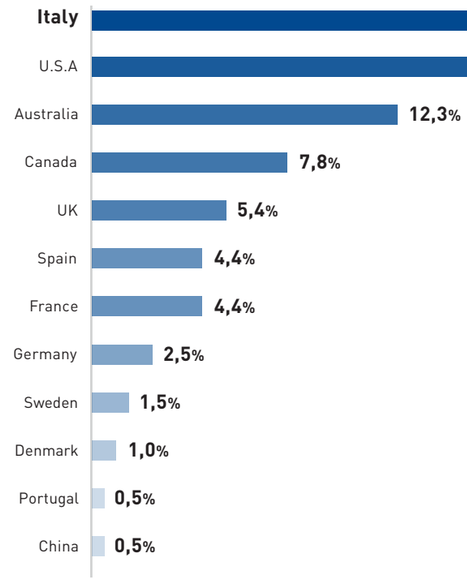
It is calculated, for example, that 1 euro invested in clinical trials in the field of oncology produces savings of €2.2 for the NHS.

THE VALUE OF CLINICAL TRIALS

source: Farmindustria



SMART CONTRACTS: VALUE-BASED AGREEMENTS. Italy is the leading country in the world for the number of innovative contracts in place between companies and the NHS; our country accounts for 36% of the world's total, ahead of the USA (24%), Australia 12%), and successively



FIRST IN THE WORLD FOR INNOVATIVE CONTRACTS TO REMUNERATE PHARMACEUTICALS

% OF MANAGED ENTRY AGREEMENTS OF WORLD TOTAL

source: McKinsey, 2017

Canada (8%), the UK (5%), France (4%), Spain (4%) and Germany (2%). Value-based agreements, as the experts refer to them, are deemed 'smart' and cost-effective because pharmaceutical companies are reimbursed a medicinal product's cost solely on the basis of its ascertained therapeutic value. In other words, it must be determined if the medicine administered to a patient is actually efficacious or not.

This is the remuneration system of the future. Being particularly well suited for innovative medicinal products and personalised medicine, it is currently at the centre of international attention. Although still at an early stage in development, Italy decided to introduce MEAs, or Managed Entry Agreements, in 2006, subsequently following them up with monitoring registers managed by AIFA to guarantee appropriateness and applicability. As a result of these agreements, pharmaceutical companies, between 2013 and 2017, returned € 3.5 billion to the NHS.

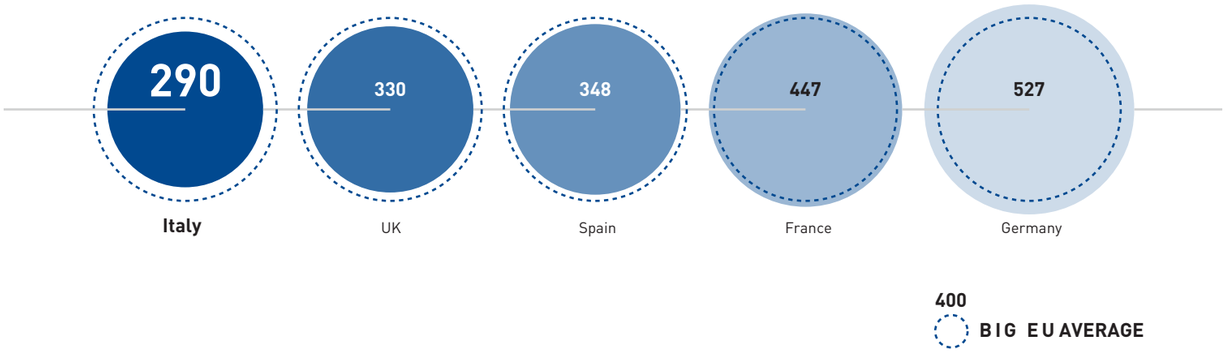
PHARMACEUTICAL SPENDING. In Italy, public pharmaceutical spending per head is much lower than in other major countries: actually, as much as 27% lower than the average spending in Germany, France, the UK and Spain. Levels of service being equal, this figure reflects the fact that our prices are inferior to the prices practised by our main competitors.

Moreover, as a percentage of GDP, pharmaceutical spending is also lower than the rest of Europe. In Italy it has remained fixed for years at 1%, against an EU average of 1.2%. Overall, and even including private expenditure, spending per capita on pharmaceuticals in Italy remains 12% lower than the average spending in the major EU nations.

THE LOWEST SPENDING, PER CAPITA, ON PHARMACEUTICALS

€ PER CAPITA, ESTIMATES ON TOTAL SPENDING, 2017

source: Aifa, IQVIA, Eurostat, foreign Associations



PHARMACEUTICALS AND VACCINES FOR SUSTAINABLE SPENDING. Medicinal products and vaccines are also an instrument to make welfare services more efficient. For example, they eliminate costs by obviating hospital admissions, preventing or slowing the course of pathologies, curbing the disbursement of pensions or social assistance allowances and alleviating the caregiver's burden. In addition, patients benefitting from better treatment can in many cases manage their illness by continuing to work and by maintaining an active role in society.

The contribution made by medicinal products and vaccines is fundamental for making a holistic evaluation of a diagnostic-therapeutic path, and not least because this approach can take better account of patients' needs. In order to measure sustainability, total patient costs must be factored in not merely the costs accruing from individual services.

THE PHARMACEUTICAL INDUSTRY AN INVESTMENT FOR ITALY. Any form of cost-benefit analysis to take stock of our pharmaceutical companies' operations would balance their direct and indirect (i.e. upstream industries) contribution - in terms of employment, investments (in production, R&D, and the environment) and taxes paid - against the amount annually earmarked to them by the NHS.

Such a cost-benefit balance has returned positive results in Italy for years (in 2017, in excess of €1 bn) and once exports are taken into account, the difference is ever greater. In other words, the pharmaceutical industry gives back to Italy an economic value that far outweighs its costs. And to this value should be added its important role in meeting the fundamental needs of our society in terms of treatment, healthcare, and the efficiency of public and private welfare. These features make it a strategic sector for the entire country and not just the regions where pharmaceutical companies operate and invest.

TOWARDS THE FUTURE

40 YEARS OF ACTIVITY IN ITALY: PHARMACEUTICAL COMPANIES INVOLVED IN RESEARCH, THERAPY AND CARING

Although they may seem many more, only 40 years have elapsed since May 1978, when Farmindustria was founded. These four decades have witnessed an unprecedented acceleration in geopolitical changes, social transformations, and scientific, medical, pharmacological and technological innovation.

These 40 years will be reconstructed in the pages that follow principally from the standpoint of health and pharmaceuticals. However, we first begin with a brief history illustrating the major global geopolitical differences before returning to the situation in Italy and recalling two events, in 1978 that are of fundamental importance for Italy and the pharmaceutical industry.

In that year the National Health Service was set up, which represented a revolution for our country and a clear improvement in the quality of life for us all. Secondly, a judgement was handed down by the Constitutional Court that made it possible to patent pharmaceuticals, a vital moment for the industry's development.

We shall recount how Italians lived, their state of health and how their health constantly improved over time. We shall also describe the most important pharmaceutical innovations to which this improvement is to be attributed. In conclusion, we shall illustrate how pharmaceutical companies have changed and learned to manage innovation in order to stay on top of these enormous transformations.

IN THE 20th CENTURY

1978. A few years earlier the world had been shaken by the oil crisis that commenced in the early 1970s. The Iron Curtain divided the world into two opposing blocks. On the one side stood the United States of America, democracy and the dollar, on the other, the Union of Soviet Socialist Republics (the USSR), the rouble and "real socialism". Two years earlier Mao Zedong had died, and China was very far from challenging the economic primacy of the USA. In 1978, the Polish Karol Józef Wojtyła, was elected pope and took the name of John Paul II. It was the period immediately prior to the 1980s: the years of the Iron Lady, Margaret Thatcher, Ronald Reagan, the actor who become president of the USA (1981-1989), and Mikhail Gorbaciov, the last secretary general of the Communist Party of the USSR (1985-1991), but also the years of the war between Iraq and Iran (1980-1988). In the 1980s environmental issues erupted into the collective consciousness with the discovery of an ozone hole in the Antarctic (1985) and the explosion of reactor no. 4 at the nuclear power station in Chernobyl (1986). We were still not using Google's search engine; the word selfie had not been invented and our status was not being shared on Facebook. The World Wide Web only arrived in 1993 and the human genome map was still a matter of science fiction.

THE SEEDS OF THE FUTURE. Despite the enormous differences between these times and our own, some novelties came onto the stage that are still a matter of discussion in our daily lives. In 1978, the European Council introduced the ECU, the European Currency Unit, which paved the way to the Euro. In 1978 the Pixar Animation Studios was founded. A year earlier *Star Wars* had been released. In the same year the CBS broadcast the first episode of Dallas and the world was soon to become hooked upon television serials. In 1979 Philips and Sony invented the CD and suddenly the music cassette became a thing of the past. On 16 April 1977, Apple II was unveiled: the home computer era had begun. 1983 was the year of the Motorola DynaTAC, the first cellular phone registered by the United States Federal Communications Commission. However, these were likewise the years of the first European institutions dedicated to pharmaceuticals: in 1975 the CPMP - *Committee for Proprietary Medicinal Products* – was set up and initiated a path that in 1995 was to see the creation of EMA, the European Medicines Agency. In 1978 the first biotechnological product was produced: insulin.

ITALY. 1978 witnessed the terrible kidnapping of Aldo Moro, but also marked the beginning of Sandro Pertini's presidency. The Basaglia law on lunatic asylums and law 194 on abortion were passed. The RAI had only recently begun colour broadcasts, Matia Bazar won the Sanremo Musical Festival and Rino Gaetano sang *Nuntereggae più*. Our National Health Service was instituted to guarantee a system of structures and services that ensured universal and equal access to the provision of health services for all citizens regardless of economic or social position in

implementation of article 32 of the Constitution, which states that: "The Republic safeguards health as a fundamental right of the individual and as a collective interest and guarantees free medical care to the indigent. No one may be obliged to undergo particular health treatment except under the provisions of the law. The law cannot under any circumstances violate the limits imposed by respect for the human person". In the same year the Constitutional Court ruled that the prohibition on patenting pharmaceuticals was unconstitutional. This was a necessary and indispensable measure because, hitherto, it had been impossible to grant patent protection to pharmaceutical inventions in Italy. The rule gave an enormous impetus to pharmaceutical investments and research while making a decisive contribution to the growth and internationalisation of the domestic pharmaceutical industry. International companies set up production facilities and registered offices in our country and the more innovative national companies were stimulated to focus on research and to develop and create new "made in Italy" medicines in order to find a proper allocation in the international markets.

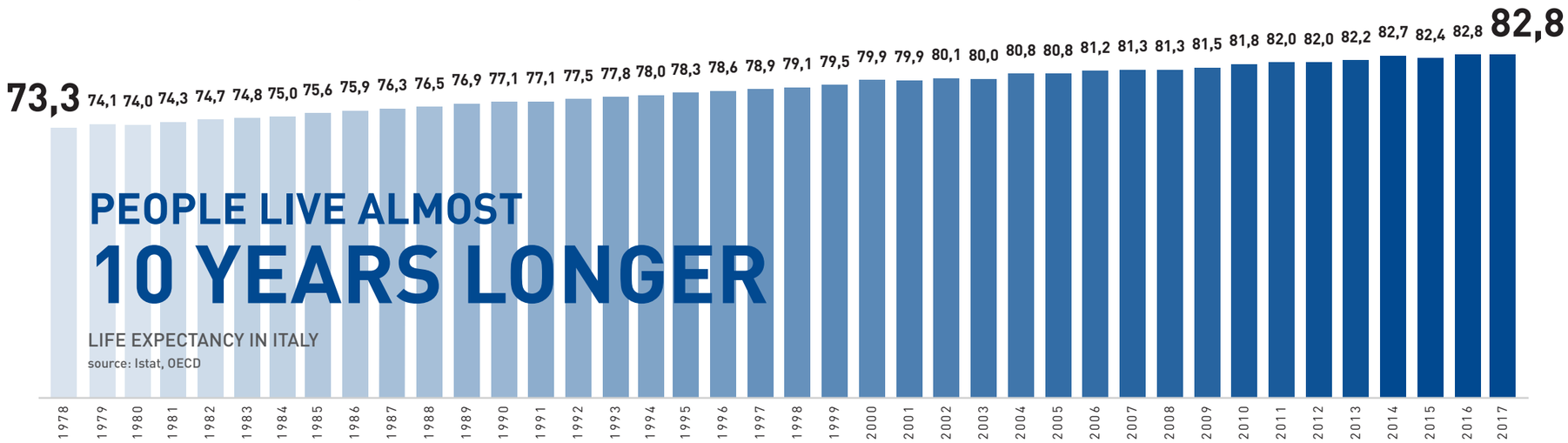
A SINGLE VOICE. Farmindustria, the pharmaceutical companies' trade association, was set up in the wake of the Constitutional Court's decision. From this time onwards all the pharmaceutical companies could count upon a single and authoritative body to represent them in Italy and abroad.

ITALIANS AND THEIR HEALTH

HOW WE WERE. In 1978 Italy's population stood at 56 million. Since then country has not become much more populous (there are now only 4.5 million more people). Foreign residents were 211 thousand and immigration was a non-issue. Today, the number of immigrants is 5 million. In 1978, GDP stood at 254 billion lire: net of inflation this is equivalent to € 933 billion. Today's GDP is € 1,717. There were 74,000 graduates (today there are 304,608). Only 4 graduates out of 10 were women (today there are 6). Only 3 out of 10 women held a job. Today 5 out of 10 work. At 18 all male adolescents were called up do military service.

AND HOW WE WERE. Italians' health has certainly changed for the better over these 40 years. This is illustrated by one basic statistic: a girl born in 1978 could hope to live to 77 and a boy to about 70. A girl born today has a life expectancy of 85, and a boy of 81. In these 40 years Italians have gained almost 10 extra years of life: an impressive figure. The gain of ten years, as well as a much better and more satisfactory quality of life, is the result of the spread of the culture of prevention, attention to styles of living, and progress in medical science, especially as concerns pharmaceuticals. Thanks to such progress, Italy - according to the Organisation for Economic Cooperation and Development - ranks fourth for longevity after Japan, Spain and Switzerland.

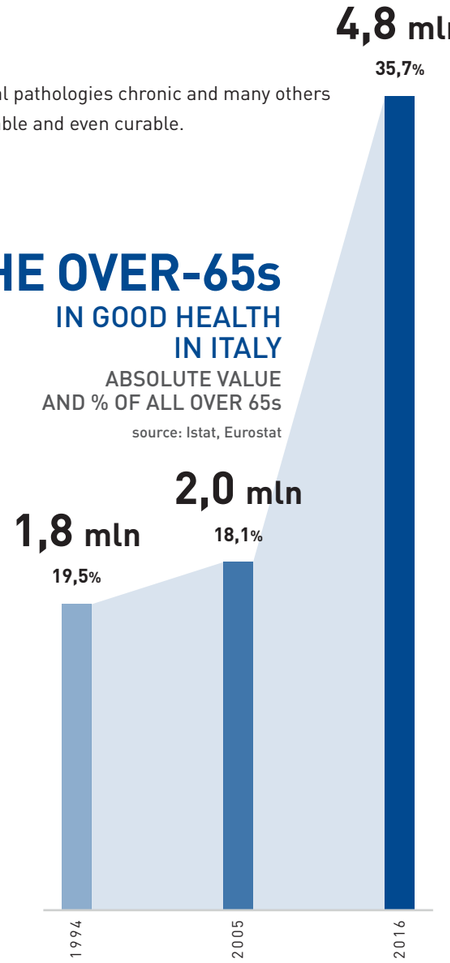
THE CHANGE IN THE POPULATION'S PROFILE. This progress has changed the Italian population's vital statistics. In 1978 the over-65s were 7 million. In 2017 they amounted to 13.5 million. People live longer and better, largely thanks to to medicines that have made some



mortal pathologies chronic and many others treatable and even curable.

THE OVER-65s
IN GOOD HEALTH IN ITALY
ABSOLUTE VALUE AND % OF ALL OVER 65s

source: Istat, Eurostat



OUR PRINCIPAL FOES ARE LESS FRIGHTENING. The ratio of deaths to the population is also decreasing. Compared to 1978, there has been a 46% reduction in the overall mortality rate.

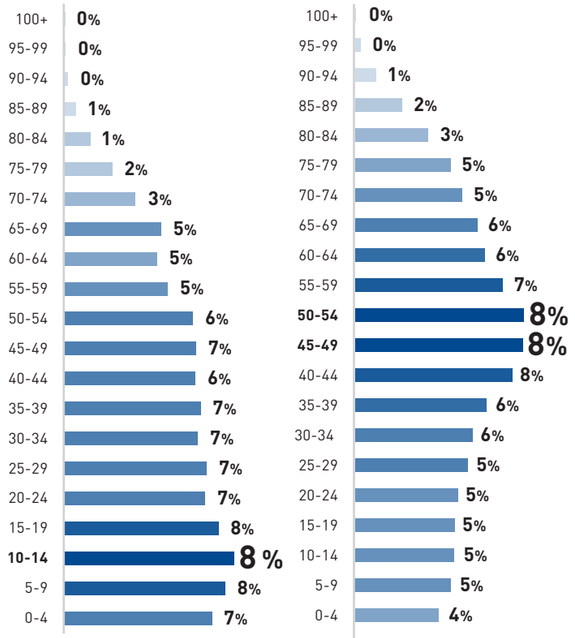
As we would expect, this decline is also recorded in the specific indicators for the different pathologies. If we consider the first five causes of death in Italy in 1980, we find a distinct decline in the mortality rate for each pathology. For cardio-circulatory system diseases the reduction has been 64%. Likewise, there has been an important 25% decline in malignant tumours: 30 years ago, only one in three of persons diagnosed with the disease lived longer than 5 years, but today - thanks to medical and pharmaceutical progress - two out of three survive.

The reduction in deaths from respiratory system diseases amounts to 47% while that from digestive system diseases is 63%. As concerns the mortality rate for HIV/AIDS, which is by now a chronic illness, mortalities have fallen by 87% since 1985 (the year when the disease's incidence was at its peak).

Yet, there are still many challenges facing pharmaceutical research before it can satisfy the remaining health needs: from medicines to treat rare diseases, to personalised medicine in order to provide more targeted and effective therapies.

THE ELDERLY
COMPOSITION OF THE POPULATION IN ITALY BY AGE, % OF TOTAL

source: Istat



WHAT BEING WELL MEANS. As Italians' health improves so the concept of health itself changes. What do Italians mean when they declare themselves to be well? In the 70s, being "well" simply meant not being ill. In this context, prevention - a concept still today closely linked to health – was basically limited to vaccination. When someone was unwell, the "authority" to whom he or she turned was the physician: and his or her decision went unquestioned.

THE SUBJECTIVE APPROACH TO HEALTH. In the 80s, but mainly in the 90s, the concept of health became more subjective. The enjoyment of good health grew into a concept that was increasingly associated with personal well-being and in which individual behaviour and choices, (what today we call life-styles), played an increasing role. Censis (Centro Studi Investimenti Sociali) informs us that if in 1987 50% of the population considered such life-styles decisive for good health, by 1998 this percentage had risen to 63%. The idea of prevention grew, and people started to do something that we now take for granted: they underwent specific medical examinations in the absence of symptoms. In 1994, 38% of women over 40 had taken at least one mammography, but by 2013 this had risen to 67%. Patients' freedom of choice also increased. When a problem arose, they could refer to information garnered from the TV and newspapers, in addition to seeking their physician's advice.

THE GREAT ALLIES. MEDICINAL PRODUCTS

GENES, THE ENVIRONMENT, BITs. If the 80s and 90s featured life-styles that influenced health, the start of the new millennium were the years when an awareness of genetic factors and the environment became an important factor in healthy living. According to Censis, only 13% of the population in 1998 believed the environment significantly influenced our health. By 2014 this figure had risen to 29%. Health decisions were more frequently becoming individual choices, in which the web – which had become the primary source of information – played a more relevant role. Yet while being a rich and detailed information source, it is not always easy to distinguish between what is reliable and what is superficial or even false.

However, thanks to IT patients can interact in a more informed manner with physicians and the National Health Service.

A PROTAGONIST ROLE, WITH PERSONALISED THERAPY AND INCREASED ATTENTION TO WOMEN. If we are healthier we owe it to the progress made in medicine, but more specifically to pharmaceutical innovation. Many medicines, including personalised ones, are available today that can cure previously incurable diseases, or which can block a pathology's progression or prevent the complications associated with it. More attention is being paid to female specificities, with 850 medicines under development in the world to treat pathologies prevalently found in women.

THE PRESENT TENSE OF THE VERB PREVENT: VACCINATE. Whopping cough, polio, tetanus: the main childhood vaccines were introduced in the 60s. The results are undisputable: for example, after the introduction of the whooping cough vaccine the disease's incidence fell from 76.2 cases per 100,000 in 1961 to 12.7 in 1981. Vaccination coverage continued to grow over time. Obligatory vaccination passed the 95% threshold recommended by the World Health Organisation in order to reach the so-called "herd immunity". The use of vaccines for population segments other than children, such as the influenza vaccination, also increased. Nevertheless, in 2014 coverage fell below 95% on account of a diminished perception of the diseases' danger and an unfounded, but increasingly widespread, fear of this tool of prevention. Last year this trend was reversed in part thanks to a heightened awareness of the risks as also to public policy decisions on the question.

ON THE SIDE OF HEALTH. THE MID 20TH CENTURY. The history of recent decades has been characterised by a series of pharmaceutical innovations. The 40s and 50s witnessed the arrival of antibiotics, a milestone in innovation that, commencing from their use during the Second World War, has helped save millions of lives. At the end of the 1960s the first measles vaccine was developed, which a few years later was to lead to the MMR vaccination, offering protection from three highly contagious diseases: measles, mumps and rubella.

FROM THE 1970s TO THE 1990s. In 1977, the first inhibitor of the Angiotensin converting enzyme (ACE) for the treatment of hypertension was discovered. The following year, 1978, by inserting small fragments of human DNA into *Escherichia coli* bacteria, the first biotechnological pharmaceutical was produced: insulin (previously insulin was obtained from animals, with the attendant risk of allergic reactions). In 1986, the first medicine based on monoclonal antibodies was approved. This medicine was noteworthy for attacking tumour cells rather than adjacent tissues. In 1987, the first medicine for the treatment of river blindness and elephantiasis, diseases mainly afflicting developing countries, was developed. In the same year the approval of the first statin marked a fundamental step in the fight against cardiovascular diseases. Ten years later, the American Drug and Food Administration approved the first anti-retroviral (ARV) medicine to repress HIV replication. The development of a new class of anti-retroviral medicines goes back to the 1990s. Their introduction led to a major drop in mortality (-50% in the USA and Europe in the space of 3 years). Proton pump inhibitors, for resistant gastroduodenal ulcers and reflux oesophagitis (that avoided the need for surgery) were introduced as well as and interferons for leukaemia, hepatitis and multiple sclerosis.

THE INNOVATIONS OF THE NEW MILLENNIUM. In 2006 the vaccine for HPV (human papilloma virus), the cause of uterine cervical cancer, was approved. The new millennium also witnessed the arrival of medicines to treat arterial hypertension, cardiac decompensation (sartans), asthma, psychiatric and perinatal pathologies. New therapeutic approaches also improved some neurodegenerative diseases such as Alzheimer's and Parkinson's disease. Direct acting antivirals (DAAs) for healing patients affected by hepatitis C were introduced in 2011. In 2012 - for the first time in 40 years - a new, and more effective, medicine against tuberculosis was introduced. Two years later CAR-T gene therapy was developed: cells programmed to combat carcinogenic cells. In 2018, trials began on the first malaria vaccine. Today, medicines exist for advanced therapies: DNA or RNA-based biological medicines, cells or tissues adapted to cure a specific pathology (e.g. rare genetic illnesses or leukaemia) or to regenerate a given tissue (such as the regeneration of the cornea). In addition to such great therapeutic leaps forward, innovation also includes a more gradual research process to improve the efficacy of existing medicines that has led to so-called "incremental improvements" and which are of great importance to patients.

- Industrial scale production of antibiotics & vaccines begins.
- Nobel prize for the discovers of cortisone
- The discovery of DNA
- First polio vaccinations
- Measles vaccination discovered
- Reduction in myocardial infarction mortality thanks to thrombolytics
- Important antihypertensives (beta blockers and calcium antagonists)

1940-1960

- Anti-rejection medicines for organ transplants
- Introduction of beta 2 agonists and corticosteroid inhalers (anti-asthma)
- Discovery of H2 blockers (non-surgical ulcer treatment)
- Triple MMR vaccine for measles, mumps and rubella
- Discovery of monoclonal antibodies of the immune system
- First angiotensin converting enzyme (ACE) inhibitor for hypertension.
- First biotech insulin produced

1960-1980

- Medicines for hypertension, heart failure and diabetic nephropathy
- Medicines for gastroduodenal ulcers and gastro-oesophageal reflux
- Orphan Drug Act for research on rare/orphan diseases is passed in the USA
- Introduction of interfons for leukaemia, hepatitis and multiple sclerosis
- Monoclonal antibody-based medicines for tumours
- Treatment for Herpes and depression
- First antiretroviral medicines for HIV/AIDS
- New medicines for parasitic infections
- First statin for cardiovascular diseases
- Identification of the hepatitis C virus

1980-1990

- Oncological progress with ever more effective medicines and vaccines
- Chemotherapy with minor collateral effects
- Medicines for arterial hypertension and cardiac decompensation (sartans)
- Therapies for osteoporosis, rheumatoid arthritis and osteoarthritis
- More selective treatment for chronic myelogenous leukaemia
- Medicines for asthma, psychiatric and perinatal pathologies
- Improved therapies for Alzheimer and Parkinson's disease
- Classes of antiretroviral medicines (combined treatment)
- Mapping the human genome, with important new treatment prospects
- Papilloma virus vaccine
- Direct acting antivirals for hepatitis C.
- More effective medicine for tuberculosis
- Trials of first malaria vaccine
- Advanced therapies (e.g. gene and somatic cell therapy, tissue engineering)
- Development of CAR-T gene therapy for carcinogenic cells

1990-TODAY

THE GREAT BREAKTHROUGHS

SOME EXAMPLES

INNOVATING TO STEER CHANGE. PHARMACEUTICAL COMPANIES

Scientific progress, especially medical science, lies behind major breakthroughs in health. But we must not forget the pharmaceutical companies' constant commitment to innovation and R&D.

FROM PHARMACIES TO PHARMACEUTICAL COMPANIES. The first pharmaceutical companies appeared in Italy before the country's unification. Unlike other countries (Germany, for instance) where a chemical tradition had given rise to the "therapeutic revolution" in the second half of the 19th century that produced the first synthetic medicines, in Italy pharmaceutical production commenced in the small laboratories of pharmacies. Apothecaries purified and standardised remedies and gradually industrialised processes and products. If, on the one hand, this genesis entailed delays in the growth of large international companies, on the other, it laid the foundations for small and medium-sized companies that are today often associated with courageous family entrepreneurial initiatives, in keeping with the country's industrial tradition. However, such small indigenous companies were soon flanked by a number of important international companies - with production facilities or just administrative offices – even before the dawn of the 20th century. Their presence was to increase in the years of the economic miracle thanks to incentives offered for foreign investments, especially in the Centre and South. Unlike other sectors, these investments created lasting value and still constitute fundamental territorial assets. Today - taking account of turnover, investments, employees, export sales and taxes paid - internationally-owned companies account for 60% of the entire pharmaceutical industry, with Italian capital companies making up the remaining 40%.

A well-balanced mix, and the only one of its kind in Europe. Beginning in the 1980s production passed from small laboratories and workshops to increasingly larger factories with ever-more specialised production. Their shared characteristic - in which, as we have seen, the Constitutional Court's 1978 rule played a crucial part - is the quality of the production and an ever-greater internationalisation. Many of those companies, which in

the 19th century were only laboratories at the back of pharmacies, are today international enterprises: about 70% of the turnover of Italian owned companies comes from foreign sales.

FROM RANDOM SCREENING TO DRUG DESIGN. At the end of the 1970s, when this chronicle begins, pharmaceutical companies, worldwide, were developing a revolutionary new approach to production processes that was to lead to the discovery of new medicines. This was the passage from the so-called random screening approach (in the absence of precise data on the mechanisms that cause pathologies, this method randomly chose molecules from the enormous quantities available and then opted for the most effective) to drug design, a more rational approach based on an increasingly precise knowledge of the mechanisms responsible for pathologies, which, in its turn was based on certified progress in medical science (the so-called molecular medicine).

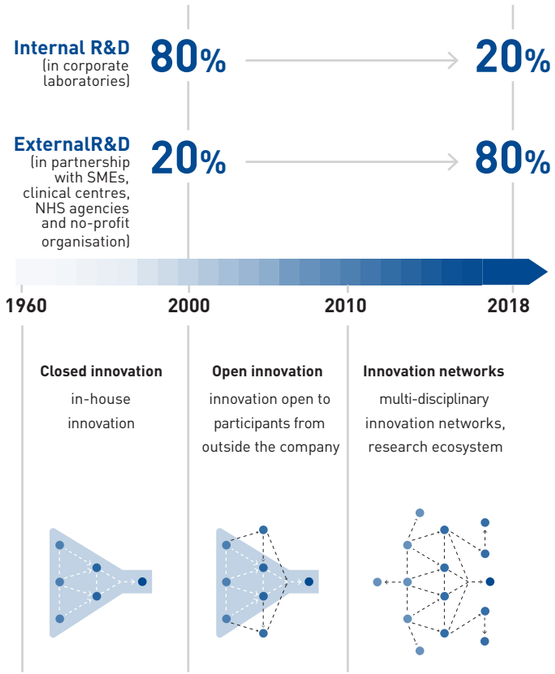
This was the start of a major evolutionary change that is still underway. Thanks to this paradigmatic transformation some highly effective and widely used medicines emerged in the 1980s. Furthermore, what were initially pharmaceutical divisions of major international chemical groups became pharmaceutical companies in their own right. The phenomenon of concentration began and was to continue into the future. Pharmaceutical globalisation was to precede economic.

EVERYTHING BEGAN WITH INSULIN. In 1978, in his laboratory at the University of California in San Francisco, Herbert Boyer created human insulin by inserting a gene into *Escherichia coli* bacteria. The procedure was derived from the DNA modification (recombinant DNA) technology that Boyer and Stanley Cohen had developed six years earlier for the purpose of altering the DNA of bacteria by introducing human genes. Thus, biotechnology was born. It was the start of a new era. Today, 40% of pharmaceutical products under development in the world are biotech. In Italy 70% of the industry's investments are earmarked for biotech pharmaceuticals, advanced therapies and rare diseases.

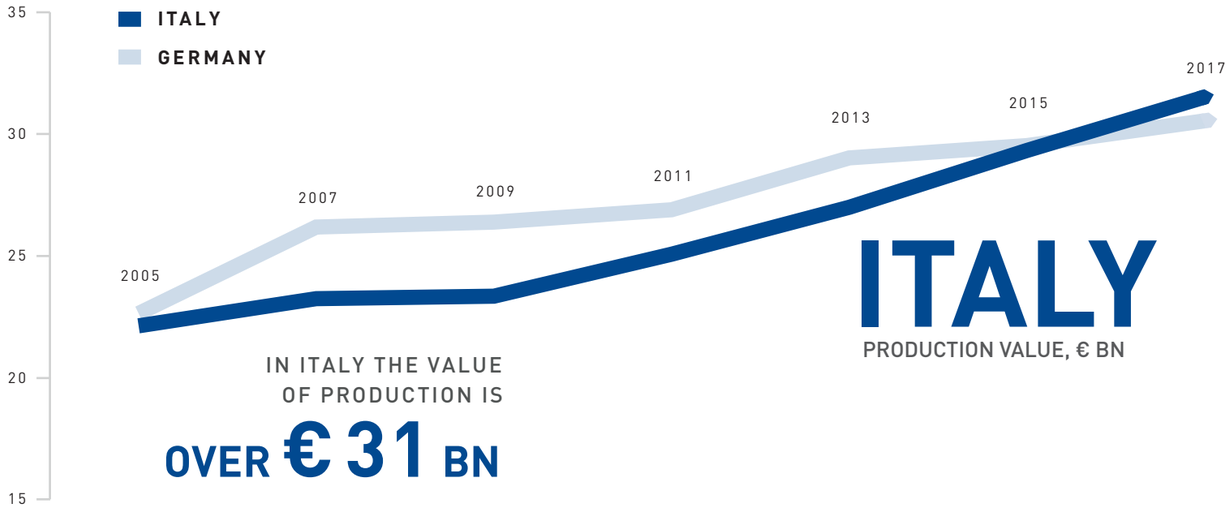
PERSONALISED MEDICINE. One-fits-all: at the start of the new millennium medicines were still administered at a ratio of one (the medicine) to all (patients). However, after its completion in 2003, human genome sequencing changed all of that for good. The new technology enabled us to understand why a medicine worked on one person and not on another and to create a new generation of medicines tailored to different genetic profiles, and hence more effective.

Pharmacogenetics was born, the precision medicine, or the science of genetic markers that shifted our focus from the disease to the patient. The issue was no longer the medicine per se, or if it could cure a disease, but rather whether it could take account of a patient's genetic features.

THE CHANGE IN HOW TO PERFORM R&D



MORE SKILLS, AND NOT ONLY IN CORPORATE LABORATORIES. The path of pharmaceutical science is now increasingly multi-disciplinary and requires ever-more specificities in terms of the skills required: physicians, geneticists, but also mathematicians, bioinformaticians, and experts in combinatorial chemistry. In proceeding down this path, companies discovered that their laboratories were no longer large enough to embrace the best skills necessary. Thus, they opened themselves up to the outside world, in search of better and more diffuse skills. Consequently, innovation from an in-house activity has become a partnership involving the best players on the market. In place of the division between private and public, research has become a joint venture. Today, 80% of pharmaceutical innovation is the fruit of partnerships between large companies, SMEs, universities, non-profit bodies and public and private centres of excellence. Almost 80% of R&D investment by pharmaceutical companies in Italy is made in international research networks or outsourced. This virtuous orientation to the external world, has turned pharmaceutical companies - commencing from the 1990s, but mainly in the past decade - from monoliths that discovered, produced and distributed medicines into companies that choose and coordinate the best skills on the market in terms of research, production and distribution. Companies have become real hubs.



IN ITALY THE VALUE OF PRODUCTION IS

OVER € 31 BN

ITALY

PRODUCTION VALUE, € BN

FIRST PRODUCER IN THE EUROPEAN UNION

source: based on Efpia data

LARGE NUMBERS & SILICON INTELLIGENCE. If medicine, therapies and medicinal products are increasingly personalised, linked to genetic profiles and personal conduct, the mass of data to be considered and evaluated has mushroomed. We have entered the era of Big Data and of AI, which feeds upon Big Data. At the same time, the new millennium saw the entry onto the stage of immensely powerful computers able to "read" and learn from immense databases (with genome, clinical, and scientific study data and universities' libraries of molecule) and put such knowledge at the service of all physicians and researchers throughout the world. And the more widespread such knowledge, the more the quality of competition is enhanced. As a result, pharmaceutical companies have begun to cooperate on strategic ventures with leading Silicon Valley companies. In recent years, digital technology has also "contaminated" production: companies have transformed themselves into industry 4.0 enterprises, using online production systems, and in addition to medicinal products they produce data to make production processes more efficient. In Italy, 35% of companies already work with in partnership with ICT companies and 84% intend to do so in the near future.

FROM THE "SIMPLE" PRODUCT TO A PROCESS PART. Thus, synergies between ICT and pharmaceutical companies grow and the industry is now one of the sectors where Big Data is applied massively to improve all corporate processes: research, production and therapeutic access. Companies are offering an ever-larger number of products and e-healthservices (there are now over 300 thousand health apps in the world), to manage life-styles but also and more importantly to provide patient support and care. In a context of this profound transformation of care management, medicines have ceased to be a simple product and have become part of a more complex holistic therapeutic process in which they are supplemented by precision diagnostics, devices and support services.

AFTER THE BREAKTHROUGH, THE RULES. After progress in science and the discovery of medicinal products comes innovation in international regulatory systems. The first directive that served as a regulatory basis for more standardised authoritative rules in Europe dates back to 1965. Moreover, regulatory systems have slowly begun to pay more attention to the healthcare needs that medicinal products can satisfy. At the same time, mechanisms for reimbursing the cost of medicinal products have become more intelligent. In the early years of 2000 - with an important contribution from Italy, which with the support of Aifa's medicinal product registers, has emerged as an undisputed leader in this field – the system of payments by results made its first appearance: the reimbursement of medicines by the NHS according to the therapeutic results achieved.

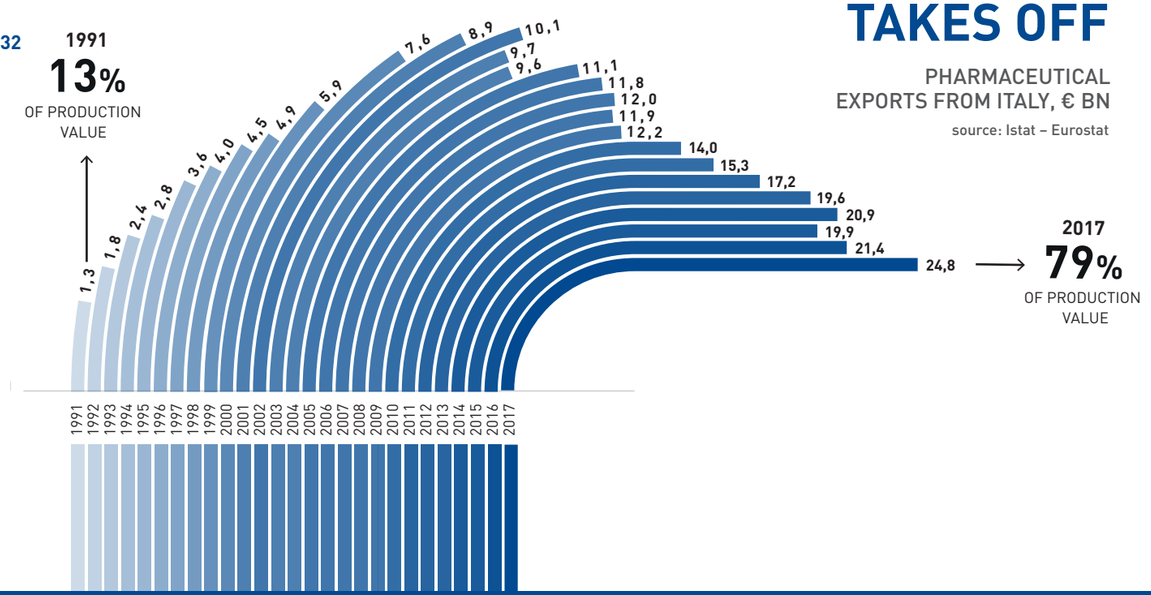
COMPANIES GROW THROUGH INNOVATION. The innovations introduced by companies to maintain their cutting-edge positions in healthcare provision have brought about major improvements in corporate performance. All major economic indicators signal enormous gains with positive repercussions not only for the companies themselves but also for the national entrepreneurial system as a whole, with which the

companies are collaborating ever more actively. Between 1978 and today, production value has grown fivefold, rising from just under € 7 billion (historical comparisons take account of inflation and the conversion to the euro to over 31 billion, making the country number one in the EU. The workforce productivity of Italian companies, thanks to the quality of their human resources, their industrial know-how and investments, has overtaken the average of our big European neighbours. Value added has tripled, rising from 3.4 to 9.7 bn.

EXPORT TAKES OFF

PHARMACEUTICAL EXPORTS FROM ITALY, € BN

source: Istat – Eurostat



FROM 57th to 4th PLACE IN EXPORTS. Exports - the index of international competitive capacity - grew fifteenfold between 1991 and 2017, escalating from 1.3 bn. to 24.8 bn. In terms of the export rankings of the 119 economic sectors in Italy, medicinal products in 1991 were 57th, in 1996 27th, in 2001 12th. In the new millennium the improvement continued unabated: 7th in 2011 and 4th in 2017 (behind the mechanical engineering and motor vehicle sectors). Our exports are growing faster than those of our European competitors and the other Italian industrial sectors. The reason is to be found in the growth in capital investments, which tripled in value, increasing from € 384 million in 1978 to € 1.3 billion in 2017, as also in investments in R&D, often benefitting start-ups and universities, and which have quadrupled over the past 40 years: from 426 million to 1.5 billion. This also explains how 3 out of the 6 advanced therapies authorised in Europe were developed in Italy. Therefore, our companies are growing together with our country.

AMONG THE PROTAGONISTS OF THE COUNTRY'S HISTORY. What these pages also chronicle is the major contribution made by pharmaceutical companies to this country's history. Existing before the country's unification, they grew as they country itself grew.

They have established some important records by enhancing the quality of our lives as well as our international image.

The major changes and the social improvements that we are experiencing today are the direct consequence of their work and their capacity to innovate and operate within and as part of a productive network. Certainly, Italy's future will be part and parcel of the future of our pharmaceutical companies.

FARMINDUSTRIA

FARMINDUSTRIA is the trade association of pharmaceutical companies, and this year marks its 40th year of activity. The association comprises about 200 companies representing over 90% of the companies in the sector in Italy. It is one of the oldest associations of Confindustria, and part of the leading group of the European federation (EFPIA).

It is also a member of IFPMA, the world pharmaceutical federation.

ITS MISSION. To represent the voice of companies operating in the country, promote competitiveness and scientific development and convey the sector's importance to policy-makers, public opinion and stakeholders in order to encourage a more favourable climate for investment and access to new medicinal products. As Europe is increasingly at the centre of economic decisions, Farmindustria now operates from both Rome and its own office in Brussels.

COMMUNICATING THE VALUE OF PHARMACEUTICALS IN ITALY. Since 2012, Farmindustria has been engaged on a roadshow entitled "Innovazione e Produzione di Valore" to narrate the role of pharmaceutical companies in Italy. Many regions have been visited and the roadshow is scheduled to visit the other regions where pharmaceutical production is important. There have also been many initiatives to valorise the specificities of the biopharmaceutical industry: biotech medicines, vaccines, blood derivatives and contract and development manufacturing organizations. In order to broaden the range of instruments for such communication, the association has produced a new, innovative and more interactive internet site and can also be found on the social networks with its own Facebook page, Twitter account and YouTube channel.

THE 360° INNOVATION ASSOCIATION.

Research and innovation constitute the core business of pharmaceutical companies. Public initiatives and documents addressed to social and political institutions characterise Farmindustria's work. Its work is also dedicated to themes such as Industry 4.0 and the new technologies for health, personalised medicine, open innovation and their regulatory and organisational ramifications.

RESEARCH MEETS HEALTH NEEDS.

Farmindustria dialogues with the institutions and all its reference stakeholders on such crucial matters as research, access to innovation, gender medicine and rare diseases. This proximity to persons also takes the form of support for many public initiatives in order to heighten attention to and respect for the sick.

TEAM WORK AND A RIGOROUS CODE OF PRACTICE.

Through 23 work groups set up with its members, Farmindustria offers its associates assistance on legislative, legal, regulatory, and scientific matters as well as on industrial relations. Its Code of Practice, one of the most rigorous in Europe, is widely respected and applied meticulously. The code not only regulates relations between companies but also their relations with the scientific and healthcare organisations. Annual certification is mandatory and entrusted to accredited third parties. Since 2016, the association has adopted a Disclosure Code, based on EFPIA's Transparency Code, which our associates adhere to on a voluntary basis. The code requires companies to disclose, and thus make publicly available, data on their dealings with physicians and their organisations. The companies are strongly in favour of this initiative as it is a further guarantee of greater transparency in an already highly regulated field.