FARMINDUSTRIA

Report on the biotechnologies of the pharmaceutical sector in Italy 2017

EY
Building a better working world

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Massimo Scaccabarozzi
President, Farmindustria

"Cutting and pasting" genetic sequences, smart pills that release their active principle only in a specific context or at a precise moment, but not forgetting vectors acting as "postmen" making deliveries to specific tissues, or artificial intelligence, and nanotechnologies.

Pharmaceutical research and technology are working in tandem to offer new and increasingly effective opportunities for treatment. With the immediate availability of large quantities of data – hitherto existing just as uncoordinated paper documents or stand-alone files – research processes can be speeded up and therapies perfected. And even if the challenges ahead are daunting, for example, cybersecurity, the operative word remains "convergence": the merging of pharma and ICT (Information and communications technology), valorising persons and transforming enterprises into solution companies; namely, enterprises offering integrated solutions.

By becoming increasingly less product-orientated and ever more human centred, medicinal products have become so much a part of the therapeutic process as to merge with services and diagnostics, while at the same time genomics has combined with big data to focus upon personalised medicines.

The merger between R&D and technological development is rapidly changing the old therapeutic paradigms.
Recently approved medicinal products designed to treat serious pathologies, as also those at an advanced stage of development, based upon cells that "learn" to recognise and eliminate diseased cells are an example of this new approach.

We are not describing a futuristic scenario. Already today international R&D has a pipeline of over 14,000 products under development, of which 7, 000 at the clinical stage.

Thanks to major innovations, the pharmaceutical scenario is growing at a dizzying rate. Within a few years investments in research and development will reach 180 billion dollars worldwide, of which 80% in partnerships with non-sector subjects. Today, R&D operates within an international network premised upon the open innovation model, a process involving various countries, research bodies, public and private actors and companies.

However, this represents a challenge not only for the Italian pharmaceutical industry but also for Italy as a whole system. Our companies are ready to compete in the full awareness of the many strongpoints they possess: from production, valued at € 30 billion, and exports that account for over 70% of production, to a highly qualified workforce, now numbering 64,000 employees. They can also count upon an outstanding level of excellence, for example in biopharma, where 282 projects are under development, as also in vaccines and advanced therapies (3 of the 6 authorised in Europe were produced in Italy), in orphan drugs, blood derivatives and gender medicine.

If our pharmaceutical companies have achieved such successes it is also – as the President of Efpia has recognised – the result of state healthcare policies that rank among the most innovative in Europe. Nevertheless, an appropriate form of modern governance is still needed if we are to reward innovation, rise above the concept of spending caps and view pharmaceutical spending as an investment in a system that valorizes also saved costs.

The pharmaceutical industry is a show piece for Italy. Moreover, it intends to remain as such and make its contribution towards creating a nation that is ever more competitive in the global economy.

Eugenio Aringhieri
President, Farmindustria's Biotechnologies Group

Thanks to new medicinal products and scientific progress, healthcare has undergone a radical transformation.

Never before has so much technology, able to revolutionise the prevention and treatment of illnesses, been at our disposal. Genomics, big data, machine learning, 3D modelling, wearable sensory devices, robotics: pharmaceutical companies now apply a totally different approach to the development of medicinal products.

Change is a constant that accompanies all our activities. It requires us to redesign borders and renew our capacity to generate innovation.

The path has been mapped out and the direction is clear: new digital technologies must be understood as strategic assets for the development of new projects.

And it is precisely in this context that biopharma research, the jewel in the crown of modern science, comes to the fore. Biotechnologies are a concrete example of transversal innovation: science and high tech joining forces to create extraordinary projects.

Progress is making giant strides and, pari passu, the development of new medicinal products must adopt a logic totally divorced from the traditional approach.

This distinctiveness enables small and medium-sized companies, endowed with a leaner structure, skills and strongly innovative orientation, to adjust themselves rapidly and grasp opportunities as they arise.

This is good news for our country, characterised as it is by a significantly high presence of such companies.

The old rule that a large company automatically meant an outstanding one no longer holds. Today, a company is distinguished by its capacity to innovate, its ability to produce (better than its competitors) and its ability to focus its creativity on areas where results are needed.

The Italian biopharma sector is well consolidated and continues to grow. The 209 companies operating within its territory, and which have invested € 679 million in biopharma R&D, represent a key growth driver for the entire country.

However, doing business in an eco-system without boundaries is ever more challenging. And no simple solutions exist for complex problems. In order to be competitive, skills must be sought within the companies' own production milieu in order to create synergies with all other sectors.

It is unlikely that a company will be able to deploy all the resources it needs to develop a medicinal product. Hence, it must choose the right partners, and follow an open innovation approach if it is to share and integrate its own specialisation within a network of excellences.

How is Italy positioned with respect to this fast-changing world? For the first time it seems that investors, industry, the universities and the government share the same objectives. Digitalisation and innovation are on everybody's agendas revealing a widespread awareness of the great growth opportunities that exist for our country.

We must set store by the younger generations, giving them the means to develop and perfect their specialisations in top-quality universities. However, in order to work well they must strike the right balance between skills and the propensity to tackle challenges.

This is the right time to play our part as a country, and we must do so by constructing new growth opportunities, building upon existing excellences, and facing the future with new hope.

We have every confidence that we shall succeed.

Biotech is now a consolidated and constantly growing part of the pharmaceutical industry

Importance of biotech in Italy

Thanks to its specialised skills, quality researchers and a capacity for innovation, Italy plays an increasingly important role in biopharma on the world stage.
In 2015, the incidence of our country on total biopharma sales was 5%, representing a 1% increase on the previous year[1].

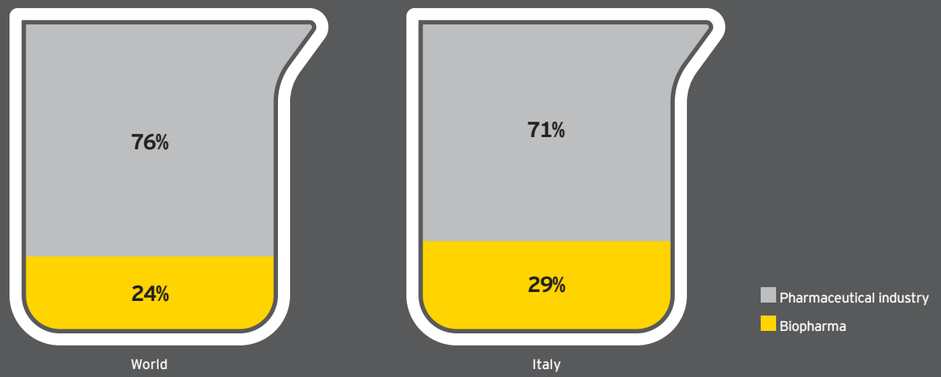
1. EvaluatePharma, World Preview 2015 - Outlook to 2020, 2015

Positive Trend for Biopharma products in Italy

+7%

the year-on-year growth in the turnover of Italian biopharma companies recorded in 2015

Biopharma turnover as a percentage of the pharmaceutical industry's turnover[2]
(2015)



2. Analysis EY; Farmindustria, Pharmaceutical Indicators 2017; EvaluatePharma, World Preview 2015 - Outlook to 2020, 2015

In Italy and abroad, Pharma is ever more biotech

Biopharma products in Italy: the figures of a thriving business

209 companies

Large, medium-sized, small and micro companies operating in the biopharma sector, committed to innovation

8,460 million euro in turnover

Biopharma confirms its importance in the pharmaceutical industry

697 million euro invested in R&D

Investments in R&D by biopharma companies for biotech medicinal products are growing year by year and represent ongoing innovation for the benefit of patients and the country

3,864 R&D biotech employees

Increasingly better qualified professional personnel and researchers with capacities recognised and rewarded worldwide

The data in the 2017 Report refer to 2015

The data refers to companies that perform production and marketing in Italy in one or more of the following areas: R&D on biopharma products and/or vaccines for human use, R&D on correlated services (drug delivery, or the development of technologies for transporting medicinal products to a specific site and drug discovery, namely the provision of services correlated to obtaining the final product or other correlated services), the production of biotech products and/or vaccines, the marketing of biotech products and/or vaccines, the provision of correlated services (drug delivery, drug discovery)

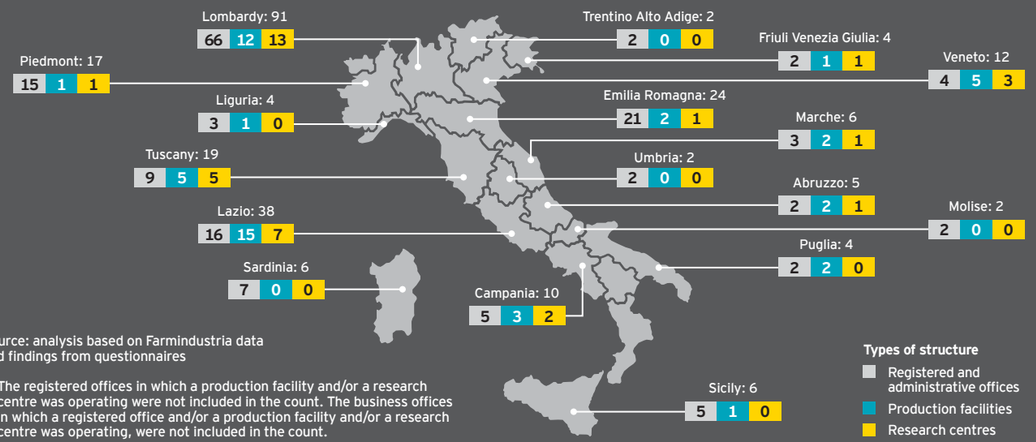
Countrywide operations

35 research centres, 52 production facilities and 166 registered and business offices distributed over 17 regions: an extended network of biopharma companies through which, every year, biotech medicinal products are developed, manufactured and marketed in Italy and abroad.

Lombardy with 13 centres emerges as the main research pole. On the other hand, Lazio, with 15 production facilities, is the first region in terms of production. Alongside Lombardy and Lazio, Tuscany is the third region where the biopharma sector is by now a consolidated reality.

Research Centres

Geographical position, and number of Biopharma company structures[1]



Source: analysis based on Farmindustria data and findings from questionnaires

1. The registered offices in which a production facility and/or a research centre was operating were not included in the count. The business offices in which a registered office and/or a production facility and/or a research centre was operating, were not included in the count.

In Italy and abroad, Pharma is ever more biotech

Some pathologies for which biotech is a source of innovation and hope for patients

Alzheimer's Disease

Alzheimer's disease, the most common form of senile dementia, has been estimated (2015) to afflict 47 million persons worldwide. Furthermore, its incidence is forecast to double by 2030, especially as a consequence of improved life expectancy. A monoclonal antibody currently under trial has provided some encouraging results when this disease is treated at an early stage: this is a biotechnological medicine that could improve the lives of innumerable patients[1].

Metachromatic leukodystrophy (MLD)

Metachromatic leukodystrophy (MLD) is a neurodegenerative disease that causes the loss of motorial and neurocognitive capacities. It manifests in an acute form in children under 12 years. Following a collaboration between Italian scientific institutes and research centres, an innovative gene therapy has been developed that by exploiting the capacities of the HIV virus to "transport" a therapeutic gene into cells, has enabled nine children affected by MLD in a symptomless phase, not to develop the disease three years after treatment. This important result confirms Italy's commitment to combating rare diseases; a European level of excellence[2].

Merkel cell carcinoma

The Merkel cell carcinoma is a rare form of skin cancer, principally caused by viral infection, and which may entail major complications for patients. Thus, when metastasis appears the survival rate at 5 years falls to 50%[3]. In 2017 EMA's Committee for the Medicinal Products for Human Use delivered a positive opinion for the approval of a new monoclonal anti-body, designated an orphan drug by EMA, which would represent the only pharmaceutical therapy available to patients that can offer them a better quality of life and a higher survival rate[4].

1. B. Duthey, Priority Medicines for Europe and the World - A Public Health Approach to Innovation; 2013; Alzheimer's Disease International, World Alzheimer Report 2015 - The Global Impact of Dementia an analysis of prevalence, incidence, cost and trends, 2015
2. Telethon, the HIV virus used to treat two serious genetic diseases 2016; M. Sessa et al, Lentiviral haemopoietic stem-cell gen therapy in early onset metachromatic leukodystrophy: an ad-hoc analysis of a non-randomised, open-label, phase 1/2 trial, 2016
3. P. Allen, Prognosis and Treatment of Patients From a Single Institution, 2005
4. F. Fuggetta, Merkel cell carcinoma: the response to chemotherapy is limited and the survival rate low, 2017

The Institutions' role in innovation

Interview with:
(MM) Professor Mario Melazzini, General Manager of AIFA (Italian Medicines Agency)
(GL) Dr Giovanni Leonardi, General Manager for Research and Innovation in Healthcare, Italian Health Ministry

What role do the institutions play in promoting innovation, especially as regards biotech medicinal products?
(MM) Italy was one of the first countries to pass laws and regulations on the evaluation of innovative medicinal products and the provision of access to them. The Italian Medicines Agency has established criteria for the definition of innovativeness in order to achieve two goals: first, to guarantee rapid and uniform access throughout the national territory to medicines with an undisputed therapeutic added value with respect to the alternatives available, and second, the provision of incentives for the development of medicines offering patients substantial therapeutic benefits.
(GL) As regards biopharma products, Innovation takes places in specialised research centres and in companies. The Health Ministry, for its part, has not only set down strategic guidelines but is also coordinating the actors involved and funding innovative projects and new technologies. For example, a call to tender for a value of € 146 million and addressed to research centres, young researchers, Italian researchers abroad and industrial co-financing projects for finalised research was issued in 2016.

Can the institutions promote the spread of *Open Innovation* (OI) and *Technology Transfer* (TT) processes through such initiatives?
(MM) The regulatory agencies are fully aware of the potential of open innovation. In both Europe and the United States, they are committed to promoting and stimulating best practices for the transfer and sharing of knowledge and technologies, for example by creating networks designed to induce a series of public and private actors to share objectives and projects in strategic health areas.
(GL) Apart from the Netval network, which links together 57 universities and 6 non-university public research bodies for the purpose of valorising university research, there is a multi-disciplinary group created to build at network of TT offices among research institutes in Italy. The initiative sets out to survey the state of the art, harmonise the internal regulations and operating rules between institutes and establish a *"Technology Transfer School"* to train and heighten researchers' awareness of the question.

Does the implementation of European regulations on clinical trials[1] represent an opportunity or a risk for our country?
(MM) The centralisation of evaluation procedures at the European level will probably entail the migration of resources towards some European clinical research hubs. Italy has made a bid to become one of these hubs, given its scientific excellence and the Italian Medicines Agency's recognised competence and reliability in evaluating clinical trials. And this is yet another point in favour of Milan's candidacy to host EMA's new headquarters.
(GL) It represents an opportunity to obtain faster and safer trials, but nevertheless it must be accompanied by concrete actions. For example, thanks to coordinated action between the Ministry of Health and the National Anti-Corruption Authority, a "fast track" project has been created to hasten the evaluation of clinical trials. This is a valuable tool for interaction between actors operating in the system for trialling medicines as it is aimed at reinforcing dialogue and generating shared proposals for solutions to emergent problems, by, inter alia, providing institutions and companies with streamlined processes and standard contractual formats.

1. New European regulations on clinical trials for medicinal products (EU 536/2014) are expected to come into force in October 2018. According to this new scheme the evaluation of trials will be coordinated by a single national regulatory authority that will act as an interface and provide a first evaluation of the study; and upon this evaluation the other regulatory authorities of the member states will make a final decision on the authorisation. This coordination between the European regulatory agencies of medicines will lead to the authorisation of a study protocol identical for all the states involved in order to streamline and simplify procedures, and the latter will, moreover, be integrated and coordinated at the European level.

The main areas of innovation in international biotech

Oncology and infectious diseases

Oncology is the therapeutic area with the highest number of new therapies recorded each year: over 28% of new medicinal products in the United States between 2011 and 2015 were for the treatment of cancer[1]. Moreover, the attention given to the prevention of infectious diseases has increased with the growth in the use of vaccines, whose consumption rises every year by 8%[2].
In conclusion, a new class of antibiotics is under development, ready to combat the bacterial infections that are resistant to today's medicinal products[3].

Orphan drugs: ongoing innovation

Thanks to innovation, an increasing number of therapies are emerging for rare diseases. It has been estimated that, globally, orphan drugs will account for 32% of the growth in prescription medicines in 2022[4]. Between 2011 and 2015 orphan drugs represented 42% of the new medicinal products available to patients in the United States, which is double the figure of 21% recorded in the period 1996-2000[1].

1. QuintilesIMS, Lifetime Trends in Biopharmaceutical Innovation, 2017
2. Research & Markets, Global Vaccines Market by Technology, Disease, End User & Type - Forecasts to 2021, 2017
3. The Guardian, New class of antibiotic raises hopes for urgently-needed gonorrhoea drug, 2017
4. EvaluatePharma, World Preview 2017, Outlook to 2022, 2017

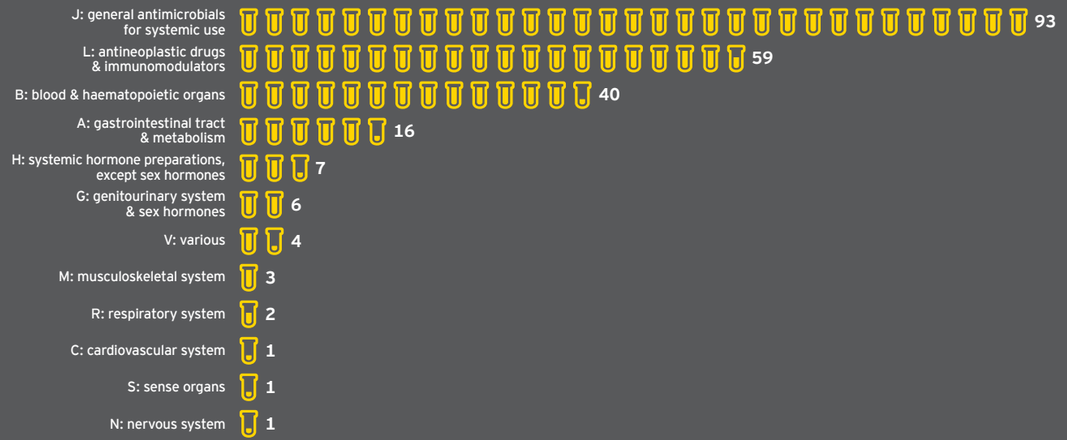
The biotech products marketed in Italy treat ever greater numbers of pathologies

More therapies, more benefits for patients

There are 233 biopharma products available in Italy to satisfy patients' therapeutic needs.
Over 80% of the biotech products currently marketed (192) refer to the prevention and treatment of infectious diseases, neoplasms, autoimmune diseases and hematic pathologies.

The anatomical, therapeutic and chemical classification system (ATC) is used for the systemic classification of medicinal products and managed by the World Health Organisation. Medicinal products are divided into various groups according to the target organ, the mechanism of action, and the chemical and therapeutic characteristics

Number of marketed biotech products by ATC class



Analysis based on data deriving from questionnaires issued to 29 respondent companies in the sample 2017; Farmindustria-EY, Rapporto sulle biotecnologie del settore farmaceutico in Italia 2016 (Report on the biotechnologies of the pharmaceutical sector in Italy 2016); Italian Medicines Agency, Medicines Databank

Pharma 4.0: biopharma opens up new horizons

Various categories of biotech products for different pathologies

Recombinant DNA proteins: the basis of many innovative therapies currently available

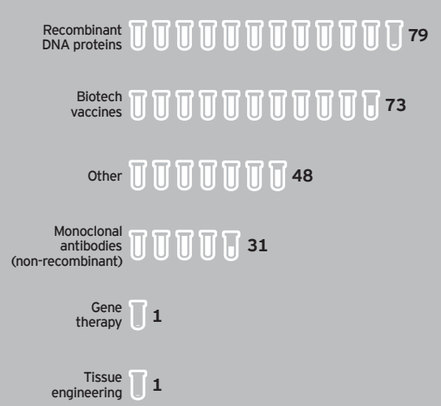
Most of biotech products available in Italy are recombinant DNA proteins: 79 medicinal products in over 10 therapeutic areas.

Monoclonal antibodies: significant applications in oncology and autoimmune diseases

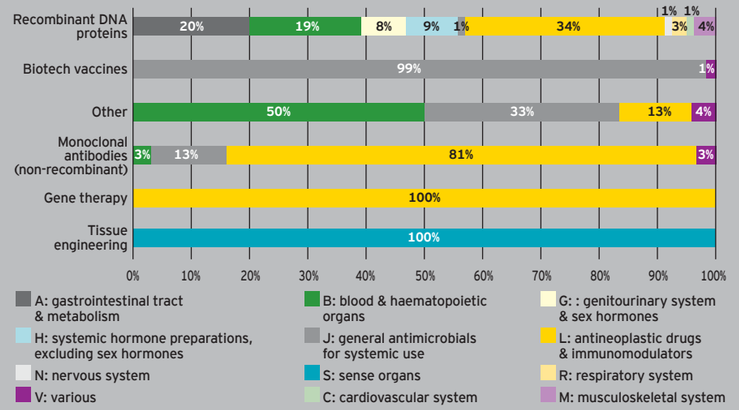
Monoclonal anti-bodies, represented by 31 products, constitute one of the most important categories of biotech products in Italy. Of these 31 products, 25 are dedicated to the treatment of autoimmune pathologies and cancer.

Recombinant DNA proteins, biotech vaccines and monoclonal antibodies are the main categories of medicinal products marketed in Italy that can provide new therapeutic opportunities to patients affected by rare diseases, cancer and infectious diseases

Number of marketed biotech products by type



Number of marketed biotech products by ATC class and type (% of total)



Analysis based on data deriving from questionnaires issued to 29 respondent companies in the sample 2017; Farmindustria-EY, Rapporto sulle biotecnologie del settore farmaceutico in Italia 2016 (Report on the biotechnologies of the pharmaceutical sector in Italy 2016); Italian Medicines Agency, Medicines Databank
The percentages may not add up to 100 on account of the rounding up of some absolute values

Biotech offers hope for the treatment of rare diseases

21 biotech medicines designated as orphan drugs available in Italy

These represent new hopes for therapeutic solutions and principally refer to patients affected by gastrointestinal, metabolic, oncological and autoimmune diseases. 11 have been designated as orphan drugs by both EMA and the FDA, while 7 have only been recognised by EMA and 3 only by the FDA.

Rare diseases: institutions and companies are ever more committed to research for new therapies

- Over 160 clinical trials authorised for rare diseases in 2016 (compared to 66 in 2010)[1]
- 71 orphan drugs approved in Italy, of which 5 in 2016[2].

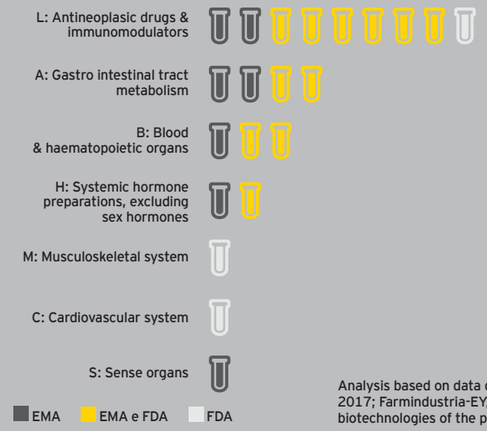
1. AIFA (Italian Medicines Agency), Clinical trials of medicines in Italy - 15th National Report, 2016; AIFA, (Italian Medicines Agency), Clinical trials of medicines in Italy - 10th National Report, 2011
2. AIFA (Italian Medicines Agency), L'uso del farmaco in Italia (The use of Medicines in Italy) - National Report, 2016

Treatment for rare diseases: categories of medicinal product available in Italy

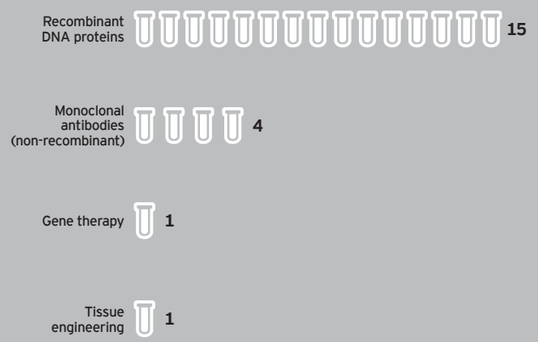
71%
recombinant DNA proteins

19%
monoclonal anti-bodies

Number of marketed biotech orphan drugs by ATC class and with orphan drug type designation



Number of marketed biotech products by type



Analysis based on data deriving from questionnaires issued to 15 respondent companies in the sample 2017; Farmindustria-EY, Rapporto sulle biotecnologie del settore farmaceutico in Italia 2016 (Report on the biotechnologies of the pharmaceutical sector in Italy 2016); Italian Medicines Agency, Medicines Databank

Research: the engine of innovation

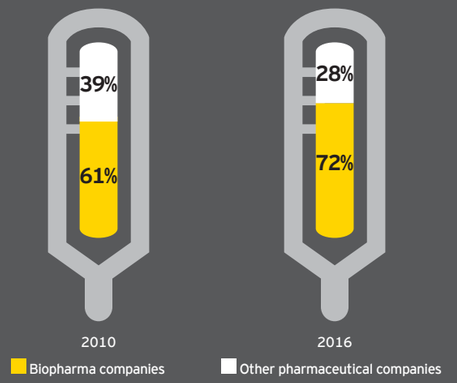
In 2016, biopharma companies invested almost € 2 billion in Italy on production and research (considering biopharma as well as non-biopharma investments), which amounted to 72% of all investments in the pharmaceutical industry. In 2010 this percentage was 61%.
In a scenario of overall economic recovery involving all sectors of the economy, overall investments in production and research by biopharma companies in the previous year were double those of all other companies in Italy.

In 2015, investments in research and development for biotech products alone amounted to € 697 million

Ongoing investments sustaining innovation

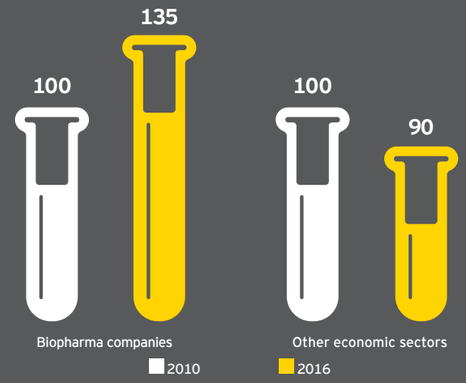
+5%
total investments in production and research by biopharma companies compared to 2015

Investment in production and research by biopharma companies (% of all pharmaceutical industry investment)



Source: Farmindustria

Investment growth in production and research by biopharma companies compared to other economic sectors (index 2010=100)



Source: Farmindustria

The intensity of biopharma research is its distinguishing feature

The intensity of the research and development of the biopharma companies, in terms of value-added activities and employee numbers, is almost double that of other medium and high technology sectors.
The ratio of investments to biotech R&D specialist staff is growing strongly: +9% from 2014 to 2015.

Pharmaceutical companies play a fundamental role in biotech development, representing 86% of its growth when calculated as an average as between turnover, R&D investments and R&D personnel.

The biopharma sector in Italy is the first for R&D intensity and innovation

Intensity of R&D activities by sector[1]
Data 2016 (biopharma companies' index =100)

Source: Farmindustria analysis based on Istat data and corporate sources

1. Average of ratios (R&D investments/Added-Value) and (R&D staff/total staff)
2. Medium to high technology manufacturing: manufacture of basic chemicals, manufacture of phytopharmaceuticals and other chemical products for agriculture, manufacture of paints, varnishes and enamels, printing inks, synthetic glues, manufacture of soap, washing powders and detergents, polishing products, perfumes cleaning and cosmetics, manufacture of other chemical products, manufacture of synthetic and artificial fibres, manufacture of machinery and mechanical equipment (Nace code: DK), manufacture of electrical machinery and equipment n.e.c., construction of locomotives and railway rolling stock, manufacture of motorbikes bicycles, manufacture of other means of transport (source: ISTAT)

The challenge of innovation: how to create a successful model

Human capital as the key element in research and innovation

Certified expertise in a sector of excellence

Biopharma companies employ highly qualified personnel: 83% of their employees have at least a specialist degree, and 14% a research doctorate, PhD or MBA.

Italian excellence in the fight against cancer

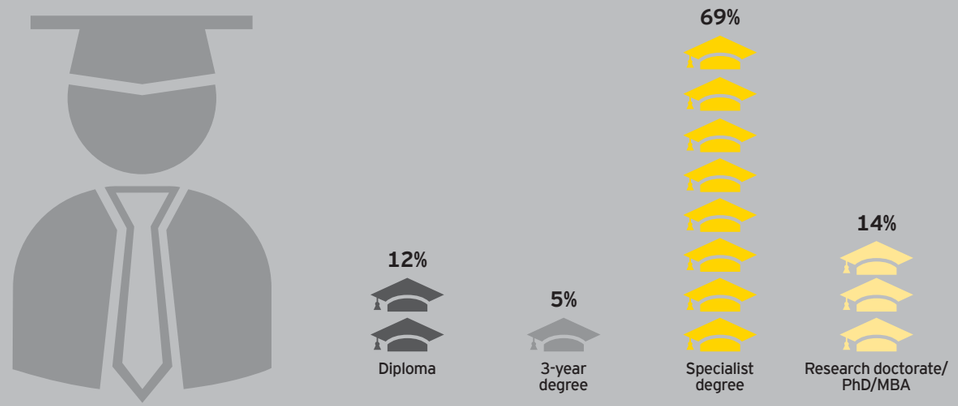
8 Italian researchers have received awards from the *American Society of Clinical Oncology* for work in the cancer field[1], thus confirming the important role played by Italy on the international stage.

1. La Repubblica, Lotta ai tumori: i giovani ricercatori italiani più promettenti, 2016 (The fight against cancer: the most promising young Italian researchers)
2. IlSole24ore, Le biotech fanno posto ai laureati, 2015 (Biotechnologies offer jobs to graduates)

Outstanding job opportunities

91%
of graduates in biotechnologies find employment within five years from graduation[2]

Breakdown of biotech R&D personnel by academic qualification[3]



3. Percentages calculated on the 33 respondent companies included in the sample 2017

Technology Transfer in Italy: a bridge (under construction) between research and the market

Investors, companies and institutions are all aware of the great opportunities that exist for change and innovation as regards biopharma products in Italy. All actors seem to agree on the importance of working together to create a cooperative network, invest in existing skills and excellences and promote value-creation.

The universities and private and public research centres in Italy are highly esteemed but adequate strategies are needed to valorise them correctly. Specialisation in research and development activities promotes the creation of specialist skills, which represent the basis for innovation. In Italy, centres of excellence must be reinforced by focusing upon specific research areas, and endowing them with specialist technologies and knowledge, thereby permitting the creation and diffusion of best practices. Some projects, such as the "Human Technopole" in Milan, are already under way but an appropriate entrepreneurial humus is also needed to transform innovation into value creation.

In Italy, private and public commitment must concentrate upon creating an ecosystem favourable to innovation, the financing of research and the valorisation of its practical applications in order to guarantee an integrated and coherent approach throughout the entire development process, from scientific discovery right up to the production and patient access.
Laws and strategic, forward-looking government measures are needed. Recently, for example, laws have been passed to stimulate the financing of research, such as the innovative start-up instrument and the patent box. However, such measures have only had limited application in the specific context of biopharma products.

One model which could be source of inspiration is France's *Crédit d'Impôt Recherche* (CIR), a tax credit for companies based upon R&D expenditure (30% of the value of R&D up until €100 million and then 5% on further expenditure). Thanks to this start-up instrument, innovative companies, SMEs (European definition) as also companies that have initiated composition procedures with creditors can benefit from the immediate reimbursement of non-utilised credit (other companies can reap benefits from the measure after three years). Such measures are particularly useful for small biotech companies that are unlikely to post profits in their early years, thus enabling them to repay R&D investments with a tax credit that can be ploughed back into the company. Moreover, it is important to attract investors through tax exemption measures and by promoting Open Innovation mechanisms. Thus, it would also be useful to create a centralised, national Technology Transfer Office that could simplify relations between the universities and industry. Investors specialised in biotech have expressed special appreciation for a recent joint initiative of the Cassa Depositi e Prestiti (state-controlled deposit and lending institute) and the European Investment Fund that launched ITAtech, an investment platform with an initial allocation of € 200 million dedicated to the financing of Technology Transfer processes. In the wake of this initiative many projects have been started, such as Aurora-TT, aimed at investing in the Italian biopharma sector, by contributing the financial resources and strategic skills necessary for the economic valorisation of the technologies and skills generated in the context of scientific research.

This section is the result of a brainstorming session whose participants were Eugenio Aringhieri (President of Farmindustria's Biotechnology Group), Fabrizio Landi (President of the Tuscany Life Sciences Foundation), Graziano Seghezzi (a Partner of Sofinnova)

The challenge of innovation: how to create a successful model

Research and development of Biopharma in Italy: areas of innovation and opportunities

Interview with:

(CC) Carlo Caltagirone, Director of the Santa Lucia Scientific Foundation and member of the National Committee on Biosafety, Biotechnologies and the Life Sciences

(NP) Nicola Palmarini, Global Manager of Aging & Accessibility Solutions, IBM Research and member of the Gerontological Society of America

What is the state of R&D in the biopharma sector nationally and internationally?
(CC) In Italy companies are focused upon Phase II and Phase III clinical research, which addresses the marketing of products, while basic research is mainly carried out in collaboration with specialised laboratories outside Italy, both public and private. However, Italy's attractiveness for clinical research is growing thanks to Europe's enhanced role in the international pharmaceutical industry.
(NP) At the international level, research is increasingly "specific" in nature. Companies and universities compete to attract the best skills and focus their operations on specific and complex themes. University spin-offs, an increasingly common phenomenon in Italy, are a clear example of the value generated by applied research.

What are biopharma's main areas of R&D innovation?
(CC) As regards applied biotech research, the principal areas of innovation certainly include neurodegenerative diseases, such as Alzheimer, Parkinson and SLA. Advanced innovative forms of treatment based upon monoclonal antibodies, microbiome and immunological therapies are currently being trialled.
(NP) Today, for example, doctors and researchers enjoy real time access to scientific literature and cases regarding various forms of cancer from all parts of the world and are assisted in their decisions by AI processes. They can count upon language analysis to identify signs of cognitive deterioration years before its onset or deploy *wearable devices* and nanotechnology to monitor therapeutic efficacy.

How can innovation be facilitated?
(CC) Through specialisation. Innovation in Italy takes place in so-called "research hospitals", highly specialised structures with a mono-thematic focus, endowed with specialist technologies and skills. By being able to access a greater number of cases and their accumulated experience innovative techniques can be trialled with extraordinary results.
(NP) The institutions play an important role. Clear guidelines are needed in terms of taxation, intellectual property and work. However, this is not enough. Innovative mechanisms must also be introduced. In the United States, collaboration between institutions and companies has led to the creation of co-working spaces for biotech companies, where laboratory benches replace desks and instruments and skills are shared.

Can Italy play a significant role in international R&D?
(CC) Standard bioethics and advanced biotechnologies, highly qualified researchers and top quality technological infrastructures allow Italy to play a role of primary importance. The application of mechanisms that cultivate collaboration between researchers and companies and align their objectives will greatly assist this activity.
(NP) Certainly, we have a government that is strongly interested in innovation and researchers who can boast an excellent international reputation, also thanks to their capacity to think in non-conventional ways. Instead of the term "brain drain", we should use the expression "travelling brains". It is not important where knowledge is based but rather where its roots lie.

The results of innovation in Italy: a large and promising pipeline of biotech medicinal products

A broad array of projects, at an advanced stage

A pipeline in Italy of 282 innovative projects. Over 59% are at an advanced stage of research, namely Phase II and Phase III clinical trials. Many benefits are expected in upcoming years for patients afflicted by numerous pathologies.

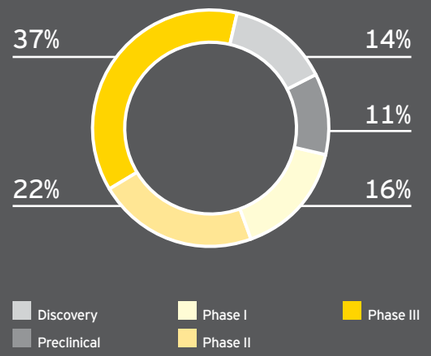
Ongoing innovation spurred on by complementarity among biopharma companies

Pharmaceutical companies[1] with 84% of their projects in Phases I, II and III are mostly concentrated in the more advanced phases. Lean biopharma companies[2], with specialist skills and highly-focused technological know-how, on the other hand, are mainly to be found at the early stages.

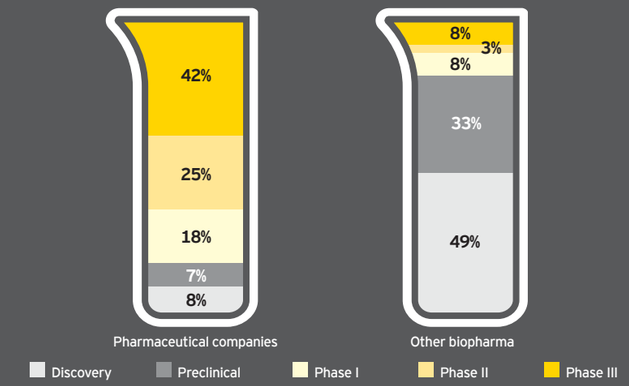
Among the projects under development 27 have been designated orphan drugs, i.e. medicinal products for treating patients afflicted by rare diseases

1. Companies that have already obtained a marketing authorisation (M.A.) for at least one biotech or synthetic medicinal product, or contractor manufacturers specialised in biotech medicinal products for customers who generally also supply biological raw materials
2. Biopharma companies operating in Italy that have not yet marketed their own products

Projects under development by phase[3]



Analysis of products by development phase & company type[3]



3. Analysis based on data deriving from questionnaires issued to 49 respondent companies in the sample 2017; Farmindustria-EY, Rapporto sulle biotecnologie del settore farmaceutico in Italia 2016 (Report on the biotechnologies of the pharmaceutical sector in Italy 2016); Company information
The percentages may not add up to 100 on account of the rounding up of some absolute values

The biotech pipeline in Italy has had an expected impact on numerous pathologies

Projects in multiple therapeutic areas

There are no fewer than 13 ATC categories in which there is at least one biotech project under development. Technological innovation enables new pharmacological targets and new therapeutic applications to be identified that can improve the life of patients afflicted by pathologies with both a high and low incidence.

Oncology, the first therapeutic area for projects under development

Antineoplastic and immunomodulators medicines under development number 130, and of these, more than half are at an advanced stage.

Number of biotech projects by principal therapeutic area

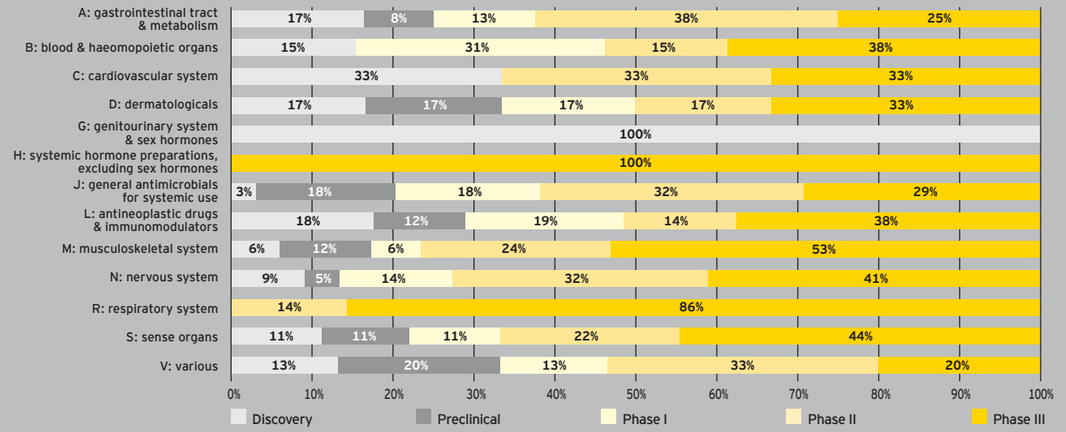
130
Oncology and immune system

34
Infectious diseases

24
Gastrointestinal tract

22
Nervous system

Biotech products under development by ATC class, percentage incidence of number of products by Phase[1]



1. Analysis based on data deriving from questionnaires issued to 49 respondent companies in the sample 2017; Farmindustria-EY, Rapporto sulle biotecnologie del settore farmaceutico in Italia 2016 (Report on the biotechnologies of the pharmaceutical sector in Italy 2016); Company information
The percentages may add up to 100 on account of the rounding up of some absolute values

Innovation expected from the biotech product pipeline

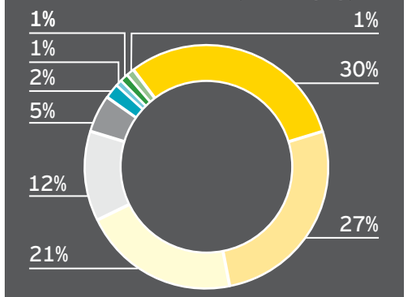
Recombinant DNA proteins and monoclonal antibodies guide research

At 166, recombinant DNA proteins and monoclonal antibodies represent about 60% of all biotech projects in the pipeline. These, in point of fact, are innovative medicinal products with the greatest number of therapeutic applications.

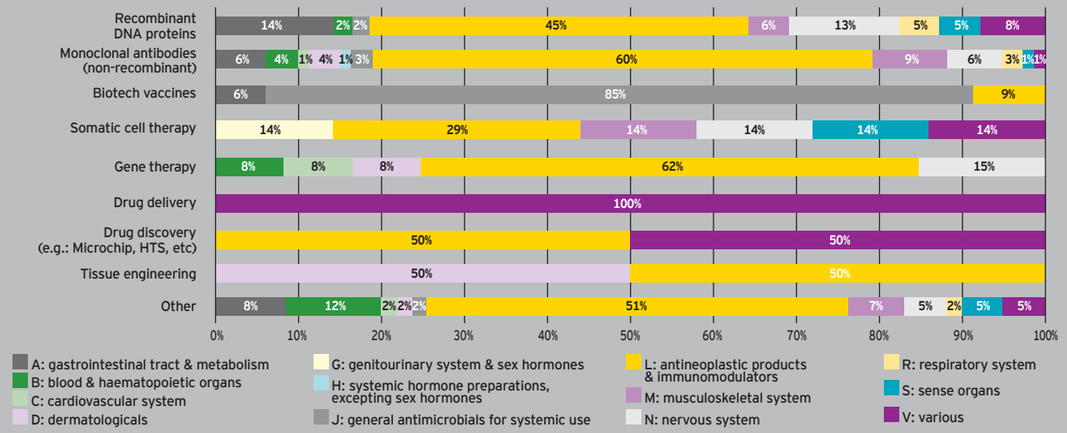
The monoclonal antibodies have received the strongest stimulus in the past 30 years thanks to technological progress and today represent 27% of the biotech projects under development. They are principally used in oncology and autoimmune diseases.

1. Analysis based on data deriving from questionnaires issued to 49 respondent companies in the sample 2017; Farmindustria-EY, Rapporto sulle biotecnologie del settore farmaceutico in Italia 2016 (Report on the biotechnologies of the pharmaceutical sector in Italy 2016); Company information

Medicines under development by type[1]



Biotech medicinal products under development by type, percentage incidence of the number of products by ATC class[1]



1. Analysis based on data deriving from questionnaires issued to 49 respondent companies in the sample 2017; Farmindustria-EY, Rapporto sulle biotecnologie del settore farmaceutico in Italia 2016 (Report on the biotechnologies of the pharmaceutical sector in Italy 2016); Company information
The percentages may add up to 100 on account of the rounding up of some absolute values

The challenge of innovation: how to create a successful model

Advanced therapies: a new frontier for biotech innovation

Advanced therapies: a further answer for many pathologies

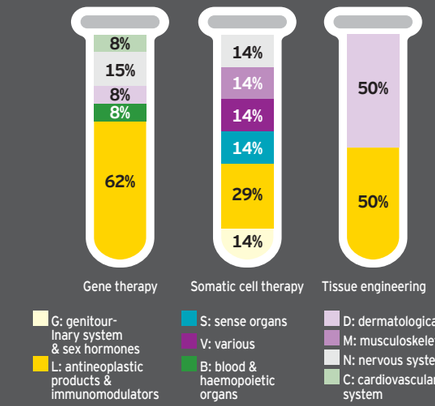
Scientific progress has made the rapid improvement in advanced therapies possible: tissue engineering, gene therapy and somatic cells are considered a recent medical frontier with important therapeutic applications, above all for rare diseases.

Advanced therapies: an answer for many incurable diseases

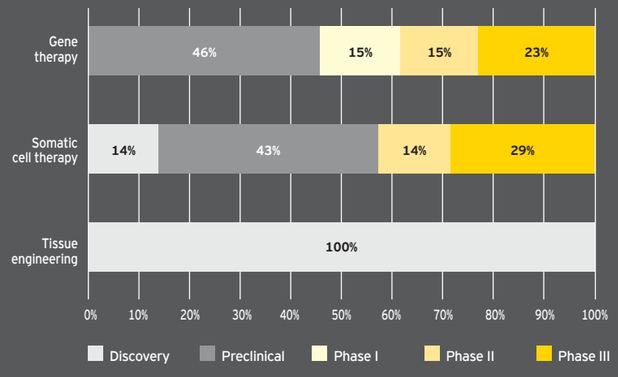
There are 22 highly innovative projects, principally somatic cell therapies (7) and gene therapy (13).
Of these 8 are in Phases II and III, 5 are destined to the treatment of patients affected by rare diseases.

Advanced therapy medicinal products are medicines based on DNA or RNA, cells or tissues that have undergone significant modifications.
3 out of the 6 advanced therapies authorised in Europe were developed in Italy

Advanced therapies: projects under development by ATC class and type[1]



Advanced therapies: projects under development by type & by Phase[1]



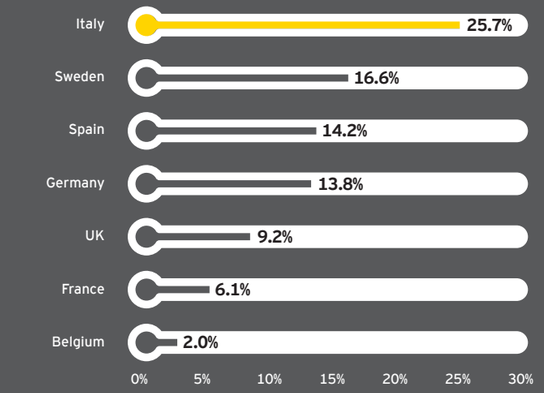
1. Analysis based on data deriving from questionnaires issued to 12 respondent companies in the sample 2017; Farmindustria-EY, Rapporto sulle biotecnologie del settore farmaceutico in Italia 2016 (Report on the biotechnologies of the pharmaceutical sector in Italy 2016); Company information
The percentages may add up to 100 on account of the rounding up of some absolute values

Biosimilars in Europe and Italy

Europe is first in the world for the number of approved biosimilar medicinal products (22 at the end of 2016) with the possibility of yet further growth in the coming years: 16 biosimilars were awaiting approval by EMA at the end of 2016. The analysis of biosimilar sales data in the first 7 European countries in 2016 put Italy first for value and quantity. Thus, 27% of all biosimilar sales in the 7 leading European countries refer to Italy, which is an even higher percentage than its share of all sales of medicinal products (18%). Likewise, per capita consumption of biosimilars in Italy was much higher with respect to countries such as Germany and Sweden. Altogether, the percentage share of biosimilars compared to the total sales of single molecules is higher than in other leading countries and higher than the European average (26% compared to 13%).

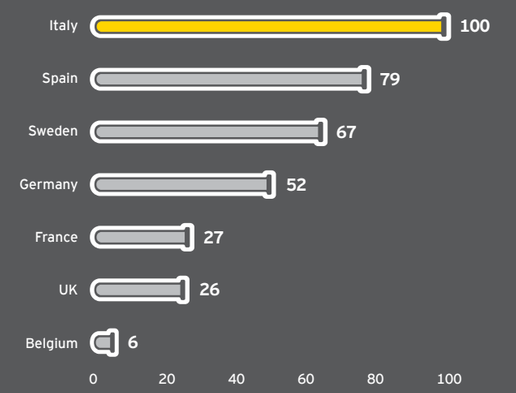
Italy is the leading European country for the sale and consumption of biosimilars, which in 2016 recorded a year-on-year growth of 51%

Biosimilars market share by consumption in Europe
(% of total)



Source: analysis based on QuintiliesIMS data

Per capita biosimilar consumption in 2016
(*standard units*, index Italy=100)



Source: analysis based on QuintiliesIMS data

The challenge of innovation: how to create a successful model

Focus on the new biosimilar regulations

A biosimilar is not the generic equivalent of a biotech medicinal product because the latter has structural peculiarities that prevent a wholly identical molecule from being reproduced.

As Italian Medicines Agency (AIFA) has decided not to include biosimilar medicinal products in its transparency lists, originator biologicals and biosimilars cannot be deemed automatically interchangeable.

This principle was upheld by the legislator with law no. 232/2016 (the 2017 Budget Law), which under article 1, subsection 407, lays down that "automatic substitutability as between a reference biological medicinal product and its biosimilar is not allowed and nor is automatic substitutability permitted between biosimilars".

This law also introduced some important measures regarding biosimilars, among which:

- The possibility that only the European Medicines Agency or the Italian Medicines Agency (for their respective remits) ascertain the existence of a biosimilar relationship between one biosimilar and its biological reference;
- The obligation that public procurement procedures make use of framework agreements with all economic operators, whenever there are more than three medicinal products based on the same active principle;
- However, different active principles cannot be put out for tender in the same procurement batch, even if their therapeutic indications are the same.

Therefore, even if an appropriate use of biosimilars can free up resources, such use must, on the other hand, always have the patient's health as it main objective.

The reason is that a physician's choice or the opinion of the regulatory agencies cannot be overridden by tender procedures based upon purely economic approaches that could endanger patients' right to therapeutic continuity.

This right, together with the principle of the physician's prescriptive freedom, is clearly set forth in the 2017 Budget Law.

The choice of using a given biological medicinal product must be made by the physician, on the basis of all the information available, and with the correctly informed consent of the patient.

It is not possible to limit the physician's full freedom of choice with respect to array of therapeutic treatment at his/her disposal, for example by fixing predetermined objectives.

In July 2017, a number of scientific societies[1] issued a joint document[2] to draw attention to the principles of the physician's decision-making autonomy and to the principle of therapeutic continuity contained in the 2017 Budget Law, declaring that they are to be considered valid regardless of the number of marketed medicinal products using the same active principle.

The issuing of clear regulations demonstrates the institutions' commitment to guarantee equal access to available therapies. Now the regional administrations have the task of applying them throughout the entire territory and maintaining their spirit.

1. Associazione dermatologi ospedalieri italiani (ADOI), (Association of Italian hospital dermatologists) Federazione delle Associazioni dei Dirigenti Ospedalieri Internisti (FADOI) (Federation of Associations of Interns, Hospital Staff and Managers), Società Italiana di Diabetologia (SID) Italian Diabetology Society), Società Italiana di Farmacologia (SIF), (Italian Pharmacological Society), Società Italiana Nefrologia (SIN) (Italian Nephrology Society), Società Italiana di Reumatologia (SIR) (Italian Rheumatology Society) and Società Italiana per lo Studio dell'Emostasi e della Trombosi (SISTET) (Italian Society for the Study of Hemostasis and Thrombosis)
2. Joint document on biosimilar biological regulations contained in article 1, subsection 407 of law no. 232/2016, July 2017

Innovation in reimbursement models in Italy and in Europe

Patients' access to advanced therapies and the sustainability of health spending are recurrent items on the agendas of institutions and companies. Thanks to new reimbursement mechanisms, such as Managed Entry Agreements (MEAs), both price and reimbursement time can be determined for a medicinal product on the basis of its therapeutic efficacy. In this sense Italy is at the forefront of Europe.

Negotiating price and reimbursement conditions in France, the United Kingdom and Germany

In France, the decision on the reimbursability of a new biotechnological medicine and any co-payment arrangements is the remit of the *Commission de la Transparence de la Haute Autorité de Santé*, which measures absolute and relative benefit and risk. During price negotiations, conditional reimbursement contracts may be stipulated, although they are rarely used. The system of reimbursement in the United Kingdom, now currently under review, is based upon a cost-efficacy evaluation represented by cost in relation to the number of quality-adjusted life years saved. Some instruments have been introduced to make the model more flexible: PAS (Patient Access Scheme: discounts or ceilings for reimbursable dosages), value thresholds (for medicines destined to patients with a low life expectancy), and Cancer Drugs Funds (ad hoc funds for cancer medicines without or awaiting recommendation).

In Germany a new biotechnological medicine is first sold at a free market price. Subsequently, according to the evaluations of its therapeutic added-value, its reimbursement price is negotiated. In the event that the evaluation is negative, the medicine is subjected to a reference price for its respective reference class, and if no agreement can be reached on price, the weighted average price in 15 European countries can be applied.

Italy, at the forefront of innovative reimbursement models

- 153 registers in 2016
- 507 thousand treatments carried out in 2016

Italy is the only country in Europe to have introduced a medicine register system that provides for the traceability of patients by specific pathologies, thus enabling risk sharing MEA agreements to be implemented and price discounts made according to patients' clinical response.

Italy is the most active and innovative country in Europe as regards the stipulation of MEA agreements. Recourse to MEAs is very frequent for oncological medicines (innovative and with a limited target population), for which performance-based mechanisms are commonly used (especially payments by result, which in 2016 represented over 65% of the MEAs approved), with the exclusion of products with a certain and proven efficacy, earmarked for a wider population and for which the use of financial-based MEAs is preferred. Such innovative agreements have enabled various medicines to be approved that have not yet been recommended in the UK or evaluated with a modest or nil incremental benefit in France, thus guaranteeing benefits for patients.

Sources: N. Martini, C. Jommi, R. Labianca, Un nuovo modello di governance per il market access dei nuovi farmaci in oncologia, 2015 (A new model for the governance of new medicinal products to treat cancer); A. Ferrario, P. Kanavos, Managed Entry Agreements for pharmaceuticals: the European experience, 2013; Rapporto OSMED - L'uso dei farmaci in Italia, 2015; L. Garattini, G. Casadei, Risk sharing agreements: What lessons from Italy? International Journal of Technology Assessment in Health Care, 2011; Temas, Managed Entry Agreements (MEAs) in Italy: state of the art and their application; AIFA Registers.

The challenge of innovation: how to create a successful model

What is biotech future in Italy and abroad? The companies' viewpoint

In the world, as in Italy, the reference context for biopharma products has changed and is still rapidly changing.

Three elements are altering needs and solutions:

1. **Technological development.** In the health field, new elements such as the capacity to perform diagnosis, predictive medicine, the genome, personalised medicine, nanotechnologies, and industry 4.0 have totally changed the manner in which enterprises are run and how medicinal products reach the patient. Today all the necessary skills required by companies cannot be found in-house and consequently they must possess specialised know-how and an advanced governance that allows them to establish relations with other sources of know-how and expertise in the world in order to carry out research, development and innovation.
2. **Life expectancy.** A baby born today has a life expectancy 10 year longer than its mother. Life expectancy at birth has reached 84 years in Italy, second only to Japan. This change has led to the emergence of problems such as the chronicity of some pathologies and the onset of others. Today's challenge is to associate an improvement in the quality of life for these additional years.
3. **Sustainability.** Sustainable access is a theme not only of the institutions but also of the companies and has changed the rules governing healthcare development. ▶

In recent years governments' spending powers have diminished thus leading the entire system to question the level of innovation and the competitive advantage of new medicinal products. Mechanisms of payment by result and payback have been introduced, and the efficacy of medicinal products is carefully evaluated, by shifting attention onto access.

Can Italy succeed in this new context? Entrepreneurs and managing directors certainly believe so and maintain that Italy, today, has the chance to play an important international role in biopharma. The playing field has changed and now production requires complex work and a multi-disciplinary and advanced team comprising three actors: the scientific community, companies, and the institutions (regulatory agencies and government). Today, it seems that innovation has an ever more important place in their agendas. It is an accepted fact that Italy possesses an excellent scientific community, rated among the best in the world for the number and quality of its scientific publications, with highly respected founts of innovation.

Biopharma companies continue to believe in this country, which is steadily growing in terms of investments, personnel, and the number of medicinal products currently marketed or in the pipeline. It is a constantly growing sector, with highly-qualified personnel, that invests 15 times more than any other manufacturing sector.
The Italian Medicines Agency has an excellent track record for establishing an ongoing dialogue with companies as also for its partnership role. It has been able to introduce innovative evaluation models able to determine the efficacy and innovativeness of medicinal products that are now regarded as best practices by the international community.

The government has the task of creating an ecosystem favourable to innovation by facilitating and rewarding those that implement it. For the first-time biopharma companies have instruments at their disposal to reward innovation: tax credits, the patent box and the fund for innovative medicinal products are all examples of the important place of innovation on the government's agenda.

Italy seems, therefore, to have all the characteristics to meet this challenge. However, success requires continuing investments in the following areas:

1. adapting the training courses provided by the academic world to the new needs of companies;
2. reinforcing the dialogue between the universities and companies through tools such as technology transfer and open innovation, but undergirded by appropriate mechanisms for valorising intellectual property;
3. investing in the numerous Italian founts of innovation, insofar as hubs of excellence in order to sustain and attract talent;
4. adapting the rules of access and reimbursement mechanisms to the new context through dedicated solutions, capable of reducing red tape and speeding up time to market;
5. developing a strategic plan for the country and a shared agenda;
6. modifying governance with more updated rules and paying attention to innovation.

Companies, the scientific community and the institutions, therefore, today have the opportunity to make innovation a strategic value for the country, as also, and not least, to provide benefits to patients.

This section is based upon interviews with the managing directors of some companies of the Biotechnology Group of Farmindustria and also with Biovelocita

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- Alfa Intes Industria Terapeutica Splendore Srl
- Alk Abelló SpA
- Allergan SpA
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