Italian Biotechnology Report

ASSOBIOTEC
FEDERCHIMICA
Italian Association for the Development of Biotechnology

ITA
ITALIAN TRADE AGENCY
ICE - Agenzia per la promozione all'estero e l'internazionalizzazione delle imprese italiane

In collaboration with Farmindustria

BioInItaly® Report 2014

EY
Building a better working world

Contents

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President of Assobiotec

The Assobiotec-EY Italian Biotechnology Report, now at its fifth edition, provides us with an in-depth assessment of the outstanding capacity of our biotech companies to transform innovation into valuable products and significant enterprise value, but it also offers us the opportunity for key considerations on the role that the innovative industries can play in fostering the competitiveness of the entire Country, and the measures which are needed in order to allow the sustainable and inclusive growth we are waiting for since many years.

The never ending dynamism of the Italian biotech industry, and its ability to firmly face the continuing economic-financial difficulties which force many of our companies to operate in conditions that too often bordered on the untenable, rely on the extraordinary potential of biotechnologies, the quality of our researchers, and the determination with which our entrepreneurs keep believing and investing in their business.

Indeed, biotechnologies play a major role in achieving the ambitious European objectives in environmental, economic and social spheres, including the development of innovative and more effective responses to the population's health needs, the increasing use of renewable sources of energy, the implementation of eco-sustainable production processes as well as the creation of new non-food markets for our agricultural output.

As to the quality of Italian scientists, several international reports provide us with a clear evidence of the fact that their scientific productivity is absolutely competitive, both in terms of quantity and quality. Thus, the unquestionable excellence of our research, conducted in academic and industrial centres, is the solid basis for the development of competitive innovation in the Italian industry.

Finally, the number of the true and significant entrepreneurial success stories which made headlines in the course of 2013, endorses the attractiveness of the Italian biotech industry for fruitful venture opportunities. I am referring to the cases of those biotech companies that managed to exploit the results of their research activities through considerable development capabilities, and that have been able to create shareholder value by bringing their innovative technologies and products to the market.

As well as being the expression of the outstanding results that may arise from the fruitful synergy of entrepreneurial skills, forward-looking investments and scientific expertise, these stories also remind us that there is much more we can do, and we urgently need to do, in order to fully exploit the innovation potential of this sector.

A study of the Politecnico di Milano University shows that, despite the reasonable participation by firms in the innovative start-up scheme adopted by the Italian Government in late 2012, investment data remain extremely disappointing: € 112 million in 2012 and a projection of € 110 million for 2013. Furthermore, the distribution of investments shows a strong concentration in ICT (73%), with Life Sciences chalking up 9%. Not surprisingly, only 2.5% of the start-ups which have been registered since the aforesaid scheme came into force are active in the biotech field.

However, when considering the 31% of turnover or operative costs that our pure biotech companies continue to invest in R&D, the inevitably long amounts of time needed to develop a new therapeutic product and the high levels of business risk that are part and parcel of our research projects, I simply come to the conclusion that such measure does not provide any real support for the many Italian companies who live on innovation, given not just their need to access to significant financial resources from the earliest stages of their development, but also the long time-scales involved in their investments and the intrinsically low success rate of their programmes.

The recent history of innovative industries worldwide tell us that more coherent and better structured strategies and policies are needed. And this is even more true for a sector which is also of strategic interest in order to boost employment opportunities. Employment growth in innovation industries is structural, while that of manufacturing is cyclical, and for 1 new job in innovation, we have 5 new jobs at sector level, compared to 1.6 generated by traditional industries.

In the last decade Italian biotechnology has certainly made enormous strides in all areas of applications. A number of convincing success stories are also there to prove it, and our scientists and entrepreneurs have shown an astonishing ability in doing more with less. What companies deserve is a long-term strategy and a supportive environment for all their life-cycles, to become the engine for the competitive development of our Country.

Executive summary

The present edition of the Italian Biotechnology Report, besides containing the main data for 2013, aims at highlighting the main trends of the biotech industry in Italy in the context of the broader European scenario, by also addressing a number of topics, projects and success stories that provide the best evidence of the commitment of both the scientific and business community to make of this Country a truly competitive area for the development of innovative entrepreneurial initiatives.

The Italian biotech industry: overview

Once again the biotechnology industry shows consistent dynamism and promising results, despite the continuing difficult economic situation which our companies have been struggling with for a considerable amount of time.

At the end of 2013, there were 422 companies engaged in R&D in the field of biotechnologies. Among these, more than half (264) fall under the definition of pure biotech company, as adopted by the EY Centre for International Studies in Biotechnology.

Despite a very marginal decrease in the number of firms, the Italian biotech industry ranks third in Europe after Germany and the United Kingdom in terms of number of pure biotech companies, thus representing an extremely competitive reality, which has significantly grown over the past years, and still shows the capacity to overcome the cyclic nature which is typical of other industrial sectors.

Total turnover accounts for € 7,050 million, showing a substantial stability, whilst R&D investments have grown to € 1,517 million, with a further 1% increase compared to the previous year. The number of R&D employees totals 6,626, with a slight decrease (-1%).

The vast majority (77%) of companies that operate in the biotech field are micro or small-sized entities (having fewer than 10 and fewer than 50 employees, respectively). When applying this dimensional analysis to pure biotech companies only, the percentage increases to 88%, thus confirming that the driving-force of the Italian biotech industry mainly consists of innovative SMEs and start-ups, dedicated primarily to R&D activities.

Fields of application

Similarly to what has been observed in other countries, also in Italy red biotechnology is the spearhead segment of the entire sector. Of the 422 firms recorded, 241 (57%) are active in the field of human health - with specific reference both to therapeutic and diagnostic applications - and 145 of them are pure biotech companies.

The red biotech sector turnover amounts to € 6,662 million, with an increase (1%) compared to the previous year. Most of this revenue is attributable to pharmaceutical companies; despite representing 17% of the total number of companies, they constitute 79% of total sales, compared with the 18% which originates from pure biotech companies' activities.

With a total R&D investment of € 1,382 million, which represents 21% of their turnover, red biotech companies provide significant resources in order to extend and further develop their project pipeline. Breaking down this investment by type of company, pure biotech companies represent 26% of the total, compared to 73% of pharmaceutical companies (39% Italian pharmaceuticals, 34% Italian subsidiaries of multinational companies), but the incidence of their investment on turnover is higher (31%) compared to that of pharmaceutical companies (21%).

This commitment is further confirmed by the ratios between the numbers of R&D employees and total employees: Italian pure biotech companies have a percentage of R&D employees on total (20%) which is significantly higher than that of pharmaceutical companies (11%).

As regards the other fields of application, 64 companies are active in the GPET sector (Genomics, Proteomics and Enabling Technologies) although,

to confirm the correlation between GPET and human health, most of the multicore companies which are active in the red biotech field, are also active in GPET.

With reference to the green biotech segment, out of the 94 firms in our sample, a vast majority are micro small-sized pure biotech companies, mainly operating in independent headquarter, which are engaged in a variety of projects aimed at exploiting the potential of agro-biotechnology, by improving the nutritional value of animal and plant productions as well as the sustainability of the Italian food chain.

More than two-thirds of the 69 white biotech firms in Italy are pure biotech companies; most of them are start-ups or academic spin-offs located within science parks or incubators, exploiting innovative technologies involved in the process of transformation of biomass as well as in the sustainable production of chemicals, materials and fuels. Although Italy still lacks a national strategy for the Bioeconomy, a number of companies active in industrial biotechnology enjoy a true competitive edge, at a world level, in terms of technological leadership.

Therapeutic pipeline

In Italy too, the biopharmaceutical industry remains the driver of the entire biotech sector, with as many as 176 companies that invest heavily in the development of highly innovative molecules and therapies.

Executive summary

Overall, the Italian therapeutic pipeline boasts a total of 403 products, of which 108 are in preclinical phase, 46 in Phase I, 126 in Phase II and 123 in Phase III clinical trials. In addition to these, there are another 67 projects which are still in the discovery phase.

If the number of products under development grows by 12%, the number of molecules that have reached Phase II (+18%) and Phase III (+17%) of clinical development has increased too. With regards to their origin, approximately 54% of the projects derive from foreign capital companies - notably multinationals' subsidiaries in Italy - and 46% from Italian capital companies, including Italian pharmaceutical companies.

Focusing our attention on the pipeline deriving from the Italian biotech companies alone, there are 187 products under development, of which 102 are in preclinical phase (55%), 24 in Phase I (13%), 50 in Phase II (27%) and 11 in Phase III (6%) of clinical development.

It is also worth highlighting that in 2013, for the first time, the European Commission granted a marketing authorisation for the first product, Defitelio®, resulting from the research activity of an Italian pure biotech company. Defitelio® is a life-saving drug developed by Gentium for the treatment of severe hepatic veno-occlusive disease (VOD) in haematopoietic stem-cell transplantation (HSCT) therapy.

With reference to the pipeline analysis by type of product, approximately 45% of the projects relate to biopharmaceuticals - or biotech drugs – which include, by definition, monoclonal antibodies (26%), recombinant proteins (10%), cell therapy (3%) and gene therapy (4%) drugs, and regenerative medicine compounds (2%). The percentage of biopharmaceuticals has progressively increased (from 36% in 2009 to 45% in 2013) over a 5-year period, versus the contribution small molecules (low molecular weight compounds), the percentage of which has fallen from 45% to 33%.

With regards to therapeutic areas, the Italian pipeline reflects the European epidemiological trend: oncology is the area with the largest number of projects

(40%) in clinical development, followed by inflammatory and autoimmune disorders (13% of the drugs), neurological diseases (9%), and by the group of metabolic, hepatic, and endocrine disorders (9%).

The levels of excellence achieved by the Italian red biotech companies are further proved by their commitment in the field of Orphan Drugs and Advanced Therapies (AT).

Indeed, out of the 47 projects currently managed by the 21 companies in our survey, which are active in the field of Rare Disease, 10 have received an Orphan Drug Designation by the EMA, 7 by the FDA and 30 by both regulatory agencies. Within the 47 aforesaid projects, 15 originate from pure biotech companies, 3 from Italian pharmaceutical companies and 29 from the Italian subsidiaries of multinational corporations. Most of these products are in the advanced phases of clinical development (4 in Phase I, 20 in Phase II and 20 in Phase III), while 3 are still in the preclinical phase.

As regards Advanced Therapies, the R&D efforts by the 18 AT companies whose pipeline we were able to analyse focus on allogeneic and autologous therapies, as well as on viral vectors and DNA vaccines, with the number of drugs under development rising from 32 to 40 over the past year. Among these, 13 are based on cell therapy, 19 on gene therapy and seven apply to Regenerative Medicine. Whilst 20 of them are in preclinical phase, 6 are in Phase I, 9 are in Phase II and 3 are in Phase III of clinical development.

All of the above figures provide clear evidence of the dynamic pace of the Life Sciences industry in Italy and are even more relevant if we take into account the fact that our analysis was limited only to those projects that are the result of Italian research. Indeed, even in the case of pharmaceutical companies with foreign capital, we only considered those projects which originate from R&D activities mainly conducted in Italy.

Once again, we can see a clear complementarity of roles between pure biotech companies, which are more focused on early-stage research and preclinical development - with almost 77% of their projects ranging from discovery to Phase I, and foreign-capital pharmaceutical companies which are almost exclusively involved in late-stage clinical and regulatory development activities - with 23% of their projects concerning Phase II and III trials. The latter finding further confirms the level of excellence and competitiveness achieved by our Country in the conduct of clinical trials.

European Benchmark

Despite the continuing of an economic crisis of global dimensions, the Italian biotech companies were able to grow and, above all, to stand firm in the face of economic-financial difficulties which forced many of them to operate in conditions that too often bordered on the untenable.

Indeed, Italy continues to rank third in Europe, with reference to the number of pure biotech companies, although this remained substantially unchanged. As regards the European scenario, the situation varies depending on the country: UK, France and Switzerland seem to be the only countries showing a considerable growth in terms of number of companies; Germany, Spain, Italy and The Netherlands are marginally growing, while no European country seems to show a decrease compared to the previous year.

With regards to the 2013 financial data relating to venture investments in biotechnology, Italy is lagging far behind compared to the other European countries: Italian biotech companies have picked up only 1.6% of the total VC investment in Europe ($ 1,613 million), compared to 27.7% in UK, 11.7% in France, 10.5% in Germany, 9.2% in the Netherlands, 8.4% in Denmark, or even to 4.1% in Austria, 3.8% in Belgium and 3.2% in Spain.

Notwithstanding the emphasis placed by the European legislator on the importance of the development of a strong and dynamic Venture Capital market as a key prerequisite for the stability of the entire economic system, the European VC industry is still young, small and heterogeneous compared to the US one.

In order to find an alternative to the lack of adequate venture funding, biotech firms are more and more keen to establish strategic alliances, as well as to share resources and capabilities, with other companies.
Even if the total number of deals has slightly decreased (from 47 transactions in 2012 to 43 in 2013), we are clearly in front of a recovery of the potential value of alliances in the industry (€ 10 billion in 2013, compared to € 8.6 billion in 2012). This recovery is mainly driven by the agreements between biotech companies and big-pharma, although also the value of biotech-biotech deals showed a considerable increase, compared to the past.

In year 2013, the potential value of M&A has also increased, both in terms of number of offers (20) and total amount involved (approximately € 15 billion).
On the one hand, there is a huge increase in the potential value of the biotech -biotech deals, and on the other even the transactions between large pharmaceutical companies and biotech companies show better results.

In order to raise money, companies may also look at an IPO on the public markets, although the amount of capital they can possibly raise is influenced by markets' conditions and by the macroeconomic scenario as a whole. Even if in recent years, the number of public offerings has declined considerably following the 2007 financial crisis, the number of biotech IPOs in 2013 looked promising, with 7 IPOs being successfully closed even if none of them involved any Italian company.

Making the best of the innovation potential of Italian biotechnology

Indeed, the growing trend of biotechnology in Italy is the result of the recognized excellence of the Italian research as well as the outstanding capacity of our companies to transform innovation into valuable products and enterprise value.

As further confirmed by two recent international reports, Italian researchers are able to produce important results, achieving more and more with less and less, and with increasing success.

According to data form the Consolidator Grant 2013 scheme, through which the European Research Council funded 312 European and non-European research projects on the sole grounds of their merit, Italian scientists won 46 of the grants, ranking second behind Germany (48) and well ahead of France (33), the United Kingdom (31) and the Netherlands (27), despite the fact that Italy lags well behind all of the leading European countries in terms of R&D investments.

Further achievements emerge from the International Comparative Performance report commissioned by the UK Government, according to which Italian researchers have overtaken their US colleagues not only in terms of productivity but also in terms of quality. With 1.1% of the world's researchers and 1.5% of total global spending, Italy produced 3.8% of the planet's scientific articles, obtaining 6% of all citations, thus ranking first and six times higher than the world average in terms of citations.

Despite the fact that the VC&PE market is still underdeveloped in Italy, and that our pure biotech companies are on average modestly capitalized, the Italian biotech industry has been able to provide the business community with a number of true success stories endorsing the attractiveness of the national scientific and entrepreneurial environment for fruitful venture opportunities.
As well as being the expression of the outstanding results that may arise from the fruitful synergy of entrepreneurial skills, forward-looking investments and scientific expertise, these stories also remind us that there is much more we can do in order to fully exploit the innovation potential of biotechnology in Italy.

In the long term, excellence and success stories can make a difference only if supported by adequate policies to create a more supportive environment for the development of new ideas and entrepreneurial initiatives. This was the purpose of the so-called Growth Act 2.0, adopted by the Italian Government in late 2012, in order to foster new business ventures, as well as of several clustering initiatives aimed allowing the transfer of science from the laboratory bench to the market, through the development of a synergistic network of interactions throughout the territory, involving scientist entrepreneurs and investors.

In this respect, effective technology transfer is a key prerequisite for the competitiveness of the innovation system in Italy. As such, Assobiotec has joined a specific project - BioTTasa - funded by the Italian Ministry of Economic Development (MISE), aimed at exploiting the research results produced by the National Research Council (CNR), through the dissemination and transfer of promising technologies to the industrial and production system in the biotech sector, and the creation of innovative research spin-offs.

In the two years of activities planned, BioTTasa (Technology Transfer and Integration of Biotechnology for Health, Food and Environment) intends to develop a broad spectrum of technology transfer actions, including patent licenses, research contracts and business creation, starting from the technologies developed by the laboratories of the CNR in a number of areas of primary interest for Italian biotech companies, including diagnostics and innovative drug development, gene therapy, biosensors, biodiversity and bioenergy research services. The project involves six Italian regions (Latium, Campania, Friuli Venezia Giulia, Sardinia, Apulia and Sicily) and 28 companies active in the above mentioned areas.

European Biotech Week 2013

Though biotechnology is already part of our every-day lives, its contribution in terms of better health, safe and more affordable food, more sustainable and effective industrial processes, as well as greener products, is not common knowledge in Europe. There is a need to engage with all stakeholders in science-based discovery and discussion about the facts and benefits offered by this incredible science and its application.
The decision of launching an annual European Biotech Week (EBW) comes at a time in Europe where the knowledge and

understanding of this vibrant science and industry is still too low compared to its increasing potential to respond to some of society's most pressing challenges including helping Europe out of its economic predicament.

The very 1st European Biotechnology Week, which took place across Europe in October 2013 to mark the pivotal moment that Watson and Crick discovered the structure of DNA 60 years ago, was the occasion for European National Biotech associations to join forces with universities, charities, large and small biotech companies, and the general public to highlight biotech's achievements to date and to debate future opportunities for this booming industry.

As the Italian partner of the event, Assobiotec was the promoter of 35 initiatives throughout the Country including debates, art workshops, theatre performances, panel discussions, and a full day of Open Doors, which were attended by more than 2,500 participants. Education, promotion and awareness were the three underlying principles of the entire event, which was driven by the ambition to bring the world of biotechnologies to a large and heterogeneous audience, in an innovative and different approach.

Besides being the opportunity to grow scientific awareness in this Country, the Italian side of the EBW was also the occasion to draw the attention of citizens on the active role that Italy too needs to play in the international biotechnology challenge; not only for their positive impact on all aspects of our lives, but most importantly because biotechnologies offer an important opportunity, for their key contribution to Italy's economy in terms of its competitiveness, advancement, economic growth and employment for young and highly qualified people.

The system of biotech companies in Italy

Besides being the expression of the contribution of biotechnology for better health, safe and more affordable food, sustainable industrial process and greener products, the Italian biotech industry represents an extremely dynamic reality, which plays a key role in transforming the excellence of Italian research into innovative products and technologies, thus fostering the competiveness of the Italian economy in terms of industrial growth and new professional perspectives for young and highly qualified people.

Introduction

Once again, the performance of the Italian biotech industry confirms the key role of biotechnologies for the growth of the innovation system in our country and the competitiveness of the national economy.

Despite the continuing of an economic crisis of global dimensions, the Italian biotech companies were able to grow and, above all, to stand firm in the face of economic-financial difficulties which forced many of them to operate in conditions that too often bordered on the untenable. This was only possible due to the scientific excellence of the Italian scientists, to the astonishing ability of our entrepreneurs to wring value out of every euro invested and to the determination which they continue to show in the entrepreneurial mission.

Despite a marginal decrease in the number of companies and R&D employees, the trend of all other key parameters relating to R&D investments and turnover further confirm the competitiveness and the anti-cyclic nature of this segment compared to other industrial sectors.

Beyond their contribution in terms of investment and revenues, red biotech companies have significantly grown their product pipeline and provided the entrepreneurial and financial community with a number of true success stories, endorsing the attractiveness of our Country for fruitful venture opportunities in the biotech field.

Table 2.1

Key data of the biotech sector, details of the OECD and pure biotech companies
(Source: EY)

	2013 Report *		2014 Report	
	Total biotech	Pure biotech	Total biotech	Pure biotech
Number of companies	435	274	422	264
Total turnover	€ 7,050 million	€ 1,514 million	€ 7,050 million	€ 1,490 million
Total investment in R&D	€ 1,502 million	€ 443 million	€ 1,517 million	€ 438 million
Total R&D employees	6,726	2,473	6,626	2,457

** Data have been rectified to make sample comparison possible.*

Analysis

From our analysis, we identified 422 companies operating and investing in Research and Development (R&D) in biotechnology in Italy, at the end of 2013 (Table 2.1). Most of these firms (62%) are pure biotech companies; the remaining 38% are Italian pharmaceutical companies (4%), multinationals' subsidiaries in Italy (13%) and other Italian biotech companies (21%), which include CROs and other companies not covered by the previous categories of our classification. The number of pure biotech companies (264) increased by five and decreased by 15 units, with 14 companies which are no longer active and one which was merged in the course of 2013, bringing about an overall negative variation.

The analysis by application field, using the classification already adopted in the previous reports, confirms that the distribution of the companies in the sample is not very different from last year (Figure 2.1).

Almost half of the companies are exclusively active in red biotech (47%), proving the predominant weight of human health biotechnology, whose market is still very attractive from a scientific and entrepreneurial point of view, based on the increasing demand for better and more efficient treatments for a number of diseases which remain highly relevant in terms of both their medical and social impact. With regard to the other firms of the sample, 15% of them are active in GPET (Genomics, Proteomics and Enabling Technologies), 13% in green biotech and 11% in white biotech, while 14% operate in more than one field of application, as multi-core companies (Figure 2.2).

Referring only to pure biotech companies, most of them are active in red biotech (43%), while 17% are multi-core, 18% are active in GPET, 13% green biotech and 9% white biotech companies (Figure 2.3).

It is worth mentioning that, with respect to the aforesaid trend, the number of companies that are also active in the field of nanobiotechnology has increased further, with a total of 65 firms operating in this very promising area of scientific research. Forty-three of them are pure biotech firms, 81% of which are small or micro-sized. With regard to their field of application, 19 of them are multi-core (29%), 17 are active in GPET (26%), four are green biotech firms (6%) and one is a white biotech company (2%), whilst the number of firms

Figure 2.1

Analysis by application field, comparing years 2012 and 2013 (Source: EY)

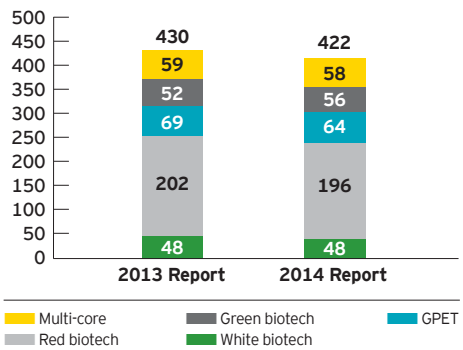


Figure 2.2

Analysis by application field (Source: EY)

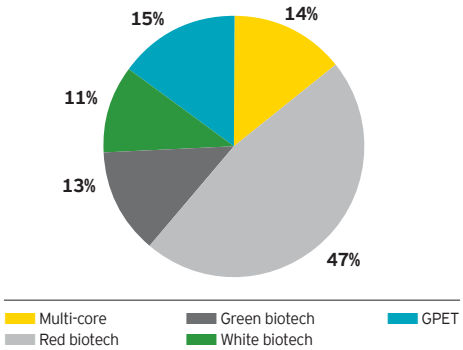
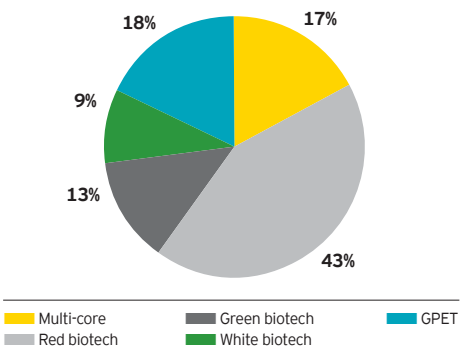


Figure 2.3

Italian pure biotech companies: analysis by application field (Source: EY)



The system of biotech companies in Italy

Figure 2.4

Italian biotech companies: analysis by application field and business model
(Source: EY)

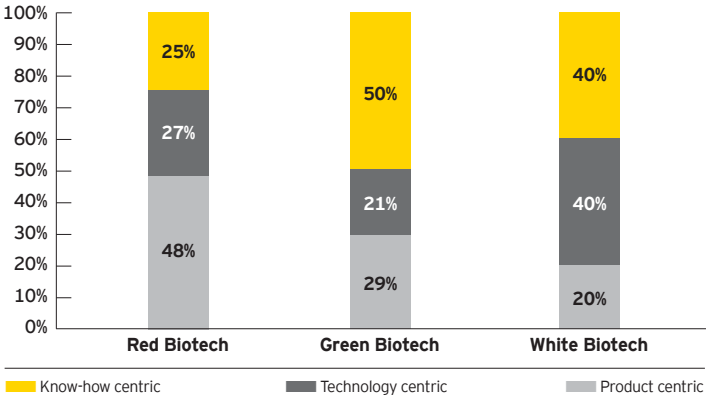
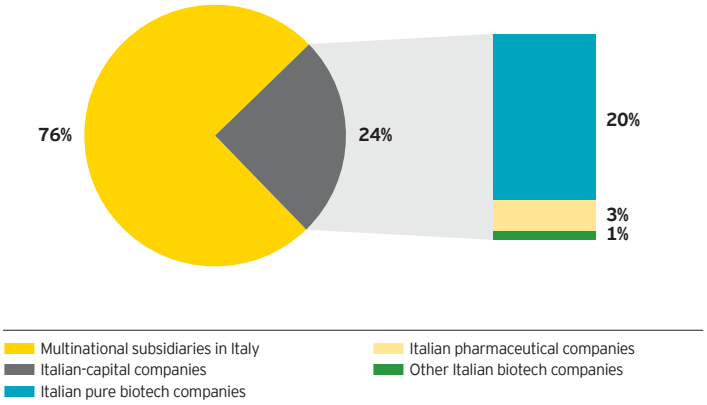


Figure 2.5

Italian-capital companies: turnover analysis by type
(Source: EY)



which are active in the red biotech field reaches 24, with a 22% increase compared to the previous year. As further highlighted in Professor Mauro Ferrari's contribution to the present Report (see Chapter 4), this confirms the role of nanobiomedicine as one of the key drivers in the healthcare industry, as well as the fact that Italy too can count on a number of research centres and early-stage companies with a high level of excellence and competitiveness in this field.

Coming to the different business models (Table 2.2) most commonly adopted by Italian biotech companies, the following can be noted (Figure 2.4):

- almost 50% of red biotech companies are focused on the development of molecules and products that originate from their internal R&D activities, thus applying the so-called product-centric model, which involves important investments in terms of time and allocated resources against significant potential revenues in the mid-long term;
- conversely, green and white biotech companies are more keen to adopt the know-how or the technology-centric model, thus focusing on the development of specific expertise and technologies to be offered in terms of services or licensed to third parties, to the benefit of a more effective management of the research or manufacturing processes.

Table 2.2

Description of the business models most commonly adopted by Italian biotech companies

Business model	Description
Product centric	The company focuses on molecules or products whose development involves significant investment of time and financial resources, but representing a significant source of revenues, or a significant increase in the turnover which originates from other products and services already on the market.
Technology centric	The company focuses on developing a wide range of products and services based on proven technologies, applied to accelerate the discovery and preclinical stages, as well as the early stages of clinical development.
Know-how centric	The company focuses on exploiting its own expertise in R&D, regulatory, manufacturing and marketing, with a view to making this available to third parties, in the form of services.

In 2012, the Italian biotech industry recorded a total turnover of € 7,050 million; using homogeneous samples, this result is exactly the same achieved in 2011. The analysis of turnover by type (Figure 2.5) confirms that 76% of revenues are attributable to the multinationals' subsidiaries in Italy almost all of which are directly engaged in red biotech research activities in our Country. The Italian-capital companies represent 24% of turnover, split between pure biotech firms (20%), Italian pharmaceutical companies (3%) and other Italian biotech companies (1%). Overall, pharmaceutical companies, which constitute 12% of the total sample, have an incidence on turnover of about 78%.

The analysis by size confirms that the majority of Italian biotech companies (77%) is micro-sized or small (54% micro

Figure 2.6

Analysis by size
(Source: EY)

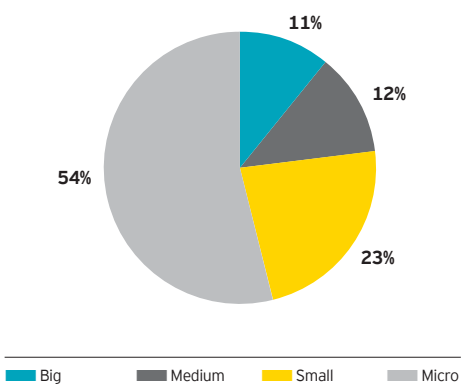


Figure 2.7

Italian pure biotech companies: analysis by size
(Source: EY)

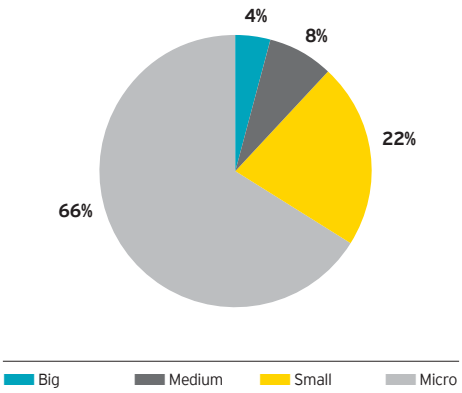
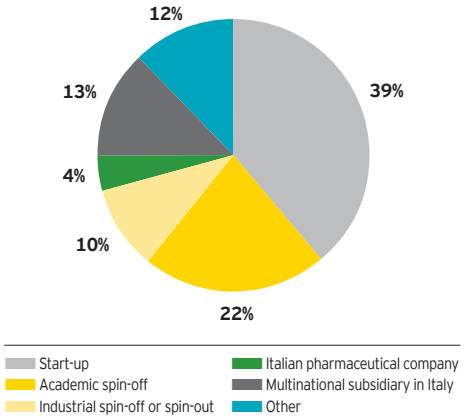


Figure 2.8

Analysis by origin
(Source: EY)



and 23% small), having fewer than 50 employees (Figure 2.6). Companies that have between 50 and 250 employees (classified as medium) are 12% of the total, while companies that have more than 250 employees (classified as big) account for 11%. Segmenting the turnover by company size, big organisations constitute 81%, medium-sized companies 10%, while small 6% and micro-sized companies 3%. Focusing the analysis by size only to the pure biotech companies (Figure 2.7), micro and small enterprises constitute 88% of the sample: further evidence of the fact that the core of the Italian biotech industry is made up of YICs (Young Innovative Companies), focused on R&D activities.

The analysis by origin confirms that the majority (39%) of firms in the Italian biotech industry are set up as start-up companies, 22% as academic spin-offs, 13% as subsidiaries of multinational companies, 10% as industrial spin-offs or spin-outs, while 4% originate from Italian pharmaceutical companies and 12% from others (Figure 2.8).

The system of biotech companies in Italy

Figure 2.9

Analysis by geographic distribution (Source: EY)

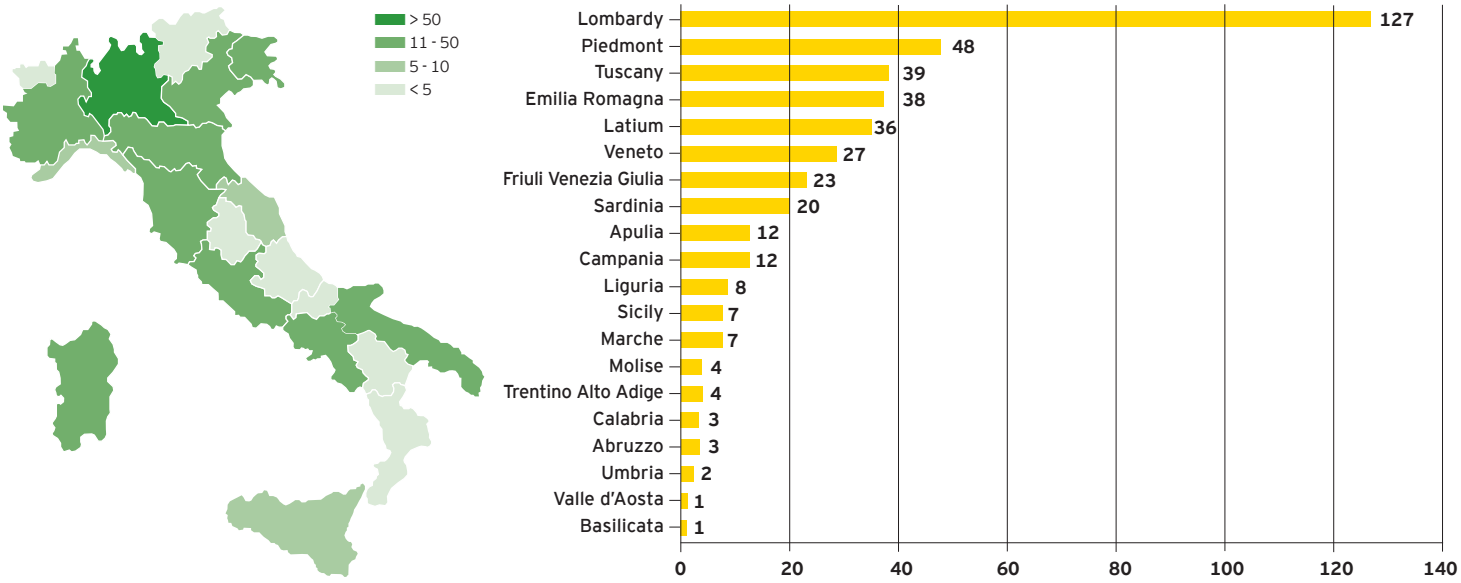
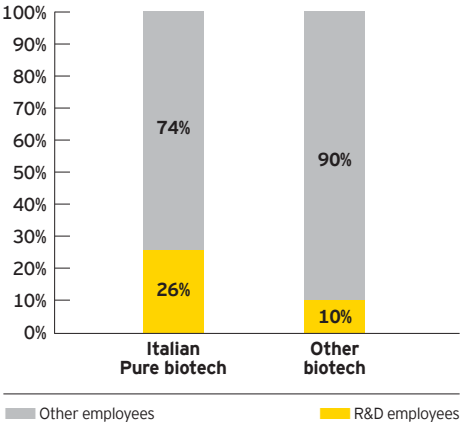


Figure 2.10

Analysis of total employees and R&D employees, comparing pure biotech companies with other biotech companies (Source: EY)



With regard to their geographical position, Italian biotech companies are mainly concentrated in northern and central Italy. Lombardy is historically the region with the highest number of biotech companies (127), followed by Piedmont (48), Tuscany (39), Emilia Romagna (38) and Latium (36).
The number of companies located in the southern regions is still relatively limited, although with some encouraging signals as in the case of Apulia where, thanks to the emergence of a lively research system and a number of clustering initiatives, the number of biotech firms has risen from 9 to 12 (Figure 2.9).

As to their location, 40% of biotech companies have independent headquarters, 41% work within science parks or incubators, while the remaining 19% are located near universities, clinical centres or research institutes.

In 2012, the number of R&D employees totalled 6,626, with a slight decrease (-1.5%) compared to 2011.
This reaches a fairly high percentage of the total employees (26%) in the case of pure biotech companies, whilst for pharmaceutical companies (multinational companies based in Italy and Italian pharmaceutical companies) and the so-called other Italian biotech companies,

Table 2.3

Key data relating to the biotech sector by Region (Source: EY)

Regions	Number of biotech companies**				Biotech companies: turnover*	Biotech companies: R&D investments*	Biotech companies: R&D employees
	Red biotech	Green biotech	White biotech	Total			
Abruzzo	2	0	1	3	0	1	18
Apulia	1	7	2	12	4	5	41
Basilicata	0	1	1	1	1	1	50
Calabria	1	0	1	3	1	11	22
Campania	7	2	2	12	2	16	62
Emilia Romagna	22	6	6	38	213	242	572
Friuli Venezia Giulia	10	12	2	23	31	12	165
Latium	24	4	5	36	1,706	229	1,280
Liguria	2	0	4	8	51	1	57
Lombardy	84	27	17	127	3,251	612	2,661
Marche	4	2	2	7	20	5	76
Molise	3	2	1	4	34	13	17
Piedmont	24	10	12	48	620	95	443
Sardinia	13	4	2	20	38	51	121
Sicily	6	1	2	7	59	34	67
Trentino Alto Adige	0	2	1	4	2	1	28
Tuscany	24	3	4	39	760	112	539
Umbria	1	1	0	2	1	2	15
Valle d'Aosta	0	1	1	1	2	1	2
Veneto	13	9	3	27	254	73	390
Total	**241**	**94**	**69**	**422**	**7,050**	**1,517**	**6,626**

** € millions* *** Including multi-core companies*

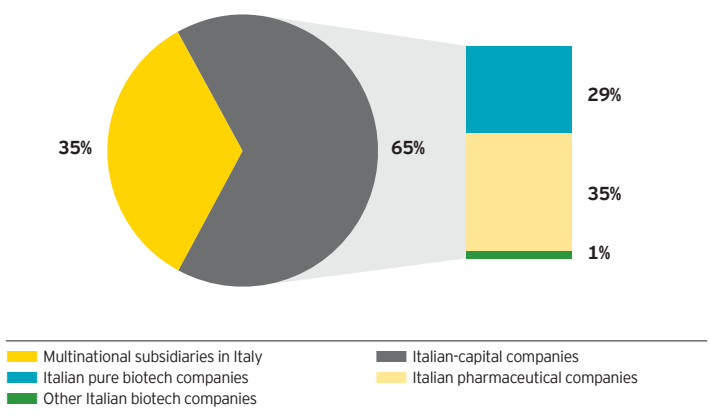
the ratio between R&D employees and total employees is 10% (Figure 2.10).

With regards to total R&D investments in 2012, these amount to € 1,517 million, with a marginal increase (1%).
An analysis of R&D investments by type (Figure 2.11) shows that such investments are generated by Italian pharmaceutical companies (35%), multinationals' subsidiaries in Italy (35%), pure biotech companies (29%) and other Italian biotech companies (1%).

With a further level of detail, Table 2.3 shows the key data relating to the

Figure 2.11

Analysis of R&D investments by type (Source: EY)



The system of biotech companies in Italy

Figure 2.12

Analysis of the 2012 net financial results by type
(Source: EY)

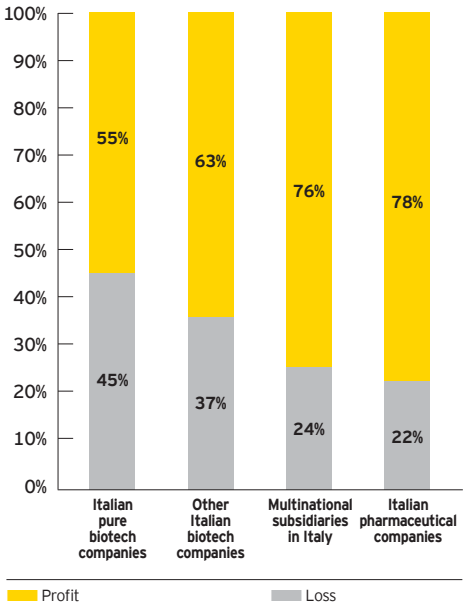
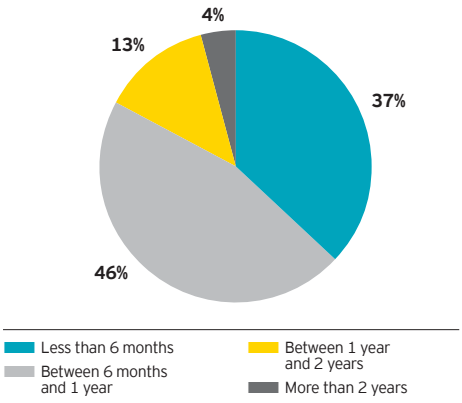


Figure 2.13

Cash availability for the pure biotech companies
(Source: EY)



biotech industry for each Italian region, with regard to the following parameters: number of companies in the different fields of application, turnover, R&D investments, number of R&D employees.

Figure 2.12 shows that 55% of Italian pure biotech companies recorded a profit in 2012. Although this percentage rises to 63% in the case of the other Italian biotech companies, to 76% for the Italian subsidiaries of multinational companies and to 78% for the Italian pharmaceutical companies, we ought to acknowledge that the comparison with the results of the same analysis in the previous reports shows that profitability is an issue for an increasing number of companies. However, most companies which reported a profit in 2012 expect to have the same result in 2013, while for some of the companies which recorded a loss, the expectations are more positive.

The analysis conducted on the pure biotech companies that have answered the 2014 questionnaire shows that, for most of them (83%), the current cash flow is hardly sufficient to cover one year's financial needs. More in detail, 37% of pure biotech companies have a financial liquidity lower than six months, 46% of them can cover their needs between six months and one year, whilst 13% can rely on one - to two-year coverage, and only 4% enjoy a two-year liquidity perspective (Figure 2.13). Almost all micro and small companies are short of liquidity - although the relationship between company size and liquidity is implicit due to the fact that most of the pure biotech companies are micro or small sized.

By exploiting the cash flow analysis per field of application, pure biotech companies (including multi-core and GPET firms) would rely on six-months - to one-year financial liquidity, while green biotech companies and white biotech companies would hardly go beyond six months.

The same questionnaire also provided more information on the measures already adopted, or at least considered by the companies, in order to face the adverse economic conditions: 58% of the companies that answered the questionnaire adopted specific measures, among others to increase operational efficiency and reduce expenditure, while 26% decided to move on to new business segments, and 25% increasingly recurred to outsourcing (Figure 2.14).

As regards the possible measures for the future, compared to the ones already adopted in the past year (Table 2.4), increasing operational efficiency and reducing cash expenditure are considered as likely, or very likely, by a growing percentage (66%) of the same companies surveyed, along with the option of seeking new strategic alliances (78%) and alternative sources of capital (68%). Equally significant is

Figure 2.14

Analysis of the main reactions to the challenges deriving from the economic crisis (Source: EY)

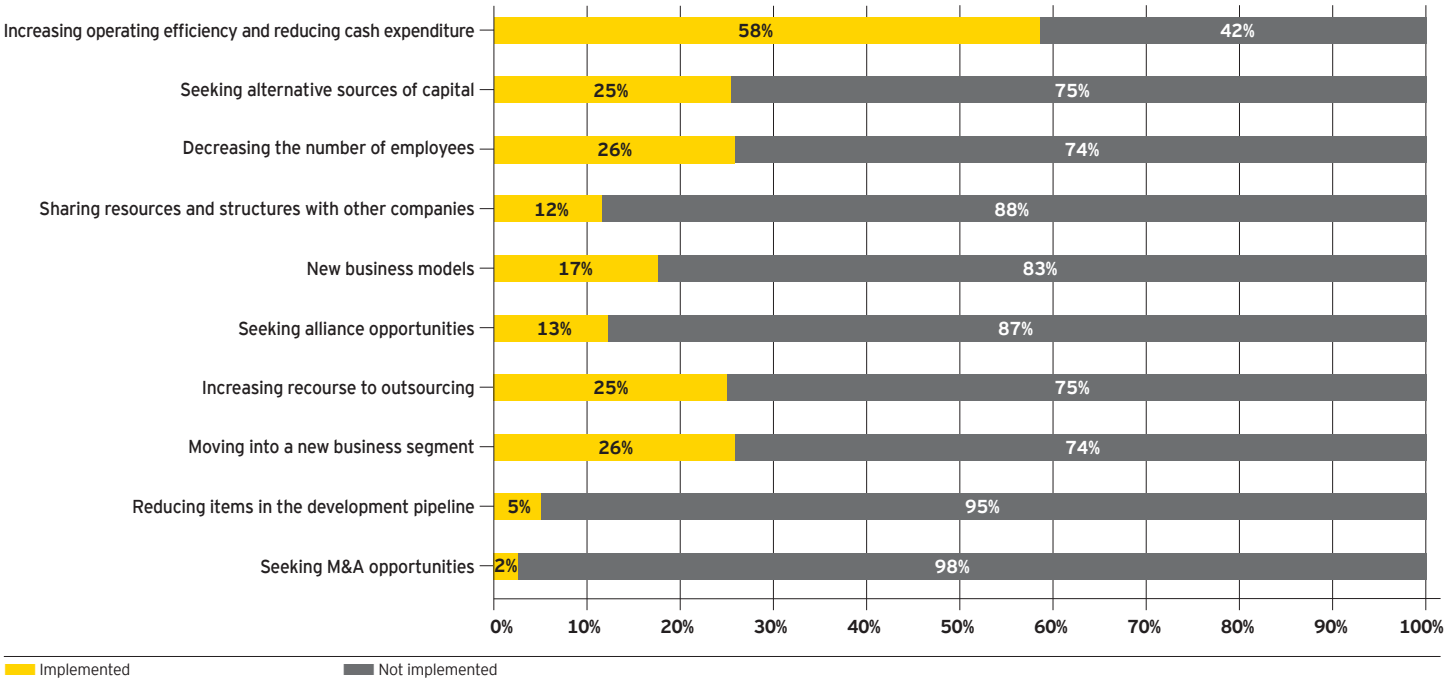


Table 2.4

Analysis of the main measures that could possibly be implemented in the future (Source: EY)

Challenges (%)	Very likely	Likely	Unlikely	Very unlikely
Increasing operating efficiency and reducing cash expenditure	46%	20%	17%	17%
Seeking alternative sources of capital	35%	33%	15%	17%
Decreasing the number of employees	25%	6%	33%	36%
Reducing items in the development pipeline	13%	13%	30%	44%
New business models	20%	16%	42%	22%
Seeking alliance opportunities	34%	44%	12%	10%
Increasing recourse to outsourcing	11%	40%	23%	26%
Sharing resources and structures with other companies	12%	10%	48%	30%
Moving into a new business segment	23%	33%	17%	27%
Seeking M&A opportunities	7%	23%	30%	40%
None	13%	13%	6%	68%
Other	100%	0%	0%	0%

Innovative start-ups: state of the art one year after the introduction

Full parliamentary approval in December 2012 of a specific economic development ruling (Decreto Crescita 2.0) has put Italy's 'innovative start-ups' on the statute book, giving them legal status and officially recognizing the key role played by these companies in the revival of Italian industry. This concrete move is also fully in line with European objectives of fostering sustainable growth, technological development, business enterprise and job creation.

Given its significance for the biotech sector, this piece of legislation was thoroughly covered in Report 2013. Innovative start-ups and SMEs in general are, in fact, numerically predominant in the biotech industry: 39% of Italian biotech companies are start-ups, and 78% of them are micro-sized and small operations.

The legislation has introduced a range of specific measures to help innovative start-ups in their first four years of activity. The measures set out to simplify corporate governance and labor organization procedures in accordance with the companies' needs while also facilitate access to channels of investment and, in particular, to the venture capital market, thus responding to the lack of capital invested in new technologies and supporting those business initiatives which, in their early years, consume more resources than they can produce.

The measures introduced include exemption from some elements of company law, thus, for example, allowing start-ups incorporated as limited liability companies (S.r.l. - Società a Responsabilità Limitata) to take advantage of specific provisions normally reserved to stock corporations (S.p.A. – Società per Azioni) (the free determination of the rights given to shareholding partners, the issuing of participating financial instruments, the possibility to publicly offer and negotiate quotas of ownership). There is now greater flexibility for start-ups in the employment of temporary staff and alternative forms of contribution for staff and suppliers by means of work for equity schemes.

Crowdfunding is also foreseen in the legislation, giving start-ups an additional innovative channel through which to raise capital from a broad base of smaller investors while, given the high risk profile of this area of investment, specific tax breaks have been introduced to encourage both individuals and corporate entities to invest in the R&D activities of start-ups.

In order to be eligible for the measures contained in the new legislation, as well as having been incorporated for no more than 48 months and having as its sole main business purpose the development and marketing of innovative, technically advanced products and services, the company cannot be the result of a merger, a demerger or the sale of a company or part of a company, cannot have an annual turnover exceeding € 5 million and cannot distribute profits.

The company must also meet at least one of the following requirements: R&D expenditure amounting to at least 15% of the total value or cost of production (whichever is greater); at least one third of its workforce with post-graduate qualifications or involved in post-graduate activity; being the holder or licensee of a patent.

The initial legislation also specified that, when the company is incorporated and for the following 24 months, the majority of quotas of ownership or shares representing the company capital had to be held by individuals. This corporate governance provision was fortunately annulled by a subsequent ruling (D.L. 76, 28 June 2013), thanks also to intervention by Assobiotec. The provision constituted, in fact, a severe restriction for biotech firms. Given the amounts of investment available since the early stages of their development, most of these firms need volumes of venture capital that are not compatible with such restrictions.

The response of the start-up community was quite positive. Since the law came into force, 1,227[1] new start-ups have been registered, but only 31 of these (2.5%) are active in the biotech field. With reference to their field of application, 12

of the Italian Growth Act 2.0

are red biotech companies, 8 are active in GPET, 5 are green biotech firms, 5 multi-cores and one is a white biotech company. A further analysis by geographical area shows that most of them are located Lombardy, Veneto and Emilia Romagna (with four start-ups each).

Studies carried out by the Permanent Observatory of the Politecnico di Milano university[2] relating to the prospects of the start-up environment in Italy show that, despite an extensive network of science parks (40), accelerators and incubators (97), co-working initiatives (65) and institutional investors (32), not only the number of innovative start-ups is relatively small (1,400), but also that only 8% of these (113) managed to raise start-up capital, that the investment data, as a whole, remains disappointing (€ 112 million in 2012 and a projection of € 110 million for 2013), and that there are still significant differences at a regional level in terms of start-up presence.

Stronger growth is only possible with the implementation of policies that encourage further investment: while, in 2012, 70% of resources came from institutional investors, only 30% came from business angels, family offices and incubators/accelerators. Furthermore, the analysis of the distribution of investments in start-up sectors reveals a strong concentration in ICT (73%), with renewable energy and life sciences, the two sectors must closely related to biotechnology, chalking up 16% and 9% respectively.

It should be remembered that, even though the new legislation is an important first step in terms of stimulating the birth of new innovation-rich enterprises, it is actually failing in its aims in those very sectors where the results of R&D investment are seen in the medium-long term, as in the case of biopharmaceutical companies for whom the development of a new molecule takes much longer than the four years foreseen by the legislator.

As a conclusion, although Italy is equipping itself to exploit the innovation that is going on in young innovative companies, it is increasingly clear that more coherent and better structured policies are needed: policies that make the country more attractive to new talent, ideas and capital from both within Italy itself and from abroad.

1. Source: http://startup.registroimprese.it/, data updated 10/12/2013
2. Source: Il Sole 24 ore, 'Few innovative start-ups but the ecosystem keeps growing' ('Poche le startup innovative ma l'ecosistema continua a crescere') by L. Tre, 25/10/2013

the increasing percentage of companies considering as likely, or as very likely, moving into a new business segment (56%) or adopting a new business model (36%), increasing recourse to outsourcing (51%), or even decreasing the number of employees (31%) and reducing items in their development pipeline.

As a general comment, and taking into account that only a third of the companies of the total sample has provided us with complete and consistent answers to the questionnaire, uncertainty seems to be the key feature of the economic and financial context that the Italian biotech industry is coping with. However, despite these challenges, we are once again seeing a number of positive parameters which clearly confirm the strength of an extremely dynamic entrepreneurial reality that manages to overcome the cyclic nature typical of other industrial sectors by translating the excellence of Italian research into new products and services. But in the long term, excellence can make a difference only if supported by adequate policies to create a more supportive environment for the development of new ideas and entrepreneurial initiatives.

This was the purpose of the so-called Growth Act 2.0, adopted by the Italian Government in late 2012.
A year after its introduction, we have tried to assess its impact in terms of attracting new investment and fostering new business ventures.

Tech-transfer and scientific awareness in Europe

Transferring research results to the industrial system and increasing citizenship's awareness of the incredible applications of biotechnology in every-day life may be looked at as two different angles of the same perspective: making of the European Research Area the world's most dynamic and competitive knowledge-based market. The BioTTasa project and the European Biotech Week initiative are the expression of the commitment of Italian biotech community in this direction.

Innovation in the European Research Area

If, in a modern economic system, innovation is the vehicle that can deliver growth, then research and development are the driving force that ensure the continuity and sustainability of that growth. It is for this reason that Europe has initiated a project designed to harmonize the research and innovation systems of EU member States.
A key objective of the project is to facilitate technology transfer, the free circulation of human capital and the implementation of common research policies. With the inception of the European Research Area (ERA), an area without borders, a "common research market", the European Commission aims to increase European employment levels and competitiveness by harnessing the know-how and technological resources of cutting-edge research institutes, universities and industrial companies[1].

September 2013 saw the presentation of the first progress report on the development of EU policies. The report provided an assessment of the research systems in place in each of the single member States, revealing a significant failure on the part of many states to attain the objectives set, and a generalized decline in their investment in R&D.

EU figures show that the highest levels of R&D investment are in Germany (€73 billion), France (€44 billion) and the United Kingdom (€31 billion), and that almost 60% of all European investment originates in these three countries. Within this scenario, Italy ranks among the so-called "moderate innovators" and follows the top three with €19 billion invested, 7.7% of total R&D spending by the 28 member states.

In Italy, between 2007 and 2010, the proportion of GDP committed to R&D increased from 1.18% to 1.26%. Compared to the main European countries, this was well behind Germany (2.82%), France (2.25%), the United Kingdom (1.76%) and also Spain (1.39%).

In terms of private sector R&D spending, 2010 figures show Germany at 1.9% ahead of France (1.38%), the United Kingdom (1.07%) and Spain (0.71%), with Italy trailing at 0.67%. Behind this gap lies the size of Italian companies, 99% of which are SMEs (94.6% micro enterprises – less than 10 employees).

If we look at R&D spending in the public sector (universities and other public research institutes) as a percentage of GDP, we find Italy at 0.18%, slightly ahead of the United Kingdom (0.17%) but lagging well behind Europe's leading nations (France 0.42%; Germany 0.36%).

Moreover, and to a greater extent in Italy than elsewhere, an increase in total public spending has not meant a corresponding increase in research spending.

The ERA report also underlines the need to bridge gaps in terms of transnational cooperation and internal policies relating to equal opportunities and technology

1. Source: http://ec.europa.eu/research/era/pdf/era_progress_report2013/era_progress_report2013.pdf

transfer. The situation in Italy is of some concern: the percentage of employed researchers in Italy is below the European average. There is no specific legislation designed to increase the presence of women and, as regards the transferral of research results from the laboratory to the industry, it is proving particularly hard to create a common platform[2].

Yet, Italian researchers are able to produce important results, achieving more and more with less and less, and with increasing success.
Two recent international reports have outlined the paradoxical status of Italian research today. The first of these is the report on the "Consolidator Grant 2013" scheme, through which the European Research Council (ERC) funded 312 European and non-European research projects on the sole grounds of their merit. The grants assigned reveal an important record: Italian scientists won 46 of the grants, ranking second behind Germany (48) but well ahead of France (33), the United Kingdom (31) and the Netherlands (27).

Italy, then, is almost on a par with Germany despite the fact that it invests in R&D less than a quarter of what Europe's powerhouse nation does. Moreover, Italian researchers were 39% more successful than their French counterparts even though France invests almost two and a half times as much as Italy in research. The same applies in the case of the United Kingdom, which, despite investing twice as much as Italy, saw a third as many of its research projects funded. The Italian figures conceal two particularities: firstly, a vast majority of the Italian grant winners (32 out of 46) were female; secondly, of the 46 projects funded by the ERC, 26 originate from researchers working in institutions in other European states. In other words, the funding that they obtained will be spent outside Italy.

Further Italian achievements emerge from the second report, International Comparative Performance of the UK Research Base – 2013, commissioned by the UK government's Department of Business, Innovation and Skills (BIS). According to the report, Italian researchers have overtaken US researchers ranking first in the world not only in terms of productivity but also in terms of quality. In 2012, with 1.1% of the world's researchers and 1.5% of total global spending (estimated by R&D Magazine at over €1.15 billion), Italy produced 3.8% of the planet's scientific articles, obtaining 6% of all citations. If citations are deemed to be an indicator of the quality of publications, then the average quality of scientific articles by Italian researchers has steadily increased over the last few years, and is now six times higher than the world average.

2. Source: European Research Area facts and Figures, pp 167-173.

Tech-transfer and scientific awareness in Europe

Characterized as it is by a high degree of innovation, biotechnology is one of the sectors that suffers most – in terms of developments and applicative prospects – the lack of investment in R&D. In Italy, it is mainly the private sector that contributes to biotechnological research, providing about 55% of total investments compared to the 28.6% provided by universities and the 13.7% by public research institutes.

OECD 2011[3] data gives us a clear picture of R&D spending in the biotechnological field by both the private and the public sector, and in both European and non-European countries. Taking total spending on biotechnology R&D and the percentage of such spending with respect to total investments, we find that, each year, Italy's private companies spend in the region of €500 million, with an investment that constitutes about 3% of total R&D investment in Italy. These figures are in line with the European average even though they differ significantly from those of countries like France (€2.8 billion, or 9% of total R&D investments), Germany (€1.2 billion, or 2% of total R&D investments) and Denmark (€1 billion, or 20% of total R&D investments).

If we then go on to look at contributions by the public sector in R&D activities in the biotechnology field, the gap between Italy and the other European countries is even greater. While public biotech investments in Italy total around €150 million (about 5% of the total) they rise to €6 billion in Germany (20% of the total) to €1.3 billion (15% of the total) in Spain, and to €250 million in Norway (10% of the total).

In conclusion, there are still substantial differences within the European Union in terms of policies in support of research. The initiatives taken by the EU in the sphere of the European Research Area – including joint planning by member states, European research partnerships, the management of intellectual property, technology transfer and the opening up of the European Research Area to the international community – constitute a political response to the objective of the Lisbon Strategy to transform Europe into the world's most dynamic and competitive knowledge-based economy, capable of delivering sustainable economic growth with new and better employment opportunities and greater social cohesion.

3. Source: OECD (2013), "Biotechnology R and D", in OECD Science, Technology and Industry Scoreboard 2013: Innovation for Growth, OECD Publishing.

The BioTTasa project

BioTTasa: a bridge between research and biotech companies

BioTTasa (Technology Transfer and Integration of Biotechnology for Health, Food and Environment) is a project funded by the Italian Ministry of Economic Development (MISE), aimed at exploiting the research results produced by the National Research Council (CNR), through the dissemination and transfer of promising technologies to the industrial and production system in the biotech sector, and the creation of innovative research spin-offs.

The project is co-funded by MISE, in the framework of the Network for Industrial Innovation (RIDITT) call.

The project leader is the CNR of Rome, through the Department of Biomedical Sciences, the Department of Bio-Agrofood and the Department of Chemistry and Technology of Materials.

Beyond the CNR, the other partners of BioTTasa are the following subjects: Federchimica-Assobiotec, Agenzia per l'Italia Digitale, Innovhub - Experimental Stations for the Industry, the Consortium for Molecular Biomedicine (CBM), the Consortium for the Scientific and Technological Area of Trieste, Confindustria Trieste, Aries – the Special Agency of the Chambers of Commerce of Trieste, Sardegna Ricerche, The Industrial Union of the Province of Naples.

In the two years of activities planned, BioTTasa intends to develop a broad spectrum of technology transfer actions, including patent licenses, research contracts and business creation, starting from the technologies developed in the laboratories of the CNR in the following areas: diagnostics and innovative drug development, gene therapy, biosensors in the field of food and environment, biodiversity and bioenergy research services.

The planned actions include:

- the exploitation of the CNR intellectual property rights and know-how in the field of biotech, through specific initiatives, which are aimed at matching the offer of public research with the needs of the local market;
- the strengthening of shared laboratory facilities;
- the creation of high tech spin-offs;
- the promotion of the technologies and the laboratory facilities identified;
- the implementation of training activities in the field of technology transfer;
- the establishment of a cooperative network for the dissemination and strengthening of the capacity of local companies and institutions in the field of knowledge management, and access to funding for industrial research.

In order to identify the facilities to be possibly shared, BioTTasa issued a specific questionnaire, aimed at the recognition of the existing infrastructures - both of the CNR and the partners - related to the thematic areas outlined above.
These facilities will be identified and evaluated in accordance with specific parameters, such as:

- the availability of multidisciplinary expertise and of multi-purpose, high innovative potential scientific instrumentation;
- the integration, at the same place, of public research institutions and companies open to technology transfer;
- the presence of the potential required for the development of industrial research, pre-competitive development and training;
- the ability to exploit research results;
- the presence of scientific and industrial collaborations, outside the laboratory, even on an international scale.

The assessment will be also functional to the possible allocation of funds for the recruitment of qualified personnel to be employed in the selected facilities.

Moreover, a number of promotional activities will be implemented, aimed at presenting the facilities and their structure, as well as the scientific and technological expertise, equipment and services they can offer.

Tech-transfer and scientific awareness in Europe

Analysis of the technological requirements of biotech companies

With a view to creating a network of cooperation between the public and private sectors, and with the precise objective of boosting companies' research capabilities by exploiting the expertise available in research centres involved in the project or by sharing the technological platforms available, assessment has been made of companies' technological requirements.

The project involves a number of Italian regions – Latium, Campania, Friuli Venezia Giulia, Sardinia, Apulia and Sicily – and spans diverse fields of research, from agro-food to innovative pharmaceuticals, from biogenetics to services for research.

The companies

Of the 118 companies analysed in the national sample, only 28 are located in the regions participating in the BioTTasa project: Latium (10), Campania (7), Friuli Venezia Giulia (1), Sardinia (5), Sicily (3) and Apulia (2). These firms are concentrated in regions where there are a large number of technology parks or modern industrial areas (Table 3.1).

In order to get a clearer idea of the types and geographical distribution of participants in the BioTTasa project, the following table lists the above-mentioned 28 companies by region (Table 3.2).

Most of the companies analyzed are active in the health sector or in multiple areas, with their core business adaptable to market needs. Fewer companies, only three in each, fall into the green biotech and GPET categories. Just one firm is classified as white biotech (Table 3.3).

The analyses covered in this chapter allow us to compare the answers provided by the 90 companies not involved in the BioTTasa project ("non-BioTTasa sample") with those participating in the project (28 in total) and thus to understand trends and the most relevant data.

Infrastructures

The presence of in-house infrastructures is a necessary condition for the development of innovative technologies even though recent data show that outsourcing to service providers is increasing. In general, companies utilize outsourcing so as to be able to access expertise or equipment not available in-house and, at the same time, achieve some reduction in costs.

Table 3.1

BioTTasa sample – companies by region

Region	Companies
Latium	10
Campania	7
Sardinia	5
Sicily	3
Apulia	2
Friuli Venezia Giulia	1
Total	**28**

Table 3.2

BioTTasa sample – companies present in the sample

Companies-BioTTasa sample	Region
Agritest	Apulia
Promis Biotech	Apulia
Arterra Bioscience	Campania
Bionucleon	Campania
Biopox	Campania
Biouniversa	Campania
Bluesodlab	Campania
EpiC-Epigenetic Compounds	Campania
Inbios	Campania
Sprin	Friuli Venezia Giulia
AlgaRes	Latium
C4T	Latium
Mavi Sud	Latium
Micro Biological Survey	Latium
Merck Serono	Latium
Okairos	Latium
Sigma-tau industrie farmaceutiche riunite	Latium
Syntech	Latium
Takis	Latium
Ylichron	Latium
Bioecopest	Sardinia
Bio-Ker	Sardinia
Chrono Benessere	Sardinia
Lea Nanotech	Sardinia
ViroStatics	Sardinia
Abiel	Sicily
Biomedical Research	Sicily
IOM Ricerca	Sicily

Table 3.3

BioTTasa sample – companies by biotech category

Biotech Category	Companies
Red biotech	11
Green biotech	3
White biotech	1
GPET	3
Multi-core	10
Total	**28**

This strategy is in line with the physiological growth of the hi-tech sector: a sector with a large number of small, young, very innovation-oriented firms still closely linked to academia.
Such firms do as much research as possible in-house but turn to larger operations for the use of sophisticated state-of-the-art equipment that is prohibitively costly for smaller operations. For their part, the larger companies, especially those already structured along established business lines and who need to switch their pipelines, tend to contract smaller firms and academic research centres to carry out very early-stage research projects. In addition, the larger companies will scout smaller firms and research centres for projects that they could then carry forward themselves.

In each case, both types of company move towards an exchange of information, something that is easier when the language, instruments and facilities are shared. Joint laboratories, for example, are fertile land for the exchange of information, staff and know-how – in other words, for *cross-fertilization*.

Fig 3.1 shows how, in the Italian market, most of the companies analysed (about 80%) carry out their research in-house, while still maintaining a certain propensity for outsourced research: 63% of the BioTTasa sample and 44% of the non-BioTTasa sample.

Unfortunately, uncertainty remains as regards those companies which did not respond but which still constitute a substantial part of the sample (Figure.3.2 and Figure 3.3).

The fragmentation and competitive nature of the market have generally prevented collaboration based on the sharing of research technology. Consequently, it is usually public institutions which become involved in joint research projects. Almost the entire sample, in fact, reported that the providers of specific research equipment were either university institutes or Italy's public-funded National Research Council (CNR). This phenomenon also bears witness to the fact that many start-ups and spin-offs are directly linked to the leading universities in the biotechnology field, such as those of Siena and Piedmont.

Since they are smaller and closer to academia, start-ups demonstrate great interest in collaborative projects and, in particular, in the utilization of shared third-party technology platforms.
The interest becomes even greater among those start-ups located in regions participating in the BioTTasa project (73%), where industrial activity is less developed (Figure 3.4 and Figure 3.5).

With regard to the companies' willingness to share their technology platforms with third parties, most of the firms seem slightly less interested in this option.

Figure 3.1

Research Infrastructures utilized (Source: EY)

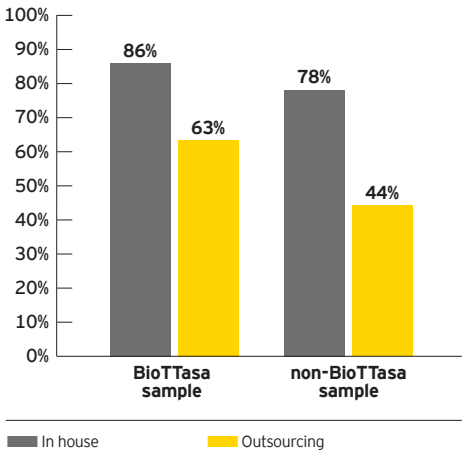


Figure 3.2

Use of outsourcing and in-house activity - BioTTasa sample (Source: EY)

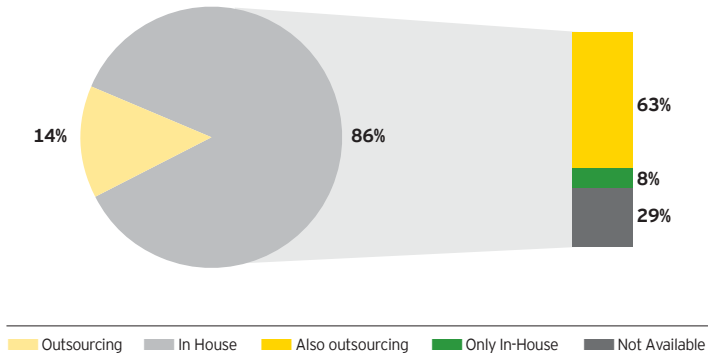
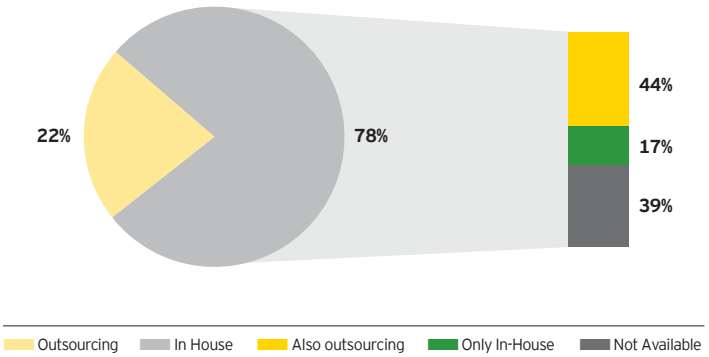


Figure 3.3

Use of outsourcing and in-house activity - non-BioTTasa sample (Source: EY)



Tech-transfer and scientific awareness in Europe

Figure 3.4

Interest in utilizing third-party technology platforms – BioTTasa sample (Source: EY)

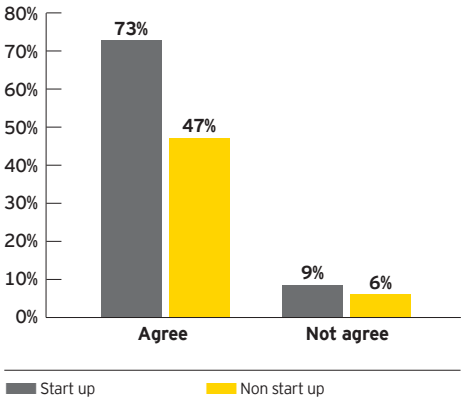


Figure 3.5

Interest in utilizing third-party technology platforms – non-BioTTasa sample (Source: EY)

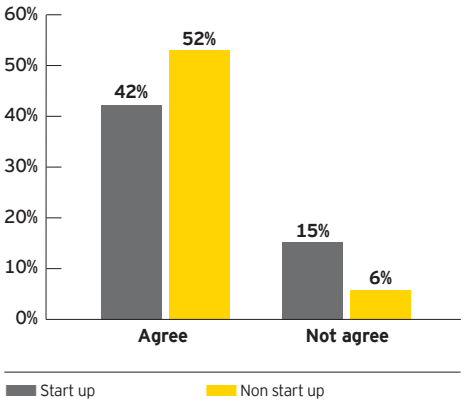
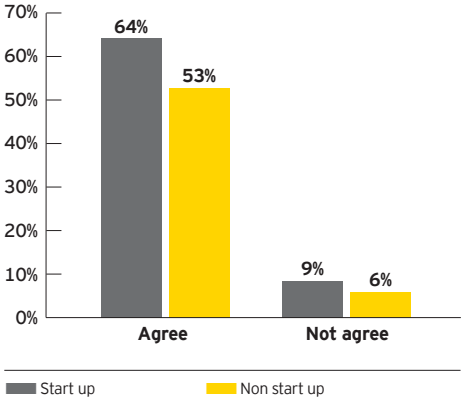


Figure 3.6

Interest in sharing technology platforms with others – BioTTasa sample (Source: EY)



Here too, start-ups are the more oriented companies towards collaboration: 64% of the BioTTasa sample (Figure 3.6) and 48% of the non-BioTTasa sample (Figure 3.7).

Collaboration with CNR and other institutes

CNR cooperates with a great number of companies in the technological field in general. In the biotechnology field, however, collaboration between CNR and companies is not yet widespread:

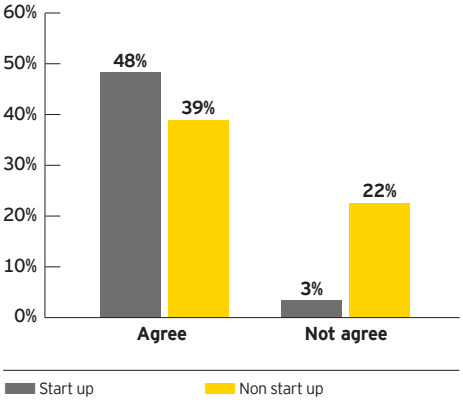
- Only 32% of BioTTasa companies reported a partnership with CNR; 17% named the CNR institute with which they are cooperating while in only one case was a partnership with two CNR institutes reported.
- Of the non-BioTTasa companies, 16% reported ongoing partnerships with CNR institutes, with 8% of the sample indicating which institute and only four companies reporting partnerships with two CNR institutes.

Still on the subject of collaboration, the analysis also looked at areas of interest that may be the subject of future collaboration with CNR and at research subjects deemed predominant:

- diagnostics and development of innovative pharmaceuticals
- gene therapy
- agro-food and environmental biosensors
- biodiversity and bioenergy
- research services.

Figure 3.7

Interest in sharing technology platforms with others – non-BioTTasa sample (Source: EY)



From the analysis, it emerged that there are different reasons behind these collaborations with the CNR. While in the sphere of diagnostics (89%) and of biodiversity and bioenergy (100%), the main purpose is that of developing new products, in the sphere of research services, there is almost equal interest (43%) in developing new products and in increasing technical know-how for the advancement of new projects (Figure 3.8).

Analysis of the areas of interest is related to the various types of biotech business: red, green, white, GPET and multi-core.

What emerges is that the purpose behind collaboration with the CNR varies depending on the field of research and the type of company. In order to have a better understanding of the motives behind collaboration with CNR, we decided to focus our attention on what the analysis identified as the area in which companies show most interest: diagnostics and development of innovative pharmaceuticals.

In the BioTTasa sample, red biotech, multicore and GPET companies gave the development of new products (Figure 3.9) as the purpose of collaboration with CNR rather than the improvement of existing products and/or the advancement of existing know-how.

Similar figures can be seen in the non-BioTTasa sample (Figure 3.10).

The analysis also revealed that interest in collaboration with CNR based on the type of company varies greatly, depending on the sphere of research. Companies expressed particular interest in scientific collaboration in the fields of diagnostics and the development of innovative pharmaceuticals for the human health sector (32% BioTTasa sample; 34% non-BioTTasa sample), of gene therapy (7% non-BioTTasa companies) and in the use of dedicated research services for almost all categories of company.

Figure 3.8

Collaboration with CNR: purpose – BioTTasa sample (Source: EY)

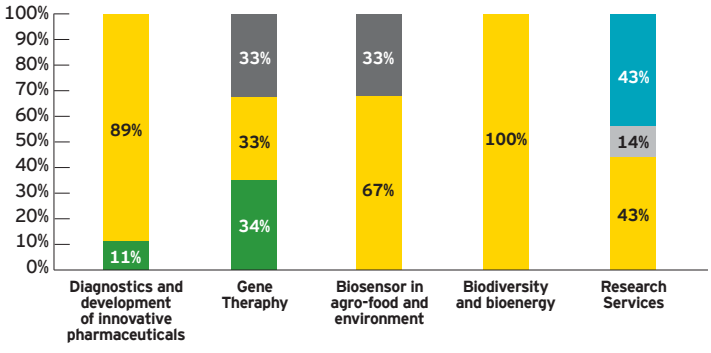


Figure 3.9

Collaboration with CNR: purpose Focus on diagnostics and development of innovative pharmaceuticals – BioTTasa sample (Source: EY)

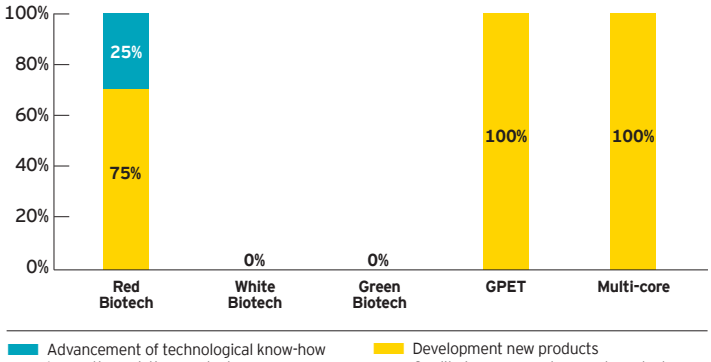


Figure 3.10

Collaboration with CNR: purpose - Focus on diagnostics and development of innovative pharmaceuticals – non-BioTTasa sample (Source: EY)

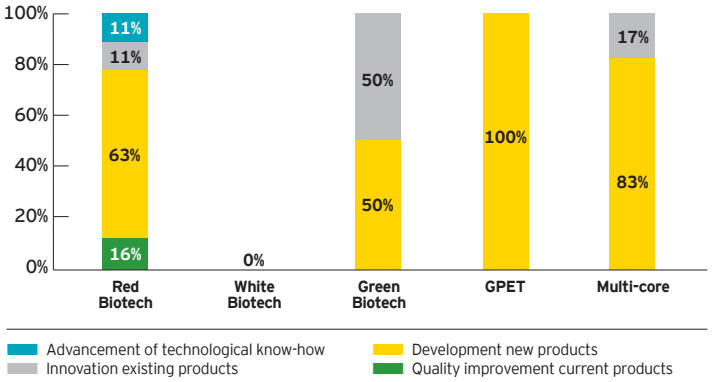


Figure 3.11

Collaboration with CNR: research areas of interest by company type – BioTTasa sample (Source: EY)

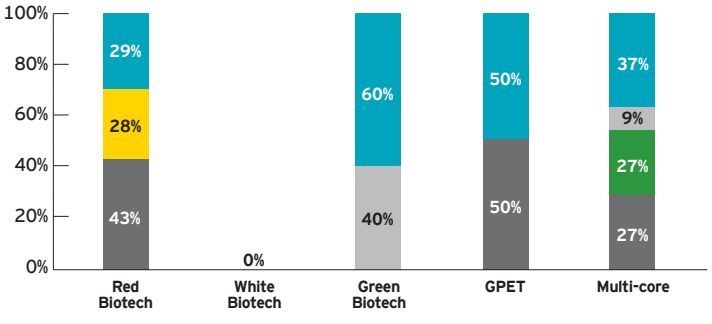
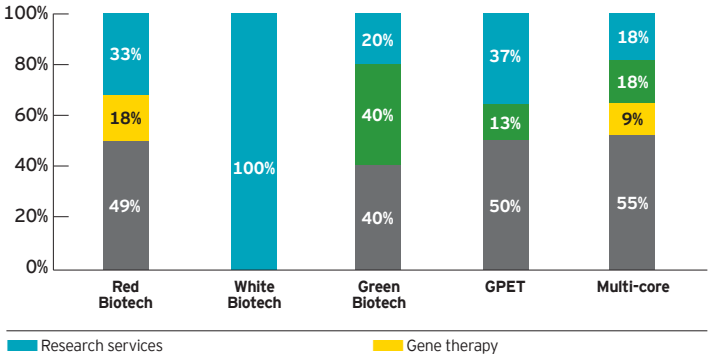


Figure 3.12

Collaboration with CNR: research areas of interest by company type – non-BioTTasa sample (Source: EY)



Tech-transfer and scientific awareness in Europe

Figure 3.13

Interest in national and international research networking – BioTTasa sample (Source: EY)

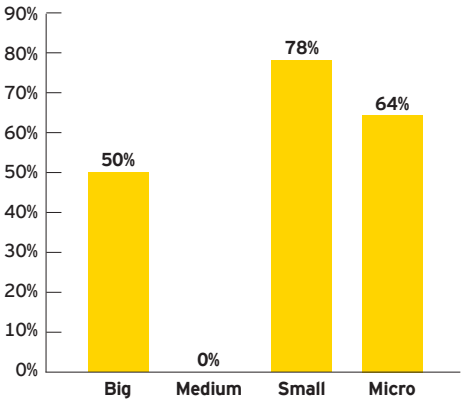
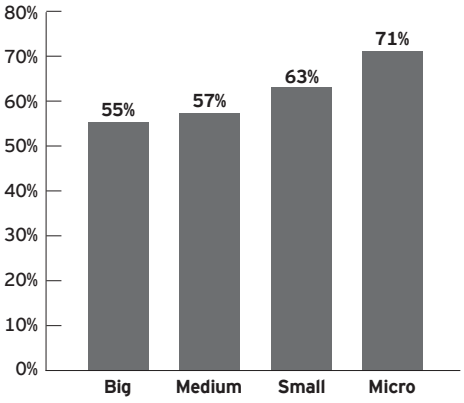


Figure 3.14

Interest in national and international research networking – non-BioTTasa sample (Source: EY)



The study continued with the analysis of the number of companies prepared to become involved in creating partnerships for the setting up of spin-offs, and with the assessment of their interest in purchasing licences or patents.

The interest in collaborating with the CNR among those firms based in the regions involved in the BioTTasa project, corresponds to their willingness towards involvement in partnerships for the setting up of spin-offs, especially in the field of diagnostics and innovative pharmaceuticals (27%), as well as in that of biosensors in agro-food and the environment (20%).

In the non-BioTTasa sample too, interest focussed on involvement in partnerships for the setting up of spin-offs in the fields of diagnostics and innovative pharmaceuticals (22%) and on research services (23%), more than on biosensors and gene therapy.

Strategy

In terms of prospects and strategic projections, there is substantial interest in the development of both national and international networks. Overall, stronger interest in the development of networks is shown by micro and small enterprises. The figures below show that, in the BioTTasa sample, medium-sized enterprises did not respond to the survey. This is probably related to the lesser presence of such enterprises in the areas on which the BioTTasa project has focussed. BioTTasa is, in fact, most concerned with the development of regions characterized by a greater presence of micro and small enterprises. The project objectives include facilitating the growth of small firms and helping them to reach the market, as well as fostering development and innovation at a national level and creating jobs. In the BioTTasa sample, in fact, 78% of the small firms would like to see the setting up of such networks (Figure 3.13). Much interest is also shown by micro enterprises (64%). The levels of interest are very similar for companies not included in the BioTTasa sample where, however, micro enterprises show greater interest (71%) than small enterprises (63%) (Figure 3.14).

Analysis of the data also reveals a high level of interest in acquiring third-party know-how for the development of new areas of business, especially on the part of start-ups. The interest is greatest among those firms based in the regions involved in the BioTTasa project (73%), with just 45% of the remaining start-ups showing such interest (Figure 3.15 and 3.16)

For the creation of new areas of business, BioTTasa sample start-ups are seen to be very interested in acquiring third-party know-how and technology (64%) (Figure 3.17). Interest among start-ups operating outside the BioTTasa project regions is much lower (32%) (Figure 3.18).

This figure, together with the preceding one, underlines the great interest that exists among BioTTasa sample start-ups in strengthening their areas of business

Figure 3.15

Interest in acquiring third-party know-how for new areas of business – BioTTasa sample (Source: EY)

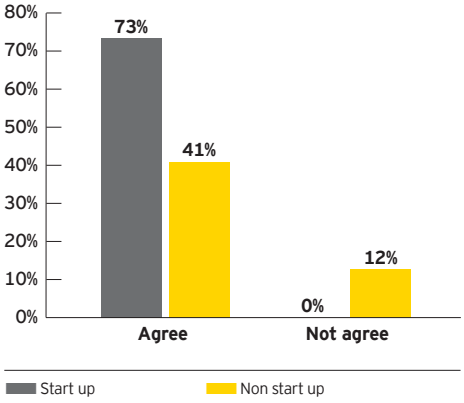
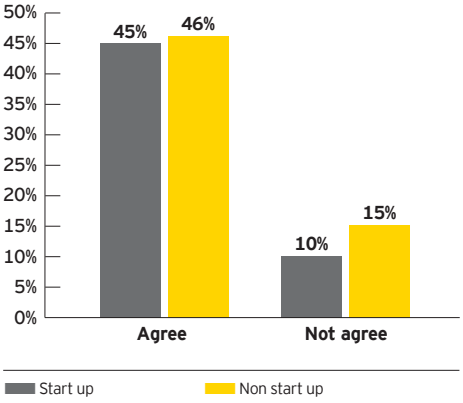


Figure 3.16

Interest in acquiring third-party know-how for new areas of business – non-BioTTasa sample (Source: EY)



and creating new ones by acquiring third-party know-how.
This is not surprising when one remembers that these firms are mainly located in regions of convergence (or Objective 1) where industrial activity is less well established; consequently, firms often have to acquire rather than maintain competitiveness.

Within the sphere of developing competitiveness, another key area of economic-financial research is that of financial and strategic assessment, through which to evaluate a company's financial standing, resources and risk factors. Unfortunately, as regards undertaking financial risk assessment, many companies declined to respond, suggesting that this element is sometimes underestimated by very young management teams and/or management with an exclusively scientific background, as is the case with many of the BioTTasa sample companies.

Only 21% and 20% of micro and small enterprises respectively were in favour of carrying out such assessment. As regards businesses in the non-BioTTasa sample, most in favour of assessment were micro enterprises, followed by small (16%) and then large enterprises (9%).

Very different, however, are the figures concerning the willingness of the companies analysed to undertake rapid strategic assessment. Data from the BioTTasa sample indicates substantial interest in such assessment among firms active in the green biotech and GPET areas (100% and 67% respectively), but with a certain degree of interest also expressed by other types of company in the sample (Figure 3.19). The level of interest is much lower among firms in the non-BioTTasa sample. Nevertheless, in this sample too, GPET (44%) and green biotech (33%) companies are those most willing to undertake rapid strategic assessment (Figure 3.20).

Intellectual property and human capital

The optimum utilization of intellectual property (IP) is an area of increasing importance, particularly in hi-tech sectors. The most widely used forms of protection are as follows:

- BioTTasa companies
  - 67% (19 companies) patents
  - 25% (7) trademarks
- non-BioTTasa companies
  - 74% (67) patents
  - 32% (29) trademarks
  - 3% (3) registered designs

No company said that they used plant variety, industrial secret or utility models for protection purpose.

In conclusion, the biotechnology sector in Italy must make greater efforts to boost forms of cooperation if it wants to grow and to enable Italian businesses to compete on the European and international marketplaces.

Italy needs to drive up investment levels and upgrade facilities, starting this process from a rationalization that the BioTTasa project is seeking to implement.

Figure 3.17

Interest in acquiring third-party know-how for new areas of business – BioTTasa Sample (Source: EY)

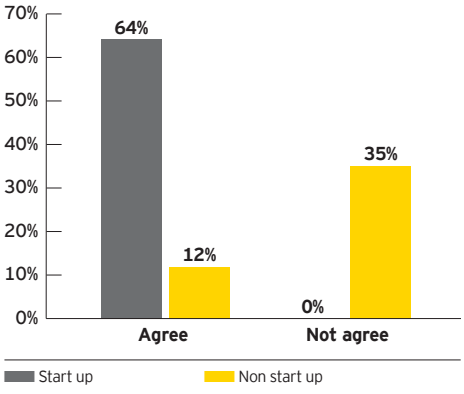


Figure 3.18

Interest in acquiring third-party know-how for new areas of business – non-BioTTasa sample (Source: EY)

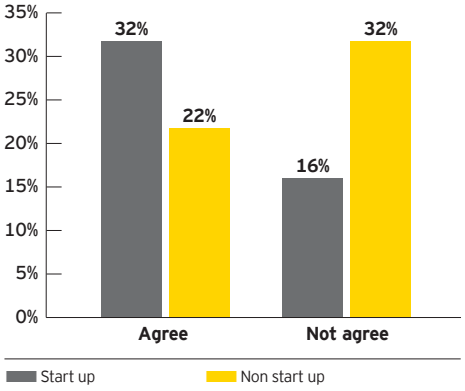


Figure 3.19

Willingness to undertake rapid strategic assessment – BioTTasa sample (Source: EY)

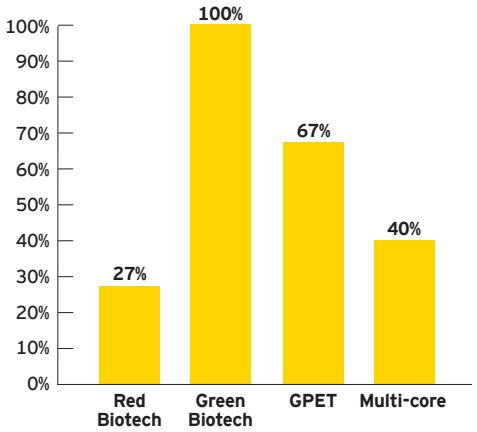
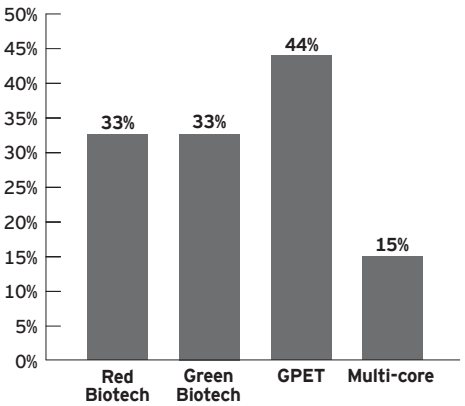


Figure 3.20

Willingness to undertake rapid strategic assessment – non-BioTTasa sample (Source: EY)



Tech-transfer and scientific awareness in Europe

2013 European Biotech Week

Acting as an institutional representative, but even more so as a virologist and researcher, I was enthusiastic about taking part in European Biotech Week, during which Europe celebrated the 60th anniversary of the discovery of the DNA structure, with Assobiotec promoting many initiatives throughout the Country as the Italian partner of the event.

What I immediately appreciated were the three underlying principles of the event: education, promotion and awareness. It was a high-calibre and very prestigious appointment, driven by the need to bring the world of biotechnologies to a large audience: something which is closely related to health, sustainability and innovation; it was a real opportunity to network and learn by exchanging know-how, knowledge and values, and also to share opinions constructively and for mutual enrichment. I am convinced that the first European Biotech Week was a fundamental step towards increasing public awareness and drawing the attention of the authorities to the positive impact of biotechnologies and scientific research on all aspects of our lives while making an important contribution to Italy's economy in terms of its competitiveness.

Italy needs to play an active role in the international biotechnology challenge, most importantly because biotechnologies offer an important opportunity for employment in a country which has thousands of highly

The Evolution of the Revolution

The decision of launching an annual European Biotech Week comes at a time in Europe where the knowledge and understanding of this vibrant science and industry is still too low compared to its actual contribution and increasing potential to respond to some of society's most pressing challenges including helping Europe out of its economic predicament.

The very 1st European Biotechnology Week took place across Europe between September 30 and October 4, 2013 to mark the pivotal moment that Watson and Crick discovered the structure of DNA 60 years ago.

Thanks to that discovery, the deeper knowledge of genes, proteins, viruses, bacteria and genetic structures in general has allowed scientists and biotech entrepreneurs to translate knowledge into applications in sectors such as healthcare, agriculture, food, energy, water sanitation and biochemical processing, all of which have changed the world for the better.

However, the contribution of biotechnology in terms of better health, safe and more affordable food, more sustainable and effective industrial processes, as well as greener products, is not common knowledge in Europe. There is a need to engage with all stakeholders in science-based discovery and discussion about the facts and benefits offered by this incredible science and its application in our everyday lives.

For the first ever European Biotech Week, European National Biotech associations joined forces with universities, charities, large and small biotech companies, and the general public to highlight biotech's achievements to date and to debate future opportunities for this booming industry, and Europe's role within it.

With close to 100 events across Europe, the week saw policy debates in individual member states about the incentives and obstacles faced by scientists, entrepreneurs, academia, end users and students in terms of making the best possible use of biotechnology. Similar policy debates were held at a European level in Brussels with the 6th European Forum for Industrial Biotechnology and the Bioeconomy as well as a debate at the European Parliament entitled "Biotech in 2020: Is Europe still relevant?" with the unveiling of this year's Most Innovative European Biotech SME award.

Member state biotech communities engaged students and the general public through laboratories visits, career fairs, open days in companies and technology museums with interactive expos. Biotech went digital with YouTube

qualified young people graduating each year, as well as being a sector that can attract public and private research funding. I firmly believe therefore, that in the coming years European Biotech Weeks will become a must-attend appointment to grow scientific awareness in this Country.

Ilaria Capua MP
Vice President of the Culture, Science and Education Committee of the Italian Chambers of Deputies

competitions as well as coming live on stage through theatrical performances transporting the public in the world of a scientist and his paper-eating clone or in the exploration of how data sharing through social media such as Facebook will meet a challenge when we get knowledgeable about our genetic profiles through genomics.

I was particularly pleased to see how Italy was such highly distinct among all the countries participating in this first edition, not only in terms of the number of activities that have covered the entire country, including islands (first of all countries), but also on the type of activities that have entertained and involved diverse public and that have inspired other countries and participants intent to prepare the edition 2014.

Despite its strong underpinnings in research and a well-established pharma industry, some aspects of biotech are deemed controversial in Italy, and this has held back the development of the sector. So it was significant the Italian Government endorsed the events.

A grand opening ceremony in Rome was followed by events, highlighting the role of biotech in medicine, biorefineries, agriculture and in fostering economic growth. We have followed for seven days, discussions on the various sectors of biotechnology, theatre performances, art exhibitions, itinerant scientific laboratories, the Telethon biotech week, open days on farms and research centres of the CNR and many, many other activities.

And there's no doubt that there was something to capture the attention and imagination of anyone with an open and inquiring mind.

Unpopular aspects of biotech were debated with school children through Play Decide, a game format designed top frame discussions about impacts, risks, concerns and benefits of advanced research. The aim was to show how biotech connects to daily life and to help gamers arrive at compromises in complex technical subjects.

I just have to thank and congratulate all those who took part in this first edition and to encourage you all to prepare for the next edition which will take place 'between October 6 and 12, 2014.

Nathalie Moll
Secretary General EuropaBio

Play Decide: an innovative approach to involve patients and scientific citizenship in the decision making process

The UNIAMO FIMR (Italian Rare Diseases Federation) no profit association aims to improve the quality of life of rare disease patients by activating, promoting and safeguarding the rights of sufferers of rare diseases with reference to bioethics, healthcare, and social policies. This mission is carried out daily with countless projects and initiatives, many of which co-funded by the Ministry of Labour and Social Policy.

The association's activities revolve around the concept of empowerment. Creating a greater sense of awareness, participation and responsibility in each individual person, organized group or community of groups or individuals is a prerequisite to promoting and safeguarding patient rights and interests and those of their families. This is the sense of almost all the activities promoted by the association which originate from the idea of "scientific citizenship". This means an area where government representatives, experts and various stakeholders can network and make decisions in keeping with their respective roles and legitimate interests.

Biomedical research and biotechnology is growing at an enormous speed, with the risk that its distance from decision-makers, caregivers and patients becomes unbridgeable.

In order to overcome the growing distance between good science and good practice, patients must be placed at the very centre of the system. This is why UNIAMO FIMR is backing the implementation of a National Rare Diseases Plan which, in accordance with European recommendations, can meet the needs of rare disease patients and those of the operators of the entire health care system.

We should draw the attention of public opinion and decision-makers to the fact that joint efforts and a new organization are not simply necessary but a must if we want to assist rare disease patients and their families better and more carefully.

There is a need to call for a discussion on how to offer training and information programs on the many frontier topics that people can and must no longer overlook.

Educating about rare diseases means also providing adequate training on a number of regulatory aspects related to the availability and to the use of innovative drugs and biopharmaceuticals in particular, so as to promote a patient-centred approach and harmonise access to treatment throughout the Country.

This is what we at UNIAMO FIMR are attempting to do, by focusing on our ability to act as an organized group empowered to identify bad practice and foster good practice, and export this outside the Country.

Rare disease patients want to be involved in the drawing up of national and European strategies and plans that address their condition. Lawmakers understand the need to involve patients, and citizens in general, so that scientific and technological decisions can reflect the needs and concerns of the public.

Yet, how can society and patients in particular become more involved in the decision-making process? This is what the European PlayDecide tool aims to do. Initially designed for patients, caregivers and patient associations, it has been reinterpreted by UNIAMO FIMR to extend participation to all the players "at stake", and involving heterogeneous and multidisciplinary "tables". PlayDecide, a discussion game among various stakeholders, aims to raise awareness of the complexity of major topics such as the new research frontiers and therapies offered by biotechnologies.

The PlayDecide meetings, held in Palermo, Bari and Lecce last October during the European Biotech Week, gave the opportunity to share ideas and opinions, in a new and different way, on these topics which remain vital for rare disease patients and are crucial for all citizens.

This was done at round tables, using real playing cards and simulating economic, political and ethical decision-making, where each participant could understand the many implications of the scientific, medical and healthcare choices which were made, even touching the very intimate personal and family sphere.

The attention was centred on two major topics – stem cells and orphan drugs – which were addressed by the participants – researchers, physicians, representatives from industries, universities and patient associations and almost 200 students – equally divided among the universities of Palermo, Bari and Salento – in an extremely professional, competent, creative and passionate manner. Goal reached!

European Biotech Week: the Italian show

As the national association for the development of biotechnology and the Italian partner of the event organized by EuropaBio to celebrate the 60th anniversary of the discovery of the DNA molecule, Assobiotec was the promoter of 35 European Biotech Week initiatives throughout the Country including debates, art workshops, theatre performances, panel discussions, and a full day of Open Doors which also saw the participation of 14 companies operating in this innovative and vibrant sector (Figure 3.21).

The Italian EBW programme has been able to involve about 2,500 participants in various events, including students, teachers, children, parents, as well as the representatives of the entrepreneurial and financial community, together with universities, public institutions and the media.

A journey into the world of biotechnology through the expertise and experiences of researchers and entrepreneurs, to tell the extraordinary interest and allow a better understanding of the world we live in both for the scientific community and for society.

The Italian programme ventured on different paths, just to stimulate, in many ways, the curiosity of a broad and extremely heterogeneous public in terms of experience, skills, interests and expectations.
The common thread of this adventure was the opportunity to learn and understand the role of biotechnology in many aspects of our lives, including healthcare, agriculture, food, up to environment safety, waste reductions or the industrial applications of these techniques.

Beyond several scientific events, focusing on the impact of biotech research and on the prospects of the bio-economy itself for the establishment of a new model of sustainable development, the Italian programme also included a number of extremely relevant aspects relating to the experience of biotechnology in every-day life, both form a cultural and social point of view.

Besides the main topics relating to the power of science and the relationship between science and society, which were dealt with on a theatre stage, a different concept of training, geared to the skills and capabilities associated with biotechnology and aimed at providing new qualified professional opportunities for the young generations, was also addressed.

Dedicated meetings with the many young talents from the Italian universities were alternated by open debates in which the various healthcare, economic, ethical or social issues related to the development and the availability of advanced therapies for the treatment of unmet medical needs or rare disease, were discussed in an direct and responsible manner among students, scientists, practitioners and patients. All of this being followed by exhibitions, itinerant scientific laboratories, open days on research facilities, which really allowed adults and children to get closer to biotechnology as a reality that deserves to be better known and understood.

The Italian edition of the European Biotech Week received the High Patronage of the President of the Republic, the Senate, the Chamber of Deputies and the Presidency of the Council of Ministers, as well as the endorsement of the Italian Regions,

Figure 3.21

European Biotech Week - Events in Italy

Provinces and Municipalities. A significant number of universities, science and technology parks, schools, museums, theatres, cultural associations and scientific foundations gave their crucial contribution to the success of the entire programme.

We wish that this 1st ever Biotech Week in Italy has contributed to increase public awareness both on the positive impact that biotechnology will increasingly have on all aspects of our life, and the key contribution of the Italian biotech industry to the entire economy of our Country, in terms not only of competitiveness and growth but also of skilled employment opportunities for future generations. In this spirit we are really looking forward to European Biotech Week second edition, in October 2014.

Red biotech

Healthcare biotechnology has a tremendous impact on meeting the needs of patients. It not only encompasses medicines that are manufactured using a biotechnological process, but also gene and cell therapies, and tissue engineered products. Also in Italy red biotech is the spearhead segment of the entire sector, with more than 240 companies and an increasing number of projects addressing diagnosis and therapy, which are aimed at optimizing the entire pathway of care both from a clinical and economic point of view.

Table 4.1

Key data relating to the red biotech sector, details on OECD and pure biotech companies (Source: EY)

Red biotech	2013 Report*		2014 Report	
	Total biotech	Pure biotech	Total biotech	Pure biotech
Number of companies	244	148	241	145
Total turnover	€ 6,618 million	€ 1,153 million	€ 6,662 million	€ 1,174 million
Total investment in R&D	€ 1,351 million	€ 367 million	€ 1,382 million	€ 366 million
Total R&D employees	5,345	1,474	5,217	1,416

** Data have been rectified to make sample comparison possible.*

The firms active in biotechnology applied to human health amount to 57% of the total number of biotech companies; besides representing numerically more than half of the Italian biotech industry, they also account for a significant proportion of the total turnover and the investments of the entire sector.

The number of red biotech companies is slightly lower compared to 2013: the loss of eight companies (six of which were pure biotech companies) has not been offset by the four new entries and the fact that one other company has expanded its business activity in the red field. As already highlighted in the previous year, we are witnessing a shrinking, which reflects the extremely challenging economic framework that many of our micro and small pure biotech companies are coping with, as well as the difficulties they continue facing in sourcing venture capital.

Beyond their contribution in terms of investment and revenues, red biotech companies have significantly grown their product pipeline and have provided the entrepreneurial and financial community with a number of true success stories – Okairos, EOS, Silicon BioSystems, just to name a few – which, as well as being the expression of the outstanding results that may arise from the fruitful synergy of entrepreneurial skills, forward-looking investments and scientific expertise, also remind us that there is much we can do in order to fully exploit the innovation potential of Italian biotechnologies.

The total number of firms active in the red biotech field is 241 (Table 4.1), 81% of which is made up of companies dedicated exclusively to human health; the remaining 19% consists of multi-core

companies operating in more than one area of application, although the vast majority of these are active in GPET applied to human health.

The analysis by type of company clearly shows that the largest part of the red biotech sample is represented by pure biotech companies (60%), while the Italian subsidiaries of multinational companies make up 17%, other Italian biotech companies 17% and the Italian pharmaceutical companies 6% (Figure 4.1).

The total turnover of red biotech in 2012 amounts to € 6,662 million, showing a marginal increase (0.7%), compared to 2011. Most of the revenue is attributable to the Italian pharmaceutical companies and to the multinationals' subsidiaries in Italy: representing 23% of the number of companies, they constitute 82% of total sales, compared with 18% originating instead from pure biotech companies (Figure 4.2). Once again, the red biotech sector maintains its leading role in the entire biotechnology industry, accounting for 95% of the total turnover.

With reference to the companies' geographical distribution, the northern and central Italian regions are those in which the largest number of enterprises active in the red sector is concentrated (Figure 4.3). Lombardy remains the region with the largest number of companies active in human health biotechnology (83), followed by Latium, Piedmont and Tuscany (24 each). However, Lombardy is also the region which is most affected by the sample changes, with a reduction of four firms.

Figure 4.3

Red biotech companies: analysis by geographical distribution (Source: EY)

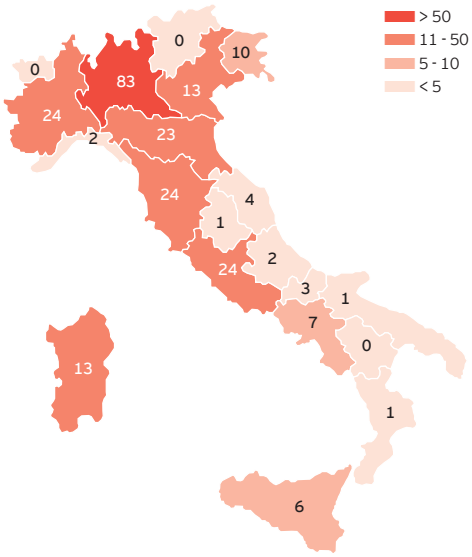


Figure 4.1

Red biotech companies: analysis by type (Source: EY)

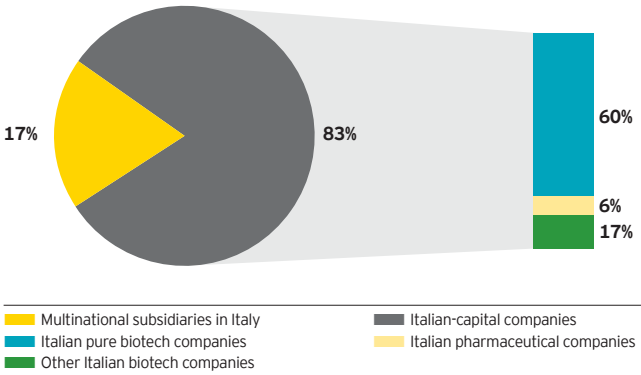
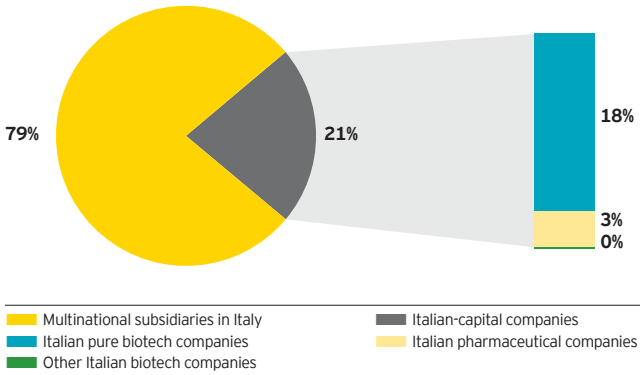


Figure 4.2

Red biotech companies: analysis of the 2012 turnover by type (Source: EY)



Red biotech

Figure 4.4

Red biotech companies: analysis by origin (Source: EY)

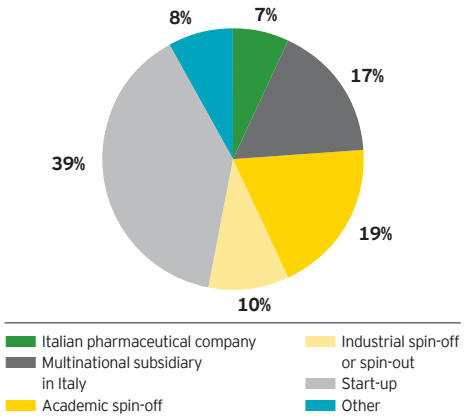
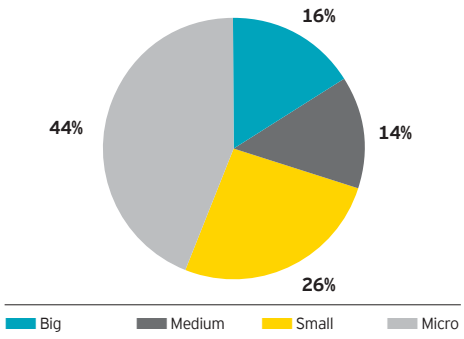


Figure 4.5

Red biotech companies: analysis by size (Source: EY)



Among the four newly founded companies, one was established in Lombardy, one in Emilia Romagna, one in Latium and one in Campania.

With regard to their origin, 39% of companies operating in the red biotech field originate from start-ups, 17% from Italian subsidiaries of multinational companies, 19% from academic spin-offs, 10% from industrial spin-offs or spin-outs and 7% from Italian pharmaceutical companies (Figure 4.4).

Consistently with the above, the analysis by size (Figure 4.5) shows that 70% of companies active in the red biotech field have fewer than 50 employees, while 14% of them are of medium size (between 50 and 250 employees) and 16% are big companies (more than 250 employees).

The considerable percentage of micro-sized companies in a start-up phase reflects one of the main features of the entire Italian biotech sector, as well as the need to support its further development and competitiveness by recognising the role and the legal status of these Young Innovative Companies through adequate financing and fiscal policies.
This was the purpose of the so-called Growth Act 2.0, adopted by the Italian Government in late 2012, which involves a range of specific provisions to help innovative start-ups in their first four years of activity.
The measures set out to simplify corporate governance and labour laws in accordance with the companies' needs, while also facilitating access to new channels of investment and, in particular, to the venture capital market.

Red biotech still makes a 91% contribution to total R&D investments of the entire Italian biotech industry, for an amount of € 1,382 million, with a 2.3% increase compared to the previous year.
In 2012 too, despite the marginal increase with reference to revenues, the share of turnover invested in R&D still represents 21% of total sales, thus confirming the clear commitment of the Italian red biotech companies in fully pursuing their research projects.

When breaking down the R&D investments per type of company, pure biotech companies represent 26% of total (Figure 4.6), compared to 73% of pharmaceutical companies (39% Italian pharmaceuticals, 34% Italian subsidiaries of multinationals companies), but the incidence of their

Figure 4.6

Red biotech companies: analysis of 2012 R&D investments by type (Source: EY)

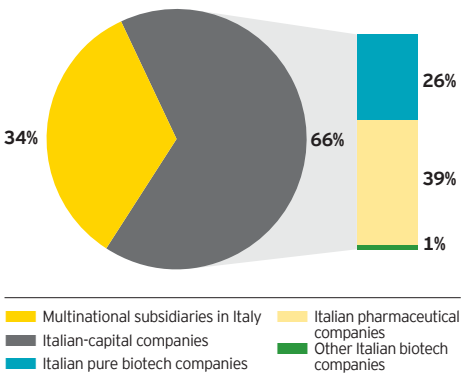


Figure 4.7

Red biotech companies: analysis of financing sources in year 2012 (Source: EY)

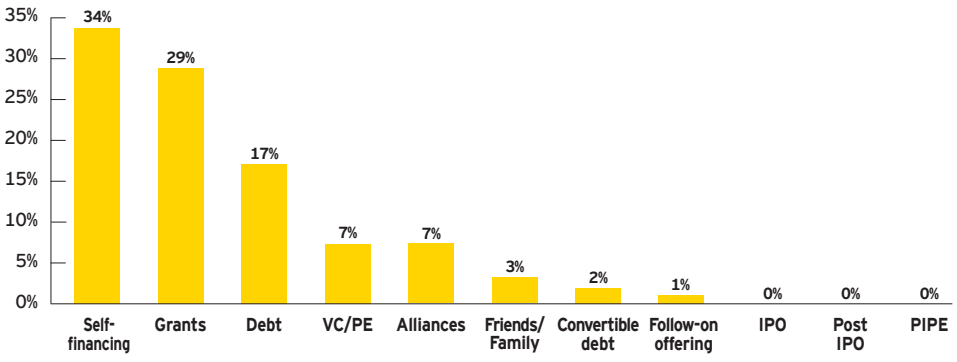


Figure 4.8

Red biotech: analysis by origin, comparison between Italian pure biotech and pharmaceutical companies (Source: EY)

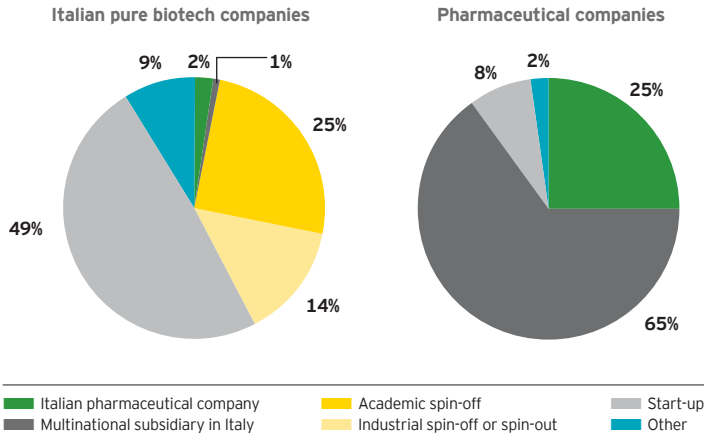
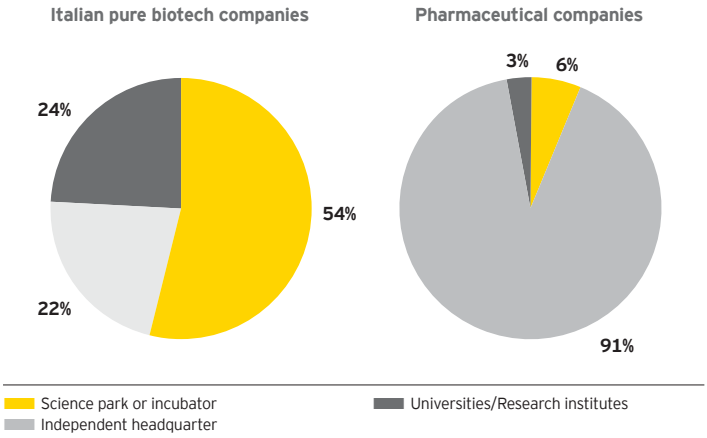


Figure 4.9

Red biotech: analysis by location, comparison between Italian pure biotech and pharmaceutical companies (Source: EY)



investment on turnover is higher (31%) compared to that of pharmaceutical companies (21%).

In order to support their R&D activities, red biotech companies draw upon different sources of funding.

About one third of the companies which answered our questionnaire claimed to use self-financing forms, almost 29% said that in 2013 they had received public grants, 17% resorted to debt and 7% to venture capital or private equity funding, as well as to strategic alliances (Figure 4.7). Convertible debt (2%), follow-on offerings (1%) and friends and family seed funding (3%) only played a marginal role.

It is worth noting here, as a general comment, that the companies' answers to the questionnaire highlight the clear difficulty in accessing both public and private funding, despite the fact that the availability of adequate financial resources is a key prerequisite in order to pursue long-term research objectives.

Pure biotech and pharmaceutical companies

According to our methodology, the distinction between pure biotech companies and pharmaceutical companies is based on their core business. Pure biotech companies are focused on the development of new therapeutic or diagnostic products exclusively based on biotechnology whilst for pharmaceutical firms, albeit included in the broader OECD definition of biotech companies, the development of biotech drugs is complementary to the development of more traditional synthesis products.

Moreover, looking at their respective R&D pipelines, while the pure biotech companies are heavily involved in the early stages of the R&D process (particularly discovery and pre-clinical development), pharmaceutical companies are mainly active in the subsequent clinical and regulatory development stages, leading to the commercialization of the product.

This complementary nature of roles, and the relevant flow of know-how and sharing of expertise and resources, is the true strength of the sector, and leads to the creation of extensive networks and clusters of all potentially involved players, including universities, pure biotech and big-pharma companies, national and supranational regulatory and government bodies, and the financial community.

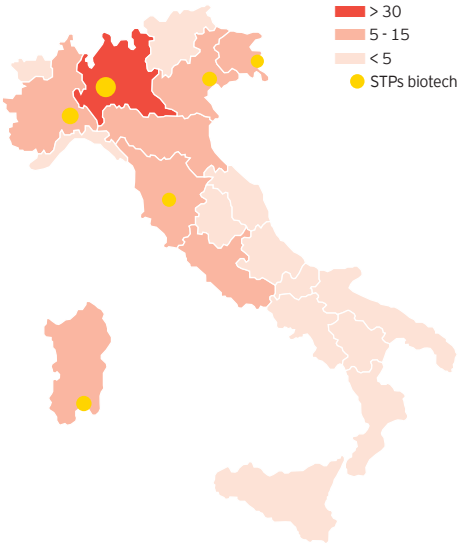
With particular reference to the origin of companies, about half (49%) of the pure biotech companies are formed as start-ups, 25% as academic spin-offs and 14% as industrial spin-offs or spin-outs. Conversely, 65% of pharmaceutical companies are subsidiaries of multinational groups, and 25% Italian pharmaceutical companies (Figure 4.8).

With regard to their location, almost all of the pharmaceutical companies have autonomous headquarters (91%), whilst more than half of the pure biotech companies operate within science parks and incubators, 24% at universities or within clinical centres or research institutions (Figure 4.9).

Red biotech

Figure 4.10

Localisation of micro and small Italian pure biotech companies and STPs (Source: EY)



Once again, the analysis of the location of micro or small pure biotech companies shows a clear correlation between their size and their proximity to science parks or incubators (Figure 4.10). Indeed, the regions with the highest concentration of micro and small pure biotech companies, such as Lombardy, Piedmont, Tuscany, Veneto, Friuli Venezia Giulia, Emilia Romagna, Tuscany, Latium and Sardinia, are those which host science parks or incubators.

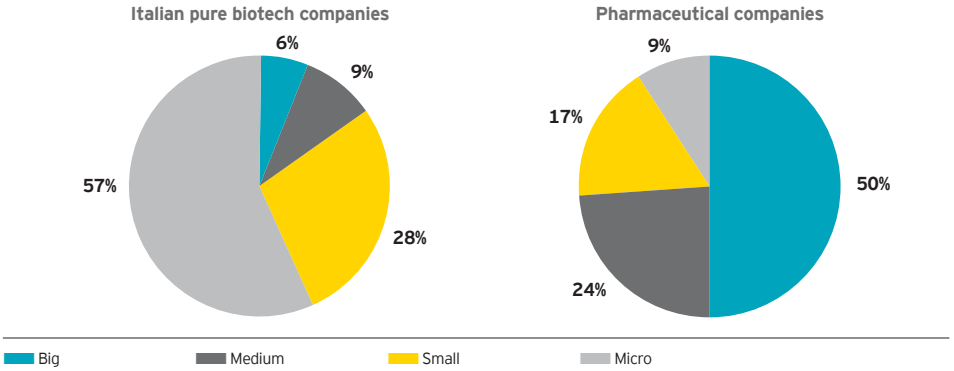
As expected, the analysis by size shows that the Italian pure biotech companies are mostly of micro or small size (85%), while the majority of pharmaceutical companies (74%) are big or medium-sized (Figure 4.11).

Furthermore, the ratio between employees in R&D and total employees (Figure 4.12) shows that the Italian pure biotech companies have a percentage of R&D employees (20%) which is higher than that of pharmaceutical companies (11%).

Based on the information provided by those companies that answered our questionnaire, revenue forecasts for the financial year 2013 are extremely prudent compared to the past. (Figure 4.13).

Figure 4.11

Red biotech: analysis by size, comparison between Italian pure biotech companies and pharmaceutical companies (Source: EY)



Indeed, with regard to pure biotech companies, the very large majority of them (92%) anticipate nothing more than stable results, whilst the minority expect either a growth (4%) or a contraction in turnover (4%). With regards to pharmaceutical companies, 79% of them would not go beyond stable results; 11% of them expect a growth and 10% a decline in revenues.

The envisaged perspective clearly reflects the financial and market uncertainties that the entire sector is facing, as well as the urgent need, for red biotech firms too, of adequate measures to create more favourable conditions in terms of available capital, as well as to remove the many regulatory and legislative hurdles that limit, delay or sometimes even prevent access to innovation, imposing on pharmaceutical companies economic restraints whose only goal is that of curbing public spending.

The red biotech companies' activities were segmented based on the different fields of application according to EY methodology (see Chapter 9 – Methodology – for definitions).

Figure 4.12

Analysis of total employees and R&D employees, comparison between Italian pure biotech and pharmaceutical companies (Source: EY)

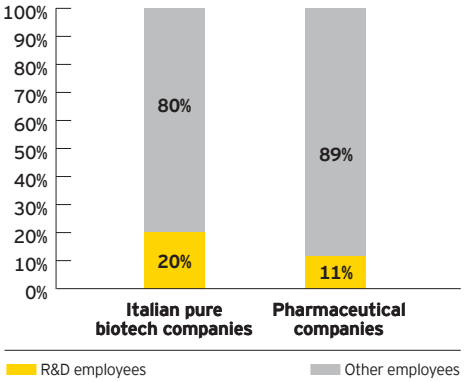
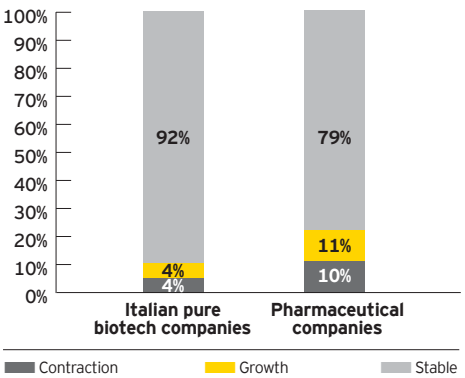


Figure 4.13

Red biotech: estimated turnover for 2013 (Source: EY)



Diagnostics

In modern medicine, diagnosis is an integral part of the treatment of any disease. This is even more true in the case of biotechnological diagnostics, which represents a significant branch of biomedical research, aimed at developing new methods and analytical tools based on molecular biology, genetics, nanotechnology, immunochemistry, and epigenetics.

Besides typing the disease, these new diagnostic tools allow the optimization of the entire pathway of care, both from a clinical and economic point of view. Indeed, the benefits of an early and precise diagnosis are tangible not only for patients, in terms of immediate and appropriate intervention, but also for the entire economic pattern, with reference to avoiding the much higher expenses the health care system would inevitably bear in order to control the worsening of the patient's conditions.

Furthermore, an increasingly accurate and sophisticated diagnostic approach, with a predictive and prognostic value, allows the physician not only to correlate the diagnosis to therapeutic regimens specifically targeted to the characteristics of the patient, but also the continuous monitoring of their effectiveness.

The development of advanced diagnostics has undergone strong acceleration in the last few decades: the new analysis techniques allow the detection of diseases until now unconceivable, and efforts are being made to fill the gap between their super-advanced diagnosis and the development of new therapeutic tools for their treatment. In this context, the study of epigenetics is fundamental.

The term "epigenetics" refers to those chemical modifications which intervene in a cell, leading to stable, long-term - not necessarily heritable - alterations in the transcriptional potential of that cell.

The term also refers to the changes themselves: functionally relevant changes to the genome that do not involve a change in the nucleotide sequence. Examples of mechanisms that produce such changes are DNA methylation (methylome) and histone modification (modification of proteins that, complexed with DNA, form the chromatin), each of which alters how genes are expressed without altering the underlying DNA sequence. For instance, DNA methylation is an important regulator of gene transcription and a large body of evidence has demonstrated that aberrant DNA methylation is associated with unscheduled gene silencing or expression, and consequently with a large number of human malignancies.

Unlike simple genetics based on changes to the DNA sequence (the genotype), the changes in gene expression or cellular phenotype of epigenetics have other causes. Lifestyle, stress, drugs, physiopathological situations and pharmacological interventions have a great impact on the epigenetic code of the cells by altering the methylome, miRNA (microRNA) expression and the covalent histone modifications.

Thus, epigenetics has recently emerged as a new and promising field, related to the possibility to use the epigenetic modifications as tools (biomarkers) for different purposes: investigating the medical condition of the patient, identifying a diagnosis and figuring out which factor gene is going to affect the patient's health, and even monitoring the effectiveness of an on-going pharmacological therapy.

Based on the need to find new biomarkers for several diseases and improve their diagnosis, the research on epigenetic biomarkers for molecular diagnostics encourages the translation of this field from the bench to clinical practice. In this context, deciphering intricate epigenetic modifications involved in several molecular processes is the challenge to be met in the near future.

Currently, some techniques are available for epigenetic studies (i.e. high-throughput technologies and laboratory), thanks to the discovery of some promising epigenetic biomarkers to be used in the clinical diagnostic laboratory, in particular in the case of a number of specific cancer diseases (lung, colorectal and prostate), as well as of new pharmacological targets with potential therapeutic applications.

The Food and Drug Administration recently approved, for the first time, two molecules that act directly on DNA methylation, and which can be used for the detection of specific blood cancers. Many other epigenetic drugs are at an advanced stage of study: these include valproic acid, a well-known antiepileptic drug which recently proved to be effective on epigenetic modifications.

Moreover, epigenetics provides an opportunity to forge ahead with an understanding of rare diseases; these rare syndromes are paradigms for a specific impaired molecular pathway, thus providing valuable information on the discovery of new epigenetic biomarkers - Sandoval J et al, Expert Rev Mol Diagn. 2013 Jun;13(5):457-71. It is therefore clear that epigenetics is more than an interesting and promising area of biomedical research as it is already providing us with attractive results.

Red biotech

The total number of companies active in the biotech diagnostic field is 75, thus accounting for 31% of the entire red biotech segment, with a positive trend compared to 2012, as four companies have extended their business in this area and an additional one was newly established in the course of 2013.

The large majority of diagnostic companies (70%) are pure biotech companies, whilst multinationals' subsidiaries and other Italian biotech companies account, respectively, for 12% and 17% of the sample (Figure 4.14). Italian pure biotech companies also contribute most of the turnover, which stands at € 611 million. As regards investments in R&D, these are estimated at € 147 million, while the number of employees dedicated to research activities amounts to 692.

Analysing the companies by size, it can be seen that more than 74% have fewer than 50 employees and consequently fall within the category of micro or small enterprises, while more than 7% are classified as big. With regard to their geographical distribution, the northern and the central regions still remain the most attractive areas (Figure 4.15)

As a general comment, in Italy too, biotechnology diagnostics constitute one of the most lively and dynamic segments in the Life Sciences industry, and an interesting space for VC investors. Indeed, optimally focused diagnostics ventures require much lower up-front investments than do traditional biotech enterprises to reach revenue generation, thus reducing the amount of investment required to achieve an exit strategy for investors. Furthermore, the time needed for the development of diagnostic products is normally shorter than that required for drugs, and the regulatory process too can be simpler and more straightforward.

2013 was also marked by the acquisition of Silicon Biosystems, one of the leading Italian diagnostics companies, by the Menarini Group.

The genomic analysis technologies developed by Silicon BioSystems are being used in clinical research to advance the development of cancer diagnostics and accelerate the age of precision medicine through personalized therapies, and will contribute to Menarini's pharmaceutical and biotechnology programmes in oncology.

The acquisition presents Silicon Biosystems, which is expected to operate as a stand-alone entity, with the opportunity to capitalize on the infrastructure and business synergies within the Menarini Group, and obtain the support and resources needed to continue developing the technologies and expand their use to clinical markets.

Figure 4.14

Diagnostic companies: analysis by type (Source: EY)

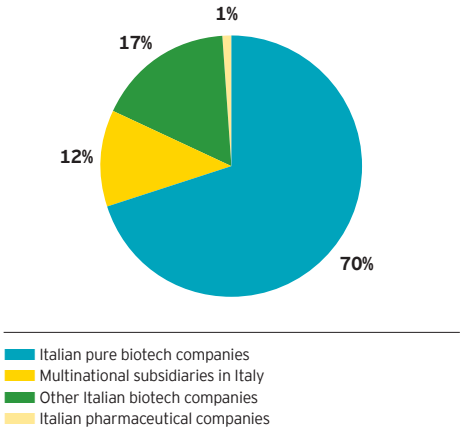
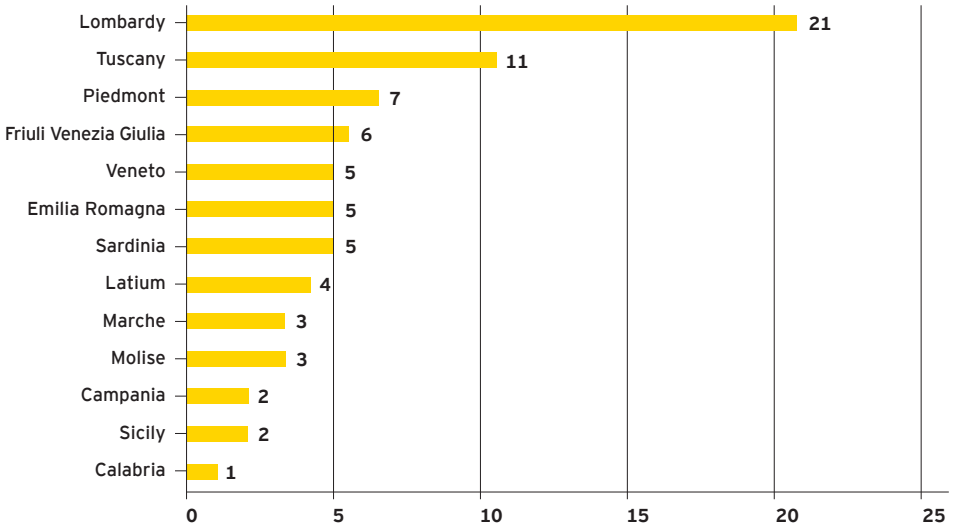


Figure 4.15

Diagnostic companies: analysis per geographical distribution (Source: EY)



Advanced Therapies

Advanced therapy medicinal products (AT) include different new generation therapeutic interventions defined as gene therapy, cell therapy and tissue engineering, and represent one of the most promising red biotech segments in terms of innovation and therapeutic progress.

Though an often debated topic, particularly with regard to stem cell applications, there is no doubt about the fact that AT open a radically new perspective for the cure of a number of unmet and radically disabling medical needs.

The availability of adequate biological resources, such as cells, tissues or biomolecules, is a key prerequisite for the development of new AT projects; bio-banks are therefore a strategic resource for those R&D companies which need access to samples, data and scientific or medical expertise.

In this framework, a winning example is the public-private partnership of the pan-European Biobanking and Biomolecular Resources Research Infrastructure (BBMRI), which besides expanding the accessibility and interoperability of the existing biological collections and the attached data, combines expertise of clinicians, pathologists, bioinformaticians and molecular biologists.

This project is aimed at facilitating access to and optimization of resources, as well as harmonizing procedures and fostering high-level collaboration. The ultimate goal is to develop personalised medicine and to increase disease prevention for the benefit of all European citizens.

The companies developing products for advanced therapies total 37, representing 15% of the total number of red biotech firms. Sixty per cent of the companies working in the AT field are Italian pure biotech, 24% Italian subsidiaries of multinational companies, 8% Italian pharmaceuticals and 8% other Italian biotech (Figure 4.16).

With regard to their size, more than half of the companies that operate in AT fall into the category of micro and small enterprises (62%).

Considering the total turnover of the 37 companies active in AT, this amounts to € 1,019 million whilst R&D investments account for € 356 million. The number of R&D employees totals 1,678. All these figures are pretty much in line with those of the previous year.

The analysis by geographical distribution (Figure 4.17) further confirms that Lombardy is the region with the highest number of AT companies (13), immediately followed by Emilia Romagna (7) and Latium (5).

Figure 4.16

Advanced Therapies companies: analysis by type (Source: EY)

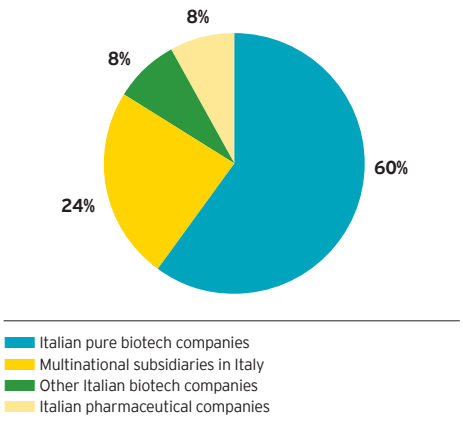
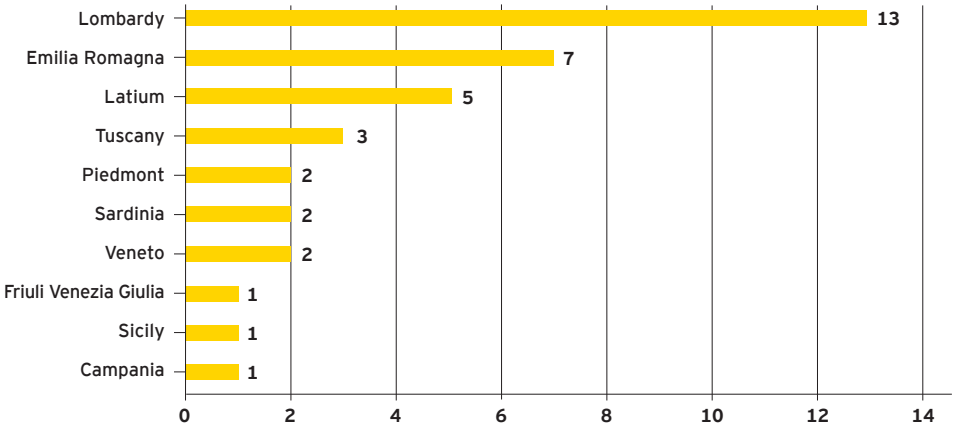


Figure 4.17

Advanced Therapies companies: analysis per geographical distribution (Source: EY)



What has to do Asimov's Fantastic Voyage with Nanotechnology?

Nano-history of nanotechnology.
The term "nanotechnology", coined by Norio Taniguchi in 1974, refers to man-made devices (a craft or "techne", from the Greek) whose size is measured in nanometres (billionths of a metre), devices comprising just a handful of atoms or whose basic components are of nanoscopic dimensions.

Essential forerunners of the world of nanotechnology are several strands of technological and scientific development (microelectronics, liposomes, the study of ultrafine particles and colloidal solutions, etc.) along with the vision of great innovators like the winner of the Nobel Prize in Physics, Richard Feynman, who made the famous *"There is Plenty of Room at the Bottom"* speech at the Californian Institute of Technology (Caltech) in 1959, like the legendary entrepreneur Gordon Moore, co-founder of Intel (*"Moore's Law"* – 1965) and like the writer Isaac Asimov (book and film *"Fantastic Voyage"*, winner of seven Oscars).

Nanotechnology takes its place in the Olympus of scientific and technological achievement with the winners of the 1996 Nobel Prize in Chemistry, Rick Smalley, Bob Curl and Richard Kroto, for their discovery of fullerenes (Carbon 60), with the development of technologies for the manipulation and microscopy of single atoms, a field which earned Heinrich Rohrer and Gerd Binnig the Nobel Prize in Physics in 1986, and, more recently, with the development of research on graphenes by Andre Geim and Konstantin Novoselov, winners of the 2010 Nobel Prize in Physics.

As regards nanomedicine, clinical use of nanopharmaceuticals began in the 1980s in the treatment of cancer. Here, too, Italy has made its mark; the first nanopharmaceutical, a lipid nanoparticle (liposome) delivered with doxorubicin and still widely used in oncology departments all over the world, was introduced at the Istituto Nazionale Tumori in Milan by the great Italian oncologist Gianni Bonadonna in collaboration with another Milan-based institution, the *Mario Negri* Pharmacological Research Institute.
The pharmaceutical use of liposomes, on the other hand, is the fruit of work by teams of scientists and entrepreneurs, like Dimitri Papahadjopulous, Nick Arvanitidis and Frank Szoka in Silicon Valley, and Chezy Barenholz and Alberto Gabizon in Israel. In 2003-2005, in the wake of these successes, the US National Cancer Institute launched the first government-supported international nanotechnology programme. It was, for me, an extraordinary privilege to participate in the development and launch of this initiative at a time of great oncological innovation spearheaded by the then director of the National Cancer Institute, Andrew von Eschenbach, another man of Calabrian origin.

Nanomedicine in the clinic.
Various classes of nanopharmaceuticals, most of them developed in the United States, are already being used in hospitals, especially in the treatment of cancer. The value of the world nanopharmaceutical market has, since 2009, always topped $ 5 billion a year, making nanomedicine the third driving force in the pharmaceutical industry, right behind synthesis drugs and biotechnologies but with a significantly higher growth rate.

Liposomes, approved nearly 20 years ago in both the United States and Europe, and used principally in the treatment of cancer, are the main class of nanopharmaceuticals in widespread clinical use. Then come the nanocrystalline

drugs deriving from technology developed by an Elan group company headed by Eugene Cooper. These boost the therapeutic effectiveness of pharmaceuticals already present on the market and used in various fields of medicine. The most widely used nanodrug is currently Abraxane, with a market estimated at around $ 1 billion a year; it is made up of nanoparticles of albumin-bound paclitaxel (taxol) and is used in the treatment of advanced cancer of the breast, ovary and pancreas.

The first nanoparticle used for therapeutic purposes but classified as a medical device and not as a drug was developed in Germany by Andreas Jordan, founder of Berlin-based MagForce AG, and has been approved in Europe for the magnetic-field-induced thermal ablation of brain tumours. It is estimated that, worldwide, there are now around 50 new drugs being clinically developed; particularly promising are nanoformulations with biotechnological active ingredients, therapeutic vaccines for cancer treatment, and gene therapies based on the principal of RNA interference.

Prospects for nanomedicine.
Even in the short term (5-10 years), the scope of opportunity for nanobiotechnologies in medicine is extremely broad and very promising. Practically every university carrying out its own research has laboratories and ongoing projects in the field. Various leading pharmaceutical companies, such as Johnson & Johnson and Celgene, are marketing nanomedicine-based products. NASDAQ-listed nanopharmaceutical companies (Alnylam, for example) are now worth billions of dollars and have, in some cases, seen rapid surges in their market value. One such case is Arrowhead Research Corporation. With the announcement of the positive results of Phase I testing of its new nanodrug for the treatment of hepatitis B, now in Phase 2a, Arrowhead Research became the fastest-growing NASDAQ-listed company in 2013. Hundreds of other spin-offs and start-ups are now operating in the nanomedical sector, not only in North America and Europe but also in several Asian countries.

Governments in all of the world's most advanced nations have, in fact, initiated research and development programmes in the sphere of nanomedicine. Italy, too, boasts cutting-edge laboratories and has seen the recent birth of a number of spin-offs. However, in order to enable these forward-looking enterprises to achieve their full potential and transform their research into ground-breaking treatments, we need to foster the best possible conditions for their development and competitiveness. In fact, we risk lagging behind in the nanodrug race as a result of the numerous and chronic problems with which Italy is still struggling: the grave shortage of public funding for research, particularly in multidisciplinary sectors like that of nanomedicine; the almost total lack of venture capital and specialized venture capital investors; tax levels that do not encourage investment; enormous bureaucratic difficulties that still make life very difficult and negatively impact the competitiveness of Italy's high-tech entrepreneurs.

Mauro Ferrari, Ph.D.
President and CEO of The Methodist Hospital Research Institute (TMHRI), Ernest Cockrell Jr. Distinguished Endowed Chair at THMRI; Executive Vice President Houston Methodist Hospital, Houston Texas; President, The Alliance for NanoHealth; Professor of Biomedical Engineering in Medicine - Weill Cornell Medical College of Cornell University, New York.

Table 4.2

Product analysis by development phase (Source: Assobiotec)

	Italian-capital companies				
	Pure biotech companies	Pharmaceutical companies	Other biotech companies	Foreign-capital companies	Total products
Preclinical	87	8	7	6	108
Phase I	17	6	1	22	46
Phase II	37	13	0	76	126
Phase III	8	3	0	112	123
Total	**149**	**30**	**8**	**216**	**403**

Figure 4.18

Product analysis by type of company (Source: Assobiotec)

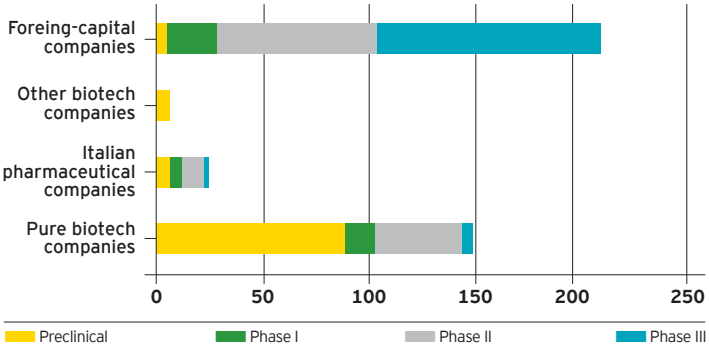
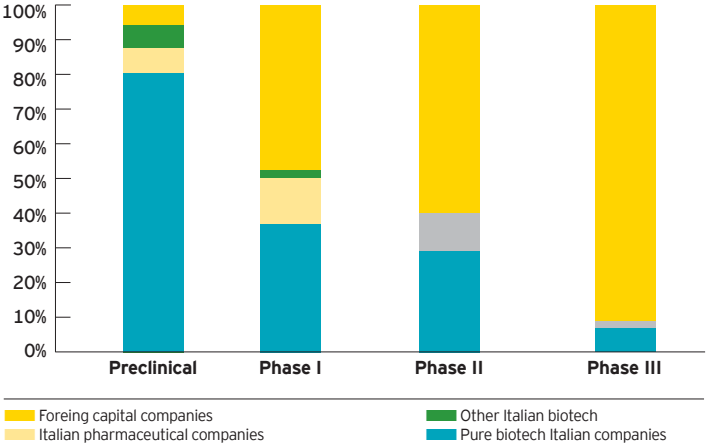


Figure 4.19

Product analysis by type of company a development phase (Source: Assobiotec)



Therapeutics: focus on the Italian pipeline

Analysis by development phase

As in other countries, biotech drugs are the spearhead segment not only for the red sector but for the entire Italian biotech industry. Research into innovative drug therapies to address the growing demand for healthcare in an increasingly more targeted and safer way involves a wide-ranging network of excellence that starts with academic laboratories and no-profit research centres - veritable powerhouses of cutting-edge innovation – and goes on to include academic or industrial start-ups through to pharmaceutical companies.
It is from the joint collaboration of all these parties, using the open innovation models typical of leading-edge research systems, that single projects are created and develop, increasing in value as they approach the market.

In addition to more than one hundred laboratories, which include public research institutes and universities and 47 IRCCS – Scientific Hospitalization and Care Institutions - the Italian biotech chain consists of 176 companies.
For some of these it was possible to trace the project and product development pipeline; more specifically, 55 Italian pure biotech companies, 7 Italian pharmaceutical companies, 21 Italian subsidiaries of multinational companies (foreign-capital companies) and 3 other Italian biotech companies, for a total of 86 companies.

With 44 more drugs than last year, the Italian biotechnology pipeline includes a

total of 403 drugs under development (preclinical and clinical phases); of these, 216 are from foreign-capital companies and 187 from Italian-capital companies, of which 149 from pure biotech companies, 30 from pharmaceutical companies, and 8 from other Italian biotech companies (Table 4.2). Additional 67 projects are still in the discovery phase, some of which originate from the laboratories of Italian subsidiaries of multinational groups.

Analysing the different projects in relation to their phase of development, 108 are in the preclinical phase (+11%), 46 in Phase I (- 8%), 126 in Phase II (+18%), and 123 in Phase III of clinical development (+17%). In detail, of the 11 additional drugs in the preclinical phase, 10 originate from pure biotech companies and 2 from Italian pharmaceutical companies; one drug that is the object of an agreement between NicOx and Merck & Co. Inc., whose phase of development has not been made public for confidential reasons and which belongs to a new class of controlled-release "NO-donating" molecules, has not been considered here.

Clinical trials are being conducted on 33 more drugs than last year, which is the difference between the highest number of trials conducted by Italian subsidiaries of multinational groups (+31) and by pure biotech companies (+4), and 2 drugs originating from Italian-capital pharmaceutical companies, one of which, a budesonide MMX formulation, was launched in 2013.

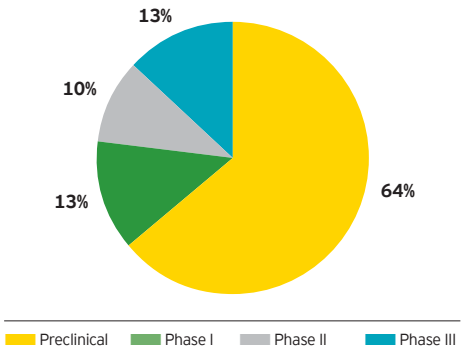
Analysing the companies' portfolios on the basis of their most advanced drug candidate, we can observe that over half of the companies (64%) have at least one drug in the preclinical phase, 13% are in Phase I, 10% in Phase II, and 13% have at least one drug in Phase III (Figure 4.20). The rising percentage of companies with at least one product in preclinical phase (64% in 2013 vs. 50% in 2010) is in line with the increased number of innovative start-ups and spin-offs in the biotech drug sector over recent years.

In 2013, the European Commission granted a marketing authorisation to the first product resulting from the research activity of the Italian pure biotech company: defibrotide is a life-saving drug used for the treatment of severe hepatic veno-occlusive disease (VOD) in haematopoietic stem-cell transplantation (HSCT) therapy. The molecule had already been recognised by the EMA and the FDA, as well as the KFDA (Korean Food & Drug Administration) as an "orphan drug" for the prevention and treatment of hepatic veno-occlusive disease.

Remaining on the topic of the contribution of pure biotech companies, 7 bio drugs entered Phase II in 2013, as well as a therapeutic vaccine for HIV.
Also in Phase II was VS411, a compound belonging to the class of first generation AV-HALTs (AntiViral-HyperActivation Limiting Therapeutics), which reduces HIV replication while strengthening natural immune defences. The work conducted on VS411 was fundamental for the development of a new class of Transcription Inhibitors (TIs), whose innovative mechanism of action is able to block viral replication, avoiding the onset of drug resistance.
The new class of TIs has an initial indication for the treatment of HIV/AIDS but has potential applications in the treatment of other viral infections, inflammation and in oncology.

Figure 4.20

Analysis of pure biotech companies by product in the most advanced development phase (Source: Assobiotec)



With regards to Phase III projects, the contribution of pure biotech companies accounts for 9 products, with a new subcutaneous immunoglobulin developed by Kedrion, which has successfully completed Phase II, and defibrotide from Gentium, which has recently obtained marketing authorisation.

Once again, the bulk of discovery and preclinical phase projects (80%) originates from the R&D activity of pure biotech companies, while foreign-capital companies are mainly involved in the advanced stages of clinical development, by supporting respectively 60% and 90% of Phase II and Phase III trials.

As for Phase I clinical trials, it is almost a fact that a substantial number of projects "expatriate" once they have concluded preclinical development. In fact, most of the studies aimed at testing safety and tolerability in man are outsourced to foreign specialized clinical institutions or CROs, which can provide levels of scientific and management expertise not yet available in Italy, due to a number of cultural, regulatory and administrative hurdles.

Table 4.3

Phase III product analysis - pure biotech companies (Source: Assobiotec)

Company Name	Product	Therapeutic area	Type of Product	Therapeutic indication	Orphan Drug Designation
Gentium S.p.A.	Defibrotide - prevention of VOD paediatric populations: treatment of VOD in adults.	Cardiovascular and Haematology	Natural Product	Sodium salt of an animal single-strand DNA complex. Defibrotide has protective effects on vascular endothelial cells particularly those of small vessels. It has extensive beneficial pharmacological effects, among which anti-thrombotic, anti-inflammatory and anti-ischemic properties. Recent clinical trials for the treatment of severe hepatic veno-occlusive disease (VOD) have confirmed the efficacy and lack of significant toxicity of the drug. Hepatic VOD is a potentially fatal complication of both allogenic and autologous stem cell transplantation. Clinical trials are aimed at determining the prevention of VOD in paediatric populations and the treatment of the disease in adults.	EMA - FDA - KFDA
Holostem Advanced Therapies S.r.l.	In vitro epidermis flaps	Dermatology	Autologous cell and gene therapy	In vitro epidermis flaps are indicated for the treatment of skin burns. Genetically modified epithelia, for the treatment of a form of Junctional Epidermolysis Bullosa, are also at an advanced phase of clinical development.	
Holostem Advanced Therapies S.r.l.	Holoclar (ex vivo corneal epithelial flaps)	Ophthalmology	Autologous cell therapy	The tissue engineered product is indicated for the treatment of corneal lesions, associated with limbal stem cells deficiency, an orphan disease without alternative therapies.	EMA
Kedrion S.p.A.	Immunoglobulin	Inflammation and autoimmune diseases	Natural Product	Immunoglobulins are antibodies that are also present in the blood. Subcutaneous administration of immunoglobulin is used to treating patients who do not have sufficient antibodies (replacement therapy), such as in the following cases: 1). patients with congenital deficiency of the production of antibodies (primary immunodeficiency syndromes); 2) patients with blood cancer (chronic lymphocytic leukaemia) that lead to a reduced production of antibodies (hypogammaglobulinaemia) and recurrent bacterial infections, that do not respond to antibiotic therapy; 3) patients with cancer of the bone marrow (multiple myeloma), with reduced production of antibodies (hypogammaglobulinemia) and recurrent bacterial infections, which do not respond to pneumococcal vaccination.	
Kedrion S.p.A.	SILKETAL	Metabolic, Hepatic, Endocrine disease and Surger	Natural Product	SILKETAL is a supportive treatment in surgery, where standard surgical techniques are insufficient, to reduce bleeding. SILKETAL is a tissue adhesive, based on fibrin glue, consisting of the two components, human fibrinogen and human thrombin. In the presence of calcium ions, thrombin converts fibrinogen into fibrin, with rapid formation of a clot that stops bleeding. Aprotinin is a stabilizer of the clot itself. In clinical trials performed in liver surgery, the application of SILKETAL has proved to be an effective haemostatic on the cut surface, contributing to the arrest of bleeding from the vessels and resulting useful in the prevention of bile leaks.	
Kedrion S.p.A.	Silketal	Respiratory	Natural Product	SILKETAL acts as an adhesive sealant or as a support for the sutures in lung surgery. Alveolar air leaks and bronco-pleural fistulas are the most frequent complication after lung resection surgery, and contribute significantly to morbidity and mortality associated with thoracic surgery interventions. In clinical trials, the use of SILKETAL has proved to be efficacious in reducing the duration of prolonged air leaks after lung resection surgery. The action of the fibrin glue mimics the final phases of physiological blood coagulation, which sees the conversion of fibrinogen into fibrin monomers that join together to form a clot.	
MolMed S.p.A.	TK – high-risk leukemias (TK008)	Oncology	Allogenic Cell Therapy	TK is a cell therapy product for the treatment of haematological malignancies, which provides for the treatment of patients undergoing haploidentical bone marrow transplantation with cells genetically modified ex vivo, to express a gene allowing prompt control and abrogation of the possible onset of Graft versus Host Disease (GvHD) reaction.	EMA - FDA
MolMed S.p.A.	NGR - hTNF - MPM, second line (NGR015)	Oncology	Recombinant Protein	NGR-hTNF is a recombinant biological drug for the treatment of solid tumours, which displays anti-tumour activity through its specific binding to blood vessels feeding the tumour mass.	EMA - FDA

Analysis by therapeutic area

The demographic structure and evolution of a population has a direct influence on its epidemiology and, as a result, on research priorities in the field of Life Sciences. The overall ageing of the population is, in fact, one of the main problems that health authorities in the Western world – and in Europe particularly – are having to come to terms with.

This applies to Italy especially where, as a result of its decreasing birth rate, the proportion of people over the age of 64 is gradually increasing. In 2012, the number of people over the age of 64 accounted for 20.3% of the population and this percentage is expected to rise to 33.1%[1] in 2050, also as a result of increased life expectancy. In a ranking drawn up by the United Nations[2], Italy is 5th in the world in terms of increased life expectancy and, in 2045-2050, will be 6th among the first 10 countries in terms of life expectancy at birth.

Among the main causes of death or disability, cardiovascular diseases rank first (220,000 deaths in 2010), and cancer second (175,000 deaths in 2010). These are followed, albeit at a greater distance, by deaths caused by diseases of the respiratory system (40,000 cases) and metabolic, hepatic, and endocrine diseases (26,000).

Over the past 30 years, due to the success of primary prevention measures allowing for early diagnosis of certain diseases, and the diagnostic and therapeutic progress which resulted from biotechnologies, the

1. Source: ISTAT, 'National Demographic Forecasts'
2. Source: United Nations, Population Division of the Department of Economic and Social Affairs, 'World Population Prospects: the 2012 Revision', August 2013

Figure 4.21

Analysis by therapeutic area and phase of development (Source: Assobiotec)

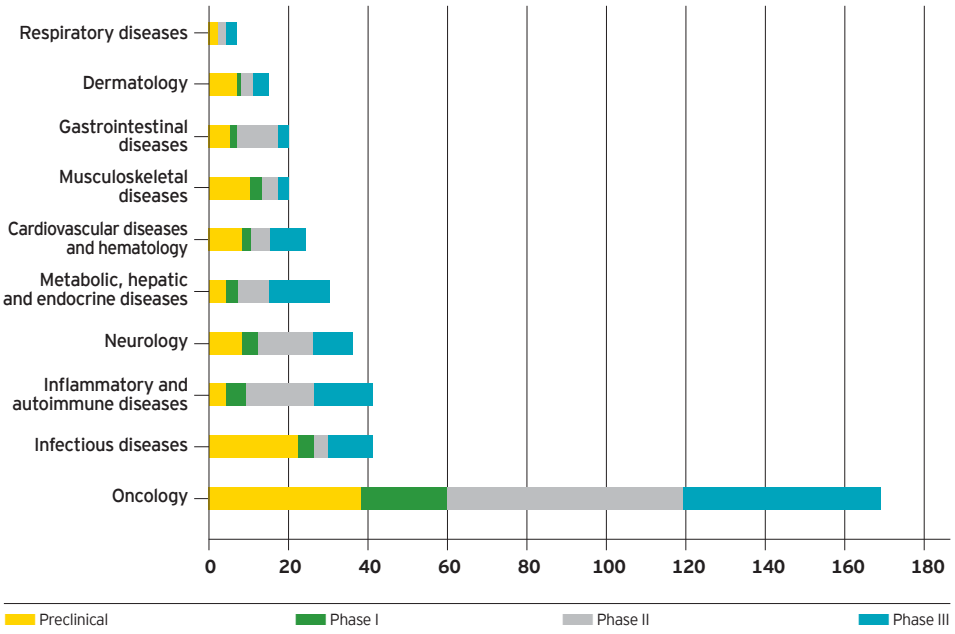
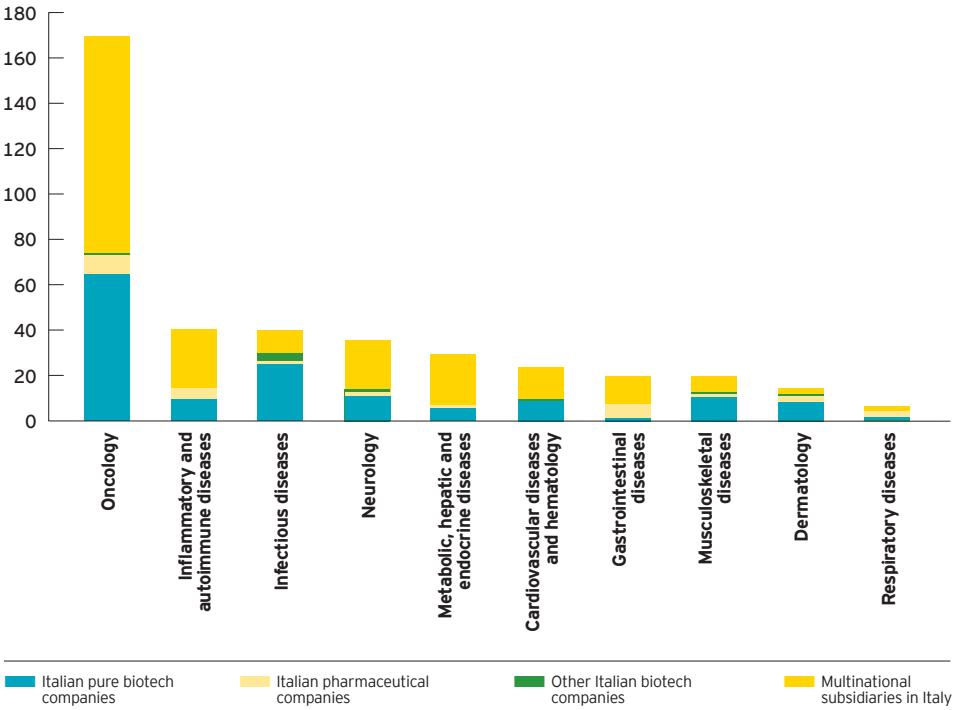


Figure 4.22

Analysis of products under development by therapeutic area and company (Source: Assobiotec)



number of deaths caused by cardiovascular diseases has fallen by 16%, despite an increase in deaths from tumours (+42% versus 1980) and from neurological, psychic and behavioural diseases[3].

It comes to no surprise therefore, that the entire Italian pipeline reflects the national epidemiological trend – which moreover follows the European trend – and that oncology is the therapeutic area with more than 40% of the drugs at a clinical development phase (Phase II and III, if biopharmaceutical companies are considered as a whole; Phase II if only pure biotech companies are considered), followed by inflammatory and autoimmune disorders (13% of the drugs), neurological diseases (9%), and by the group of metabolic, hepatic, and endocrine disorders (9%).

More specifically, development efforts carried out by pure biotech companies account for 10% of the clinical projects related the treatment of both ischemic (heart attack and angina pectoris) and cerebrovascular (stroke) diseases, which are among the most frequently-occurring arteriosclerotic diseases. Also noteworthy is the share of drugs for the treatment of diseases of the musculoskeletal system, more than 60% of which are under clinical development; 30% of these are for monoclonal antibodies, while another 30% are AT products, and regenerative medicine products in particular.

3. Source: Italian National Institute of Health, National Centre for Epidemiology, Surveillance and Health Promotion

Analysis by type of product

Approximately 45% of the projects that we were able to analyse are for biopharmaceuticals - or biotech drugs – which include, by definition, monoclonal antibodies (26%), recombinant proteins (10%), cell therapy (3%) and gene therapy (4%) drugs, and drugs for regenerative medicine (2%) (Figure 4.24).

This figure shows how the percentage of biopharmaceuticals has progressively increased from 36% in 2009 to 45% in 2013, versus the contribution small molecules (low molecular weight compounds), the percentage of which has fallen from 45% to 33%.

This trend also emerged from an analysis of the project pipeline broken down into type and development phase: as the development phase continues, the share of biotech drugs increases versus that of small molecules developed or selected using biotechnology screening methods.

Limiting the analysis to the clinical phases, biotech drugs with the highest number of trials are monoclonal antibodies; 80% of these studies are being conducted by foreign-capital companies and 15% by pure biotech companies.

Figure 4.23

Analysis by type of product and development phase (Source: Assobiotec)

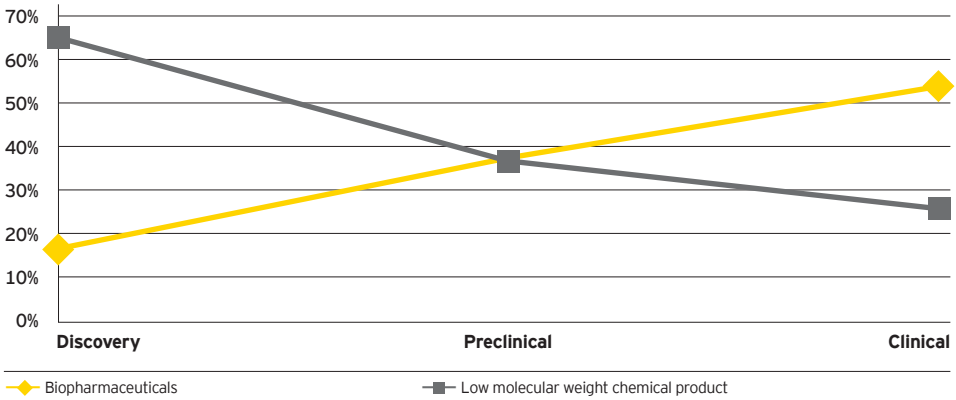


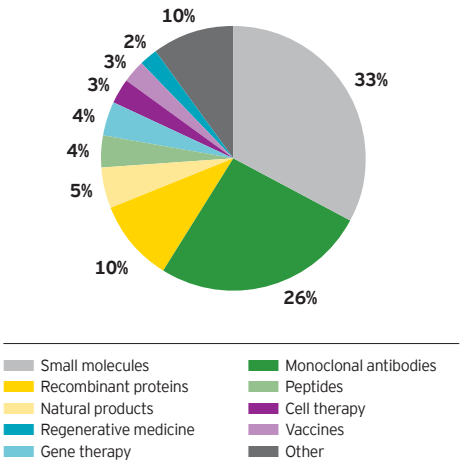
Table 4.4

Analysis of Orphan Drug Designations authorised (Source: Assobiotec)

		EMA	FDA	Both	Total
Italian-capital companies	Pure biotech companies	6	1	8	15
	Italian Pharmaceutical companies			3	3
Foreign-capital companies	Italian subsidiaries of multinational companies	4	6	19	29
Total		10	7	30	47

Figure 4.24

Analysis by type of product (Source: Assobiotec)



Orphan Drugs

Numerous biotech products fall under the definition of Orphan Drugs. This is a special category of drugs for the treatment of Rare Diseases that legislators encourage the development of, for ethical reasons, with special authorisations and price policies.

The Orphan Drug Designation (ODD) is issued by the international regulatory authorities (EMA in Europe, FDA in the USA) upon submission by the sponsor of an adequate documentation attesting that the product is intended for an indication where the prevalence of the condition is no more than 5 in 10,000 people. This indication must be associated with a disease that is life-threatening or seriously debilitating, and for which no satisfactory method of prevention, diagnosis or treatment has already been authorised; in the case a method is already available, the new drug will have to prove that it provides a considerable advantage compared to the already existing drug.

During our analysis, we were able to identify 21 Italian biotech companies that have received at least one ODD. There are 10 pure biotech companies, one Italian pharmaceutical company and 10 Italian subsidiaries of multinational groups, that together manage a portfolio of 47 products, 10 designated by the EMA, 7 by the FDA, and 30 by both regulatory authorities.

Compared to last year, the FDA has issued two more ODD's, whereas the number of products which obtained an ODD from both regulatory authorities has fallen by four (defibrotide for which Gentium recently received marketing authorisation for, is to be considered among these).

As for the number of products by type of company, 15 are from Italian pure biotech companies, 3 from Italian pharmaceutical companies and 29 from the Italian subsidiaries of multinational groups.

Most of these products are in the advanced phases of clinical development (4 in Phase I, 20 in Phase II and 20 in Phase III), while 3 are still in the preclinical phase.

As far as their indications are concerned, oncology is the therapeutic area with the highest number of products under development (26), followed by metabolic, hepatic and endocrine disorders (6), cardiovascular (4) and inflammatory (4) diseases.

Advanced Therapies

Advanced therapies have always received a great deal of interest, in scientific and regulatory terms. At this very moment, Europe is about to review the entire topic of Advanced Therapies and Regenerative Medicine and, more specifically, the ATMPs and the Cell&Tissue regulations, calling for the Member States to express their opinions on their interpretation and application.

One of the main points at the centre of discussions is the availability of appropriate preclinical evidence for testing on human beings. In particular, discussions centre on some preclinical tests built on animal models which are difficult or impossible to apply, due to the fact that AT preparations are often cell-based.

Despite continuous evolution in the regulatory framework, numerous companies are investing in what is now unanimously recognised as being one of the most promising sectors in medicine.

This is why it comes to no surprise that the number of projects for Advanced Therapies is raising constantly in Italy too.

The R&D efforts by the 18 AT companies whose pipeline we were able to analyse focus on allogeneic and autologous therapies, as well as on viral vectors and DNA vaccines, with the number of drugs under development rising from 32 to 40 over the past year (Table 4.5).
Among these, 13 are cell therapy products, 19 are gene therapy products, and 8 are products for regenerative medicine.
With the exception of four projects originating from multinational companies, which have not been included, all of these products are the result of R&D efforts by pure biotech companies.

About half of these drugs are in the clinical phase, with 9 projects in Phase II and 3 in Phase III. Of these, 30% have indications in oncology, 23% are for the treatment of infectious diseases, and approximately 15% for the treatment of disorders of the musculoskeletal system.

Table 4.5

Analysis of Advanced Therapy medicines (Source: Assobiotec)

	Cell therapy	Gene therapy	Regenerative medicine	Total
Discovery	1	1	0	2
Preclinical	3	11	6	20
Phase I	0	4	2	6
Phase II	6	3	0	9
Phase III	3	0	0	3
Total	**13**	**19**	**8**	**40**

From the behest of a community of patients to the production of therapies: the charity as a promoter of development

With only 3.5% of the meager 1.25% R&D/GDP expenditure in Italy supported by the private non-profit sector in 2011 (OECD Science, *Technology and Industry Scoreboard* 2013), one would expect a negligible impact by biomedical research charities on the development of new therapies. Nonetheless, charities act on behalf of a community of patients and their research investment is strongly targeted towards this goal.

Based on this premise, the Telethon Foundation has achieved significant results in the fight against rare genetic diseases, with particularly encouraging results in gene therapy. The research that led to this success was developed within an academic setting and, in its final stage, was incorporated into an industrial context thanks to a strategic alliance aimed at the completion of the development and registration of therapy as medication. This is an atypical process, as compared to the traditional one, entirely in the hands of the pharmaceutical industry.

The drive behind this innovation lies in the charity itself that manages the development of academic research while maintaining, from start to finish, its focus - stemming from the needs of patients and becoming a promoter and catalyst for development.

Today, besides supporting excellent basic research on genetic diseases throughout the Country, Telethon is allocating 50% of its research investment to the development of therapeutic approaches and of clinical trials. Moreover, to bridge the gap between research and the production of usable therapies, processes have been put in place to exploit the translational potential of Telethon's research, by employing economic and human resources to assist the work of researchers with business development management.

Such processes include IP protection (45 patent families filed, of which 24 active and 8 granted patents), obtaining orphan drug designations (9 ODD acquired for 6 products), scouting, negotiation and management of industrial partnerships (22 biotech and pharmaceutical partners; 3 major industrial alliances) and, finally, managing scientific data not only in terms of publication, but also for use in clinical applications.

Francesca Pasinelli
Director-General of the Fondazione Telethon - Italy

Green biotech

Nowadays, more than ever, growing the agricultural production in a sustainable manner, without increasing cultivated land, preserving biodiversity and reducing water consumption, chemical input and greenhouse emissions is felt as a tangible need. In this context, the introduction of the new techniques of genetic engineering have drastically changed the perspective of improving the productivity and the quality of a number of plant varieties, fully respecting the sustainability and the quality of the entire food chain.

Green biotech covers a number of modern techniques with various potential applications, ranging from improving specific plant varieties to checking the origin and quality of food, and extracting bioactive substances which are available in nature only to a limited extent.

Although in front of a number of regulatory hurdles, particularly with regard to the application of GMOs in agriculture, Italian biotech companies are actively exploiting the potential of the green segment, by improving the nutritional value of animal and plant productions as well as the sustainability of the Italian food chain.

Based on our survey, 94 green biotech companies have been identified in this report (Table 5.1). Compared with 2 newly established companies and an additional one that has extended its business to the green segment in the period, 3 companies must be counted as being no longer active (due to liquidation) together with one company which has abandoned any activity in green biotech.

A more thorough analysis of the sector also allowed us to identify 8 companies which were already active and fully operative, as well as 2 whose activities were considered as not relevant to our sample, and one that is no longer involved in green biotech activities.

Table 5.1

Key data relating to the green biotech sector, details of OECD and pure biotech companies (Source: EY)

Green biotech	2013 Report*		2014 Report	
	Total biotech	Pure biotech	Total biotech	Pure biotech
Number of companies	95	69	94	66
Total turnover	€ 143 million	€ 74 million	€ 147 million	€ 78 million
Total investment in R&D	€ 120 million	€ 47 million	€ 106 million	€ 48 million
Total R&D employees	854	501	843	506

** Data have been modified to enable comparison of samples*

Due to these alterations, the 2013 sample has been modified for homogeneous comparison purposes, although the overall picture does not change much.

As in previous years, the majority of companies operating in the green biotech sector is made up of pure biotech (71%), while the remaining 29% is almost fully composed by other Italian biotech companies (26%). In fact, Italian subsidiaries of multinational companies are only 3% of the sample. Our outcomes show that companies completely dedicated to green biotech are the majority (59%), while multi-core companies are 41% of the sample. The total turnover for 2012 amounts to € 147 million, with a marginal 2.7% growth compared to 2011. It is worth highlighting that an increasing part of said turnover (53%) originates from Italian pure biotech companies, even if this has only to do with the inclusion of one single big-sided company which entered the green business in the period in exam. With regards to the multinationals' subsidiaries, these contribute 31% to the total turnover, whilst other Italian biotech companies only represent (16%) a small part of the sample (Figure 5.1).

In terms of size, the predominance of SMEs within the green sector is once again confirmed: small and micro companies equal respectively 19% and 66% of the sample, followed by big (8%) and medium (7%) companies (Figure 5.2). Focusing only on pure biotech companies, the percentage of micro and small firms rises to 91%.

As regards the number of R&D employees, these have been estimated at 843 units (10% of the total) compared to 854 of the previous year.

Also in this sector the origin of companies is mainly attributable to start-ups (38%), academic spin-offs (33%), industrial spin-offs or spin-outs (7%), to subsidiaries of multinational companies (4%), and other (18%) (Figure 5.3).

Limiting this analysis to pure biotech companies alone, the percentage of organisations that originate from academic spin-offs drops to 42% compared to 44% in the previous year. With regards to their localisation, 46% of the green biotech companies operate within independent headquarters, 37% within science parks, while 17%

Figure 5.1

Green biotech companies: analysis of the 2012 turnover by type (Source: EY)

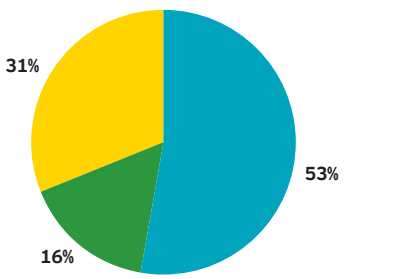


Figure 5.2

Green biotech companies: analysis by size (Source: EY)

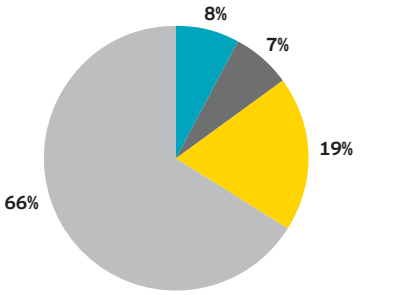
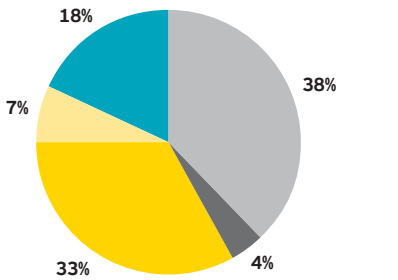


Figure 5.3

Green biotech companies: analysis by origin (Source: EY)



are located at universities or research institutes (Figure 5.4).

R&D investments in 2012 amounted to € 106 million, with a 13% contraction compared to 2011, which is substantially due to a cut in investments by one single company which is the local subsidiary of a multinational group. It is worth highlighting that for the first time, in 2012, Italian pure biotech companies represent the largest share of investment in R&D (46%), whilst not only the other Italian biotech companies (11%) but also the Italian subsidiaries of multinational corporations (43%) are followers (Figure 5.5).

Figure 5.4

Green biotech companies: analysis by location (Source: EY)

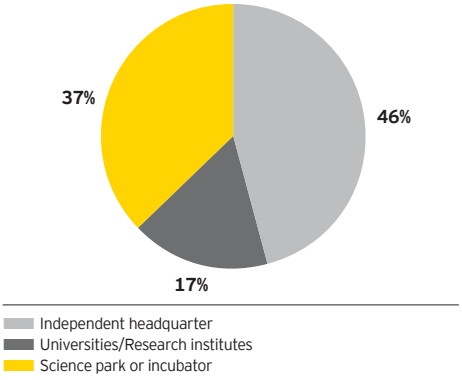
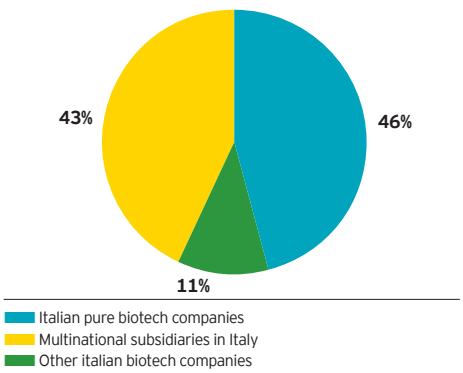


Figure 5.5

Green biotech companies: analysis of the 2012 R&D investments by type (Source: EY)



Why we should not neglect GMOs and Indust

How can we increase agricultural production in order to provide the planet's inhabitants with enough food and water for them to lead healthy, active lives? And how can such production be achieved sustainably – in not only environmental terms but in economic, social and cultural terms too – when it is already being estimated that, in 2050, the world population will total more than nine billion people and that demand for food will be even greater than now due to the improving living conditions in the emerging countries?

There can only be one answer: we need to produce more. And in order to do so without increasing the amount of cultivable land, since this would jeopardize the equilibrium of the entire ecosystems, we need to take diverse courses of action: increasing per-hectare yield and improving the shelf-life of our products so as to avoid losses that can occur at various points after a crop has been harvested.

At least 30% of the world's agricultural produce is lost as a result of environmental adversities. If we can avoid such losses, we would be able to increase yields by 30%. What we need are hardier, stronger plants that can withstand the onslaught of viruses, bacteria and fungi, the rigours of heat, cold, drought and flooding, or that can grow in saline farmland. In addition to the greater yields obtained, there would be other important benefits: the reduction in greenhouse gas emissions related to the lower consumption of fuel which would derive from the need for less treatment of crops; carbon sequestration; less use of fertilizers.

In farming, there have always been attempts to improve yield by cross-breeding and selecting the best varieties. What has made such improvements possible is the identification of the spontaneous mutations in plants that can be useful for man, and their reproduction in such a way that the characteristics of these plants can then be consolidated in future generations (domestication). However, it is with the introduction of the new techniques of genetic engineering that the prospects for improvement of plant varieties change drastically. The technique of DNA recombination – based on the structural and functional characterization of the genes involved, and on their transfer – has enabled the creation of genetically modified organisms (GMOs), which include transgenic plants. One or more genes are introduced into these GMOs in order to generate or reinforce certain characteristics.

These are the tools that basic biotechnological research puts at the disposal of the geneticist. Knowledge of the genome of single plant varieties, and of the functions of single genes within these varieties, makes it possible to attempt improvements in a very precisely targeted way, by seeking to modify those specific genes (or to utilize modifications already occurring in nature) which can activate the desired characteristics of resistance, adaptability and productivity. The range of techniques available includes the use of specific markers for the selection of varieties obtained from classic traditional cross-breeding which have characteristics of particular interest, and are destined to become the "parents" of future generations.

rialized Agriculture

With our experiments at the University of Milan, we are seeking to develop plants that grow using 30% less water. We are not adding anything: we simply inhibit the function of one of the genes in their DNA. We have been working on this for a number of years and, unfortunately, it will take many more before it will be possible to cultivate such plants. Simply because they are GMOs.

The 'NO' to GMOs is, frankly, absurd. We humans, too, are the result of a natural genetic modification that enabled the evolution of our species, and everything that we eat is the result of a genetic modification. Since time immemorial, farmers have studied their fields, picked out only the best plants and taken their seeds to use for future crops. GM techniques offer a more precise system of improvement. The BT maize which farmers in the north-eastern Italian region of Friuli would like to use, is much healthier than "normal" maize.

The view that the biodiversity of Italian agriculture and the uniqueness of our products could be contaminated by GMOs seems to be even more absurd. Inserting a gene by crossbreeding, starting from a wild species, at the risk of also inserting a host of alleles whose function is unknown, is permitted. But if, from that same wild species, you take a single gene, you study it and then insert it by means of DNA recombination into another plant, this newly modified plant cannot be cultivated in the field but must be kept under glass, in a condition of containment.

Neglecting GMOs means not understanding the future of agriculture and not realizing that we import 30% of the proteins that we consume from world markets. The European Union has invested €100 million to study, in public laboratories, the safety of GMOs. The result of these studies is hundreds of publications and documents certifying that GMOs are safe both for the environment and for our health. Basically, we have funded the best possible research and we are ignoring its findings.

And so, while Europe has realized that the political and media opposition to GMOs is seriously damaging the economy, Italy risks excluding not only GMOs but also agricultural innovation itself from an event of truly global significance, Expo 2015. This illogical opposition is the expression of an antiscientific culture that is increasingly rooted in our Country.

Chiara Tonelli
Full Professor of Genetics and Vice-Rector for Research at the University of Milan, Italy. Head of the Plant Molecular Genetic Group at the Department of Bio Sciences. Member of the European Molecular Biology Organisation (EMBO) and of the Scientific Advisory Board of the EU JPI "Healthy Diet for Healthy Life". Former member of the Advisory Group for Food, Agriculture and Fisheries, and Biotechnology of the European Commission, for the Seventh Framework Programme (FP7).

FUTURAGRA and the first example of biotechnological arable farming in Italy

Futuragra is an association of farmers who are promoting an agricultural model that combines technological innovation with a business-oriented approach, while also upholding the principle of freedom of choice.
Created in 2004 and founding member of the Farmers – Scientists Network (FSN), which brings together farmers and scientists committed to defending biotechnologies at a European level, Futuragra has, for the last decade, been fighting a legal battle to introduce genetically improved organisms into Italian agriculture.

In January 2010, with a historic sentence, Italy's Council of State ruled that the Ministry of Agriculture cannot subject to its own ministerial authorization the sowing of genetically improved plants when such sowing has already been subjected to European Union authorization.

In May 2013, the European Court of Justice, after hearing the case of Giorgio Fidenato (a farmer from the Friuli region of Italy who had sown GM maize in 2010), ruled that no national authorization can be required for the planting of GM crop varieties when such varieties have been registered in the EU Common Catalogue of agricultural crop varieties.

On the basis of this European sentence, Futuragra initiated the first legal planting of GM maize in Italy. The sowing was carried out in Vivaro, close to Pordenone, north-eastern Italy, on 1.5 hectares of land owned by Futuragra vice-president Silvano Dalla Libera.

Futuragra's aim was to make the field in Vivaro the first example of biotechnological arable farming in Italy and to gather data that would make up for the lack of public-funded research. Thanks to its "Una spiga per la ricerca" ("An ear for research") fundraising campaign, Futuragra was able to support the research activity of Tommaso Maggiore (formerly a Professor of General Agronomy at the University of Milan).

The results of Professor Maggiore's study were presented in October 2013 on the occasion of the threshing of the maize, an event open to the public. The results of the analysis of the crop, which were also confirmed by data provided just a few weeks later by the Corpo Forestale dello Stato, the authority responsible for agro-environmental protection in Italy, demonstrated not only the excellent resistance of genetically improved hybrids to the European corn borer but also the absence of pollen contamination of crops in the surrounding fields.

In the GM hybrids there was no trace of any infestation by larvae of the Ostrinia nubilalis moth, commonly known as the European corn borer, while the levels of fumonisin, a highly toxic micotoxin, were found to be 15 times lower than those present in conventional maize.

Of greater significance was the finding that, at distances of over 15 metres from the source of release, there was no cross-pollination of other crops. This demonstrates that, in order to allow coexistence, it is sufficient to ensure an isolation distance of 20 metres between GM maize and non-GM maize hybrid fields.

Futuragra concluded that, with GM maize, it is possible to achieve per-hectare increases of €465 in revenue and 3,400 kg in yield.

Giorgio Fidenato
President of Federated Farmers and Maize Growers in Udine

Will biotechnologies change the face of viticulture in Italy?

Italy holds a well-established, outstanding position in genomics applied to agriculture. Its leading-edge scientific institutes, which work on the genome sequencing of vines, apples, strawberries, raspberries, pears, peaches, rice, citrus fruit, as well as red pine, and include the Applied Genomics Institute in Udine (IGA Technology Service), the Edmund Mach Foundation in San Michele all'Adige and the Parco Tecnologico Padano in Lodi, play a truly primary role in international cooperation with other renowned scientific organizations.

As a result of leading-edge sequencing and genotyping platforms, which exploit the latest Next Generation DNA Sequencing (NGS) methods, and obviously supported by equally powerful bio-computerized platforms, these centres have succeeded in carrying out large-scale research projects into the genetic makeup of cultivated plants. Over recent years, next generation DNA sequencing has fuelled a veritable revolution in biological and biomedical research, allowing biological phenomena to be observed at a level of detail that was previously unimaginable.

The same technology can also bring major benefits to genetic improvement, by understanding the molecular mechanisms of the characteristics that are of interest to agriculture and allowing for extremely accurate, high-resolution diagnostic assays in order to analyse single cells.

This research lays the groundwork for identifying the regions of genomes that determine physiological traits and are of greater use in agriculture, both at a local and a global level. For this purpose, research groups are divided into sectors dealing both with basic research (molecular and cellular reactions) as well as applied research (development of molecular markers, identification of genomic regions and genes responsible for genetic traits) and research services, the purpose of which is to transfer research findings into practical applications with significant economic spinoffs. In fact, by integrating the latest conventional genetic methods –*plant breeding* - with molecular biology it is possible to speed up all plant selection processes, dealing with a noteworthy number of new genotypes and grouping wide collections of germoplasma that are among the largest in Italy if not in Europe.

A practical demonstration of how a knowledge tool such as genomics can translate into high-impact results on agricultural practice was recently provided by the IGA of Udine, whose staff of 25 researchers has expertise in genetics, structural and functional genomics, biology, biochemistry, mathematics applied to biological systems, information technology. The Scientific Director is Michele Morgante (an academic from the Lincei Academy in Rome).

The group of IGA researchers, after completing the first physical mapping of the vine genome, took part along with other national and international partners in a project that led to the first version of the vine genome sequence (that is, the decoding of 500 million vine DNA bases) in one year, publishing the results in "*Nature*". The completion of the vine genome sequence, in addition to taking Friuli to the highest levels of scientific research, offers short- and medium-term prospects for the vine growing and wine industry, creating new vine varieties that are of a higher quality and resistant to fungi, and characterising varieties and vine clones for nurseries.

In fact, during 2013 significant results were achieved from genetic vine improvement which was aimed at obtaining – via cross-breeding and selection with the aid of genomic knowledge – new varieties of vines for wine production that were resistant to Peronospora and mildew, two fungal pathogens that are the main causes for the widespread use of fungicides on vines. During 2013, numerous tastings of experimental wines obtained from about 10 new varieties developed by the IGA in team with the University of Udine, and resistant to the two pathogens, were held in various Italian regions in collaboration with Vivai Cooperativi di Rauscedo, the largest producer worldwide of rooted vine cuttings. These true and proper wine tastings were the last step in a long process that began more than 10 years ago. At the end of 2013, the very encouraging results from the sensorial judgements of experts in the sector (vine growers, oenologists, the trade press) led to the introduction of a national register of vine varieties to allow these to be marketed and used as soon as possible in very environmentally sustainable viticulture and with significantly lower vine protection costs.

White biotech

White biotechnology makes an increasingly important contribution to the development of a sustainable biobased economy, by using enzymes and micro-organisms to obtain innovative products in the chemistry, paper, textiles and energy sectors. White Biotechnology could also provide new chances to the chemical industry by allowing easy access to building blocks and materials not easily accessible before, and have a considerable impact in the production of biofuels and biopolymers, by using biomass as an alternative to fossil resources.

The use of living cells and their enzymes is the way to create a sustainable and environmentally-friendly chemical manufacturing industry. As such, white biotechnologies are a key-driver in chemistry, biofuels and renewable raw materials. At the same time, these technologies may boost the rural economy by providing new markets for agricultural crops and through the development of integrated bio-refineries in farming areas.

Although we still lack a national strategy for Bioeconomy, a number of companies active in industrial biotechnology, enjoys a true competitive edge, at world level, in terms of technological leadership.

Compared to the sample of the 2013 Report, the number of white biotech companies in Italy remained almost unchanged. Accordingly, the sample consists of 69 enterprises (Table 6.1), with one company having been newly established, an additional one which has extended its business to the white sector, compared to one which is no longer active and 2 which have abandoned any activity in white biotech. A further analysis allowed us to identify 7 companies which were already active in the white field and one whose activities were not in fact related to it. Accordingly, all data were modified to allow a homogeneous comparison of the two samples.

Table 6.1

Key data relating to the white biotech sector, details on OECD and pure biotech companies (Source: EY)

White biotech	2013 Report*		2014 Report	
	Total biotech	Pure biotech	Total biotech	Pure biotech
Number of companies	70	42	69	41
Turnover	€ 289 million	€ 287 million	€ 241 million	€ 238 million
Total investment in R&D	€ 31 million	€ 29 million	€ 29 million	€ 24 million
Total R&D employees	526	498	567	535

** Data have been modified to allow sample comparison.*

About two thirds of the companies operating in industrial biotechnology consist of Italian pure biotech companies (61%), 31% of other Italian biotech companies, and the remaining 8% consists of Italian subsidiaries of multinational companies which still focus their core business on white biotech. The percentage of multi-core companies active in industrial biotechnology equals 31%.

Total turnover reached € 241 million, with a 20% decrease compared to 2011 which is almost due to the drop in revenues of one single company. Once again, the whole white biotech turnover can be attributed to pure biotech companies.

The large majority of white companies (85%) are micro-sized or small (Figure 6.1), which is fully consistent with the fact that nearly two thirds of the entire segment is made of pure biotech companies.

Despite an almost zero-growth rate with regard to the number of companies, the number of white biotech R&D employees is growing (8%), with 567 units involved representing almost 23% of the total number of employees of the entire sector.

The industrial biotechnology segment is pretty in line with the main features of the whole biotech sector and with the findings of previous years.
The fact that 44% of the white companies originate from start-ups, 26% from academic spin-offs and 13% from industrial spin-offs or spin-outs appears to be consistent with what was observed in the other sectors (Figure 6.2).

With regard to their location,33% of the white biotech companies have autonomous headquarters, 39% operate in science parks or incubators, and 28% at universities or research centres (Figure 6.3).
Most of the companies are settled in northern Italy with Lombardy (17) and Piedmont (11) being the most densely populated regions.

Investments in R&D in year 2012 amount to € 29 million, thus showing a € 2 million decrease - at homogeneous samples- compared to 2011. These investments are almost all attributable (82%) to Italian pure biotech companies.

Figure 6.1

White biotech companies: analysis by size
(Source: EY)

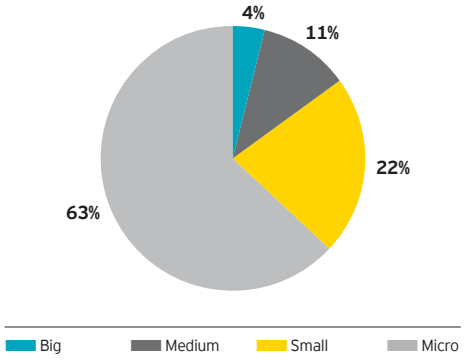


Figure 6.2

White biotech companies: analysis by origin
(Source: EY)

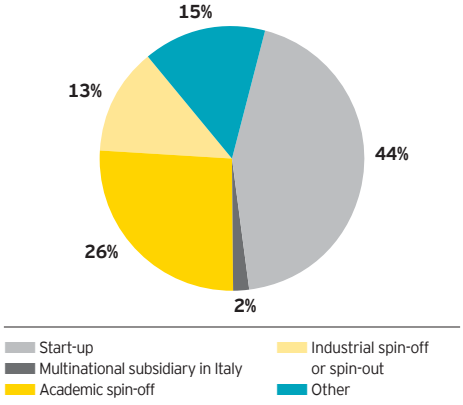
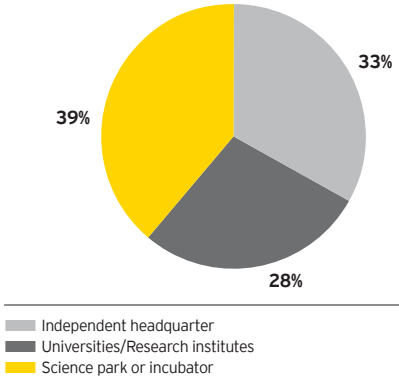


Figure 6.3

White biotech companies: analysis by location
(Source: EY)



Green technologies drive the modern economy

Interview with Guido Ghisolfi

"Green technologies are some of the driving forces behind modern economy; this is not only my view but also that of other important national and international groups which have begun to invest and diversify their production in a green vision. The objectives of such investments are long term, but the results arrive if one knows how to wait". These are the words of Guido Ghisolfi, Vice President of the Tortona-based Mossi&Ghisolfi Group (M&G Group), President and CEO of Biochemtex, and the architect of the conversion of the second Italian chemical group into one of the world's major players in the bioeconomy. The Biochemtex facility at Crescentino, near Vercelli in north-western Italy, is the largest plant in the world for the production of second-generation bioethanol.
In this full interview with Ghisolfi, we talk about the bioeconomy, research and industrial innovation because "the industrial policy of the future can't be separated from the concept of environmental sustainability". "The raw material alternatives to oil can be obtained through the use of biomass grown on marginal land, without competing with food and by applying innovative technologies. We must, however, continue to invest in industrial research to ensure the development of technological excellence in Italy; these are the variables in an equation whose results are the drivers of the competition system of our Country".

Mr Ghisolfi, could you first tell us what led one of the major producers in the world of PET for packaging, as well as the second Italian chemical group, to invest in a biorefinery for the production of second generation bioethanol?

Our Group celebrates 60 years in business and has always looked to the future: having achieved a goal, we have continued to look forward, in order to be competitive.
This philosophy has rewarded us and led us to be one of the major private chemical companies in Italy, even though we are unknown to the "general public". Our forward-looking strategy was critical when, a few years ago, we invested € 140 million in R&D, developing a technology to produce biofuels from non-food biomass. We have instigated a real revolution in rethinking chemistry as a sustainable resource, one of the areas in which to invest for the future.
Today, we can say that our vision, our ability to take risks and invest, has led us to be amongst the world leaders in the field of biofuels, and has allowed Italy to achieve an important technological advantage.

More generally, what are the investments already made by the M&G Group in the bioeconomy? What are the next steps in the Italian market and in the international market?

In 2008, we opened a research centre in Rivalta Scrivia, near Alessandria, Italy, entirely dedicated to renewable energy sources. At Rivalta Scrivia, in 2009, we put into operation a pilot plant to produce biofuels. Thanks to the research conducted in this centre, we invested another € 150 million to build the world's first demonstration plant to produce second-generation biofuels at Crescentino. Still on the subject of research, we are about to inaugurate a research centre in Modugno, near Bari, in southern Italy, where – thanks to the support of the Puglia regional authorities - we'll build laboratories and a demonstration plant to produce chemical intermediates from lignin, a co-product of ethanol production. Now we are making a number of preliminary assessments of areas in Italy that could be strategic in building new plants.

As you know, the use of biomass is subject to different trade-offs. Among these, the most controversial is that between food and fuel, the second generation of biofuels should help to overcome this. Where do you get the biomass needed to fuel the biorefinery of Crescentino?

Our Group has set-up a company that deals exclusively with the establishment of the agricultural chain that serves to fuel the plant of Crescentino. The plant is located in an area with a strong agricultural vocation and allows us to take advantage of a wide variety of biomass available at low cost in a radius

of 70 km. At present, we are using rice straw and wood chips, but we are setting up a dedicated distribution network in order to source giant cane (Arundo donax), which can be grown on marginal lands, without taking land dedicated to agricultural production for food use.

At the beginning of February, the M&G Group, together with its subsidiary Beta Renewables, was the protagonist of the European initiative "Leaders of sustainable biofuels." What are your goals?

The signatories of this initiative believe that the second-generation biofuels, and the "advanced biofuels" in general, represent one of the best industrial opportunities in the field of sustainable energy sources. The world is witnessing an increase in the number of initiatives to reduce emissions of greenhouse gases, and biofuels from non-food biomass are a key factor to achieve this goal. In this regard, we "leaders" decided to put in place a series of measures to accelerate the deployment of sustainable technologies. In fact, today we can start with the production on an industrial scale, but we further need to be supported by a legislative framework that encourages long-term investments in this sector. We need clear and precise rules, and our main partners are the European Commission and the Parliament together with governments and the various financial institutions. In order to achieve our goals by accelerating industrial processes and research into biofuels, we are open to cooperation with other international organizations who are already working in this area, such as the IEA Bioenergy Implementing Agreement and the Global Bioenergy Initiative, just to name a few.

What do you think about the action of the European Union to support the development of the bioeconomy? Is there one particular measure that is lacking today and that you believe is essential for Europe to compete in the world market?

The national and European industry is ready, and a world leader in a highly specialized and innovative sector; this has been possible thanks to the efforts and investments of important companies, supported by the European Union as a whole and by the member States. The technologies are there; what we now need is a long-term legislative framework and the introduction of specific objectives to ensure investment and market development of sustainable biofuel generation.

From Europe to Italy. In our Country, there is no national strategy for the bioeconomy. The M&G Group, however, has signed with the Government a memorandum of understanding for the development of second-generation biofuels. What does this protocol foresee?

The memorandum of understanding with the Government envisages the creation of a development project of sustainable chemistry in Italy able to offer real prospects for growth. Consistently with the guidelines set out by the SEN (Italy's national energy strategy),the Government is committed to defining a growing curve with regard to the contribution of second-generation biofuels in the overall mix of energy in order to consolidate the scenario until 2020, to mapping the availability of biomass and areas suitable for production sites focusing on areas disused, to promoting alliances with trade associations, to drawing up a schedule for the permitting procedures, promotion and co-financing of a programme of research and higher education in the field of green chemistry. For our part, we are committed to investing in localized plants that use Proesa® technology in the sites that will be identified by mutual agreement, and which meet the conditions and local requirements that will be established case by case. We are also committed to co-investing in a programme of research and development in the industry, involving in this initiative academic and industrial partners to gather national and international experts in one area, and to accelerate and maintain the competitive advantage gained in the field today. With the signing of this protocol, we kick off an important project that offers real development prospects for the Country in a growing sector, where Italian technology holds a position of world leadership.

(continued)

(continued)

Eurostat data for 2012 indicates a 2.7% contraction of gross domestic product in our Country. Istat showed that the fourth quarter of 2012 (-0.9%) was the sixth in a row with a decline in GDP, a situation comparable to that which occurred between 1992 and 1993. What policies should be put in place in Italy, in your view, to return to growth?

The "green" technologies are some of the driving forces behind the modern economy, and a number of national and international groups, including M&G, have begun to invest and diversify their production in a green vision. The objectives of such investments are long term but the results arrive if one knows how to wait.
Currently, we are in a transition phase, and the shift to the green economy, if supported by policies at a national and international level, will not result in an economic decline but rather in the creation of new jobs to replace those lost progressively from the traditional economy.

In light of your experience in green chemistry, could you help us to define a new concept of industrial policy for the Third Millennium?

The industrial policy of the future can't be separated from the concept of environmental sustainability. The raw material alternatives to oil can be obtained through the use of biomass grown on marginal land without competing with food and by applying innovative technologies. We must, however, continue to invest in industrial research to ensure the development of technological excellence in Italy. The investments made in renewable energy sources represent a viable alternative to improve the economic balance; continuous technological development and a new industrial system can create new business opportunities and qualified jobs as a result.

(Source: Bonaccorso, M., Inside the European Bioeconomy, Lulu.com, 2013)

IFIB: Italy welcomes the world of Bioeconomy

IFIB is the acronym of the Italian Forum on Industrial Biotechnology and Bioeconomy, an event organized by Assobiotec, Innovhub – Stazioni Sperimentali per l'Industria and the Italian Biocatalysis Center consortium as a networking opportunity for businesses and academic research centres in the various sectors that pertain to bioeconomy. Each of them - healthcare, environment, agro-food, energy, green chemistry, marine biotech and bio-catalysis - will be the subject of a specific session.

The Forum constitutes an opportunity to meet and help develop the bioeconomy network in the Euro-Mediterranean area, strengthening Italy's traditional role as a gateway between North and South. The event will also allow discussion of the policies needed in Italy and in the European Union as a whole to foster sustainable economic growth, and thus responding, thanks to the biotech industry, to many of the global challenges posed by the new millennium: ending our dependence on oil and other fossil fuels; supporting an increasing and ageing population; meeting the growing demand for food and tackling the problems related to climate change.

The previous edition of IFIB (the third) took place in Naples, at the prestigious Castel dell'Ovo venue, and was a huge success in terms of both attendance and the presentations made. There were around 250 participants (20% of them foreigners, from 20 different countries) and a total of 40 presentations (here too, 20% were made by foreign companies and research centres).
The 2014 edition will be held 16-17 October in Genoa, Italy, at the Palazzo della Nuova Borsa where participants will be able to schedule one-to-one meetings thanks to the Enterprise Europe Network-EEN partnering system.
This year's edition will see the original organizers team up with the Italian technology clusters in the key interested sectors: the National Green Chemistry Cluster, the National Agrofood Cluster - C.L.A.N. and the National Life Sciences Cluster - ALISEI.

Biorefineries: the role of biocatalysis for the development of environmentally sustainable and economically convenient processes

The concept of "bio-refinery" derives from the processes of oleochemical refinery, with the difference that in a biorefinery the starting material is made by renewable resources, processed and transformed following environmental, economic and social sustainability criteria. In other words, such plants, starting from different renewable feedstock, integrate chemical, physical or microbiological conversion processes of the biomass, to obtain high added value materials and eventually energy.

The European Union already indicated biorefineries as models of sustainable innovation, and Italy recently adopted an internal regulation to facilitate and speed-up the authorization process for such structures (D.M. 9 October 2013, n. 139). This is a clear signal of the awareness about the opportunities that such biorefineries offer, in terms of economic growth and local employment, generating a network of small and medium-size companies investing in innovation and strictly collaborating with the public sector.

Data from the OECD say that the percentage of chemical products coming from biotechnology will growth from 2% in 2005 to 25% in 2025, and the global market of bio-based products will reach € 250 billion in 2020.

In this frame, SPRIN Technologies - an Italian biotech company which was founded as a spin-off of the University of Trieste - offers products and services able to speed-up and optimize the converting processes within the biorefineries. The development of ready-to-use immobilised enzymes with outstanding activity and stability, such as those produced and distributed by SPRIN, and the availability of a highly specific expertise in developing bio-catalysed processes represent an important task and prerequisite in order to obtain innovative and sustainable industrial processes.

The financing perspective

In the EU knowledge- economy perspective, of which biotechnologies are a key element, the availability of adequate funding channels aimed at supporting R&D is a crucial prerequisite to foster sustainable growth. In addition to specific programmes and financial instruments to boost innovation within the European Research Area, and to enable our SMEs to achieve their full potential in the global economy, the EU vision also includes the development of venture funding as a major driver for the growth and stability of the entire European economy.

The recession triggered by the financial crisis of 2008 has resulted in the implementation of policies designed to stimulate the economy. Europe is now having to tackle a public deficit crisis and fears of further recession. The great challenge lies in stabilizing the economic and financial system in the short term while, at the same time, implementing increasingly incisive measures to kick-start growth and create new jobs.

Investments in research and innovation (R&I) are, therefore, of vital importance, not only in order to create new markets by developing innovative products and services or to ensure greater professional opportunities and foster prosperity and quality of life, but also in order to deal with some of the huge problems currently facing Europe: an ageing population, climate change, the transition to a model of industrial development that is both competitive and sustainable. Despite its undeniable leadership in many technological sectors, Europe is, in fact, exposed to increasingly fierce competition not only from its traditional rivals but also from the emerging economies.

Research and innovation are thus central to Europe 2020 strategy for intelligent, sustainable and inclusive growth. Biotechnologies, not surprisingly identified by the European Commission as Key Enabling Technologies, play a major role in achieving ambitious European objectives in environmental, economic and social spheres including the use of renewable sources of energy, the implementation of eco-sustainable production processes, the creation of new non-food markets for Italy's agricultural produce, an increasingly specific and effective response to the population's health needs.

The reference framework of EU policies in the field of R&D is closely related to the objective of establishing a European Research Area (ERA) as set out by the European Commission in 2000 and embedded in the Treaty on the functioning of the European Union.

For the European Union, the ERA is the dimension in which measures to encourage growth and innovation should be introduced, taking advantage of the removal of barriers to research and the creation of a common area, the optimum exploitation of material resources and existing infrastructures. The ERA concept also entails the building of a network of excellence that facilitates the mobility of researchers, the coordination of national and EU research programmes, and, in short, making Europe the world's most dynamic "knowledge economy".

This is the context that encompasses the Framework Programmes for research, development, technological and industrial innovation, which have been the main financial instruments used by the European Union since 1984.

We will, in the following pages, look at the main points of Horizon 2020, the new Framework Programme (2014-2020) for research and development, at the Framework Programme for the competitiveness of companies and SMEs (2014-2020) and also at the opportunities for Italy implicit in the application of the EU's Cohesion Policy.

It should be stressed that this public support for research and innovation aims to make Europe a highly competitive region in terms of its ability to attract private investment. Here, an extremely important role is played by venture capital, an element repeatedly highlighted by the European Union, which has identified the development of the venture capital market as one of the basic underlying conditions for the growth and stability of the economy. Our assessment ends with an outline of the current state of the Italian and European venture capital markets, with specific reference to the biotechnology sector.

Public EU funding

HORIZON 2020[1]

Initiated on 1st January 2014, the Horizon 2020 programme brings all European Union funding for research and innovation together in a single reference framework with the purpose of facilitating the transformation of new scientific knowledge into innovative products and services. Under its terms of reference, the seven-year programme will make available a total of around € 80 billion (+46% compared to the 7th Framework Programme) for those research centres, universities, companies and SMEs who commit themselves to the three fundamental strategic objectives of Horizon 2020, the so-called 'priorities' (Table 7.1).

Priority funding has been assigned as follows:

- € 24.5 billion allocated to the Excellent Science priority with the aim of promoting the competitiveness of Europe at a scientific and technological level, making the ERA the most attractive environment for the best researchers;
- € 17.1 billion allocated to the Industrial Leadership priority specifically in support of research and innovation in European industry, with its focus on Key Enabling Technologies, SMEs and venture capital so as to make Europe an extremely attractive area for investors;
- € 29.7 billion allocated in the sphere of the Societal Challenges priority for research activity and pilot schemes in key priority areas of common interest, such as the ageing population, food security, the development of new models of sustainable agriculture, climate change, renewable energy sources, the adoption of new systems of sustainable mobility.

1. Source: European Commission Research and Innovation, Horizon 2020

Table 7.1

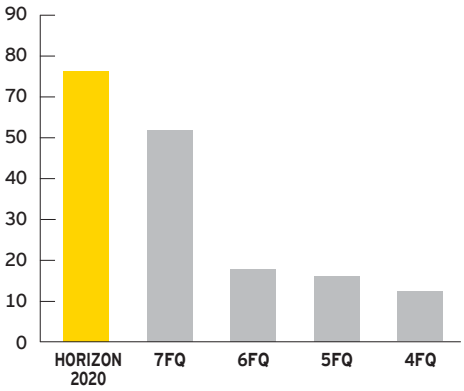
Horizon 2020 funding allocation

Project	%	€ million
THE THREE PRIORITIES		
Excellent Science	32%	€ 24,441
Industrial Leadership	22%	€ 17,016
Societal Challenges	38%	€ 29,679
CROSS-PRIORITY PROGRAMMES		
Spreading Excellence	1%	€ 816
Science with and for Society	1%	€ 462
European Institute of Innovation and Technology	4%	€ 2,711
Euratom	2%	€ 1,603
TOTAL	**100%**	**€ 76,728**

The financing perspective

Figure 7.1

Framework Programme (FP) funding levels
(€ billion)



In addition to the three aforementioned priorities, Horizon 2020 foresees four cross-priority programmes related to the development of activities and synergies that are functional to the purposes of Horizon 2020.

- European Institute of Innovation and Technology (EIT): the aim of this institution is to integrate the knowledge-research-education triangle and thus boost the European Union's innovation capability and tackle the problems faced by our society. The funding made available amounts to € 2.72 billion.

- Spreading Excellence and Widening Participation: the measures foreseen in the sphere of this specific scheme are aimed at all those EU member states and regions who need to make their R&I systems more efficient and improve their performance in terms of R&D investments while, at the same time, helping to strengthen the growth and competitiveness of the European economy. For this purpose, the sum of € 816 million has been allocated.

- Science with and for society: a series of initiatives designed to increase cooperation between science and society, and to promote responsible research and innovation, while encouraging the dissemination of culture and scientific education and, across the board, strengthening the faith of EU citizens in science by means of an increasing public commitment to the foremost areas of scientific research. Funding amounts to € 462 million.

- Euratom: initially destined to the coordination of member-state research projects promoting the non-military use of nuclear energy, the Euratom treaty now contributes to the sharing of knowledge, infrastructures and funding in the sphere of nuclear energy. It guarantees the secure provision of nuclear power within a context of centralized control. Funding of € 1.61 billion has been allocated.

All of these cross-priority initiatives put great emphasis on the development of new enabling technologies and on the concept of knowledge sharing, vital for the efficient use of the available resources and compatible with the European programme of technology sharing that is central to the creation of a common European platform.

Within the general ambit of Horizon 2020, the involvement of SMEs is of the utmost importance: it has been estimated, in fact, that the priorities identified mean that SMEs will be entitled to around 15% of total funding.

Biotechnologies, in the light of their potential as Key Enabling Technologies (growth of bioenergy and biochemistry in terms of market share is expected to be somewhere between 12% and 20% over the next two years), will be able to benefit from much of the € 13 billion in funding allocated for the Industrial Leadership priority, or the further € 22 billion allocated in the Innovation Investment Package (IIP) approved by the European Commission, the member States and the European industry.[2]

2. Source: European Commission, Innovation Investment Package (IIP).

COSME - Competitiveness of Enterprises and Small and Medium-Sized Enterprises

With more than 20 million businesses, SMEs make up 99% of the fabric of European industry and play a key role in economic growth, innovation, employment and social integration within the Union.

In order to improve the business environment in which these firms operate and to underpin development, thus enabling SMEs to achieve their full potential in the global economy, the European Union, for the period 2014-2020, has introduced a new programme of support, COSME (Competitiveness of Enterprises and Small and Medium-Sized Enterprises). This new scheme seeks to build on the activities included in the previous one, the Competitiveness and Innovation Framework Programme (CIP).

With a budget of € 2.5 billion over seven years, the COSME programme aims to boost the competitiveness of SMEs on international markets by facilitating access to funding, fostering enterprise and generating new business opportunities and initiatives as well as helping member states draw up and implement appropriate policies for the sectors involved.

More specifically, the COSME programme will seek to ensure easier access to funding for SMEs in the form of borrowing or capital by means of two distinct financial facilities:

- the Loan Guarantee Facility, which foresees a sharing of risks with financial institutions (mutual guarantee funds, banks, leasing companies) for loans of up to € 150,000 taken out by SMEs. Thanks to the sharing of risk, the guarantees provided will allow the financial institutions to broaden the range of SMEs eligible for credit and thus facilitate access for many firms that would not otherwise be able to get the resources

they need. Since 2007, over 240,000 SMEs have benefitted from loans or leasing guaranteed under the terms of the COSME's predecessor, the CIP.

- Equity Facility for Growth, an instrument designed specifically to support venture capital investments. Fund managers will have to operate on a commercial basis so as to ensure that investments are focused on those SMEs with the greatest growth potential. Here too, it should be noted that, since 2007, the CIP has freed up private equity resources totalling more than € 2.3 billion.

In addition, the COSME programme will seek to help SMEs access European and non-European markets and to make it easier for companies to set up international partnerships through specific centres and services, like those of the Enterprise Europe Network, whose participants include more than 600 business organizations in 54 countries. So far, the Network has reached two million SMEs.

COSME objectives also encompass specific initiatives to foster an environment conducive to the competitiveness and sustainability of SMEs. Improvements in the business environment will be achieved by assisting single national authorities in the implementation of EU policy relating to SMEs, with a reduction in administrative costs or by means of ad hoc projects in those sectors where there is a significant presence of SMEs or where job creation is of particular importance.

Finally, the COSME programme features a number of training schemes designed to develop, in particular, the business skills of new, young and women entrepreneurs. The schemes will run alongside exchange programmes like "Erasmus for Young Entrepreneurs".[3]

3. Source: European Commission – Initiatives - Cosme

EU cohesion policy and structural funds

As an expression of the solidarity between member states which aims to make Europe attractive, competitive and innovative, somewhere to live, work and embark on new entrepreneurial initiatives, the European Union's economic and social cohesion policy has traditionally promoted balanced and sustainable growth in order to reduce those inequalities that still exist between the various regions of the Union.

The directives and aims of this policy have thus been revised over the years as a result of the institutional, political and economic evolution of the Union. Current cohesion policy thus reflects the objectives set out in the Europe 2020 growth strategy.

More specifically, in the sphere of the EU's 2014-2020 budget (€ 960 billion), cohesion policy foresees investments totalling € 325 billion (34%) in the member states. The funding allocated will help Europe rise to the great challenges it faces in growth and employment, climate change, energy requirements, poverty and social exclusion.
One of the cohesion policy priorities is to provide support for research and innovation, with a total allocation of around € 85 billion, 25% of the total.

This type of investment in the real economy is made by using the financial facilities of the European Structural Funds, which enable intervention at a regional level and thus aid progress in less developed areas while, at the same time, funding or integrating framework programmes directly aimed at supporting research and innovation (Horizon 2020) and at fostering the development of SMEs (COSME).

Among the main Structural Funds are the European Regional Development Fund, set up to finance investment in production, infrastructures, local development projects and SME activities, and the European Social Fund, which funds training, job creation and mobility schemes.
The European Cohesion Fund can be accessed by those member states whose per capita gross national income (GNI) is less than 90% of the EU average.[4]

The European Regional Development Fund directs its resources towards priority spheres, such as support for SMEs, with the aim of doubling funds from € 70 billion to € 140 billion in seven years.[5]

Following a logic of unitarity of regional and Union policies, the use of the Funds is tied to the specific strategic reference frameworks drawn up by each single member state and approved by the European Commission. As far as Italy is concerned, the strategic reference framework approved by the European Commission for the 2007-2013 period covered a total of 52 operational programmes (including regional, national and territorial cooperation programmes).

The Regional Operational Programmes (ROPs) are those pertaining to activities within a single region. National Operational Programmes (NOPs) concern activities in specific fields (e.g. research and competitiveness) where close national and inter-regional cooperation is necessary. The European territorial cooperation (ETC) programmes foresee joint action with other EU or non-EU states.

4. Source: European Commission – Structural funds Policy
5. Source: European Commission – Regional Policy - Inforegio

The financing perspective

Figure 7.2

EU Cohesion Policy eligibility (2014 - 2020)

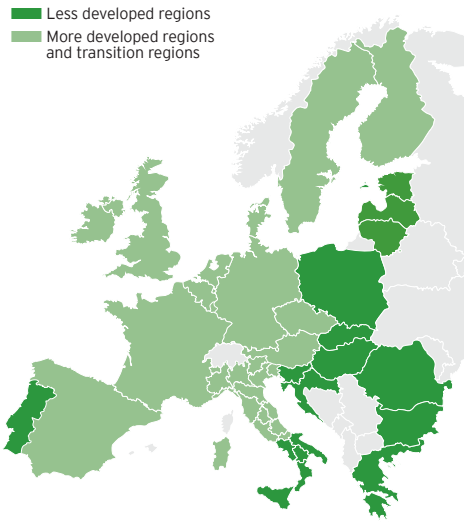
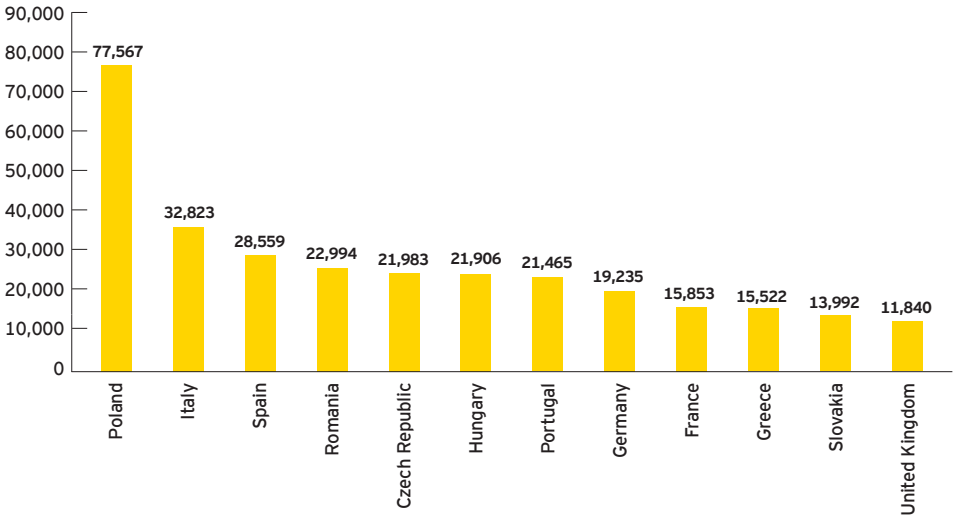


Figure 7.3

Total allocations of EU Cohesion Policy per Country - 2014-2020 (€ million)



A Structural Fund eligibility simulation carried out by the European Commission in June 2013 (Figure 7.2) indicated a number of Italian regions (Campania, Apulia, Calabria, Basilicata and Sicily) as being entitled to support.
The pro capita GDP in these regions is less than 75% of the EU average.

In quantitative terms, Italy could be one of the main beneficiaries of European funding. With an estimated share of EU resources amounting to € 32,8 million, Italy ranks only behind Poland.[4]

These incentives could, then, constitute the 'fuel' needed for the recovery of the Italian economy and of industrial activities that are increasingly competitive in terms of technological innovation. For this recovery to happen, however, Italy must make the right moves and learn how to plan the effective use of these important resources.

Venture funding

Besides public funding provided by the European policies to support research and innovation, a strategic role in encouraging the emergence of new high-tech entrepreneurial initiatives is also played by institutional investors, and venture capital investors in particular.

While, inevitably, Europe does not compare favorably with the US in a like-for-like comparison, there are signs that things are getting better, even though the gap between the US and the EU venture capital market is still wide.

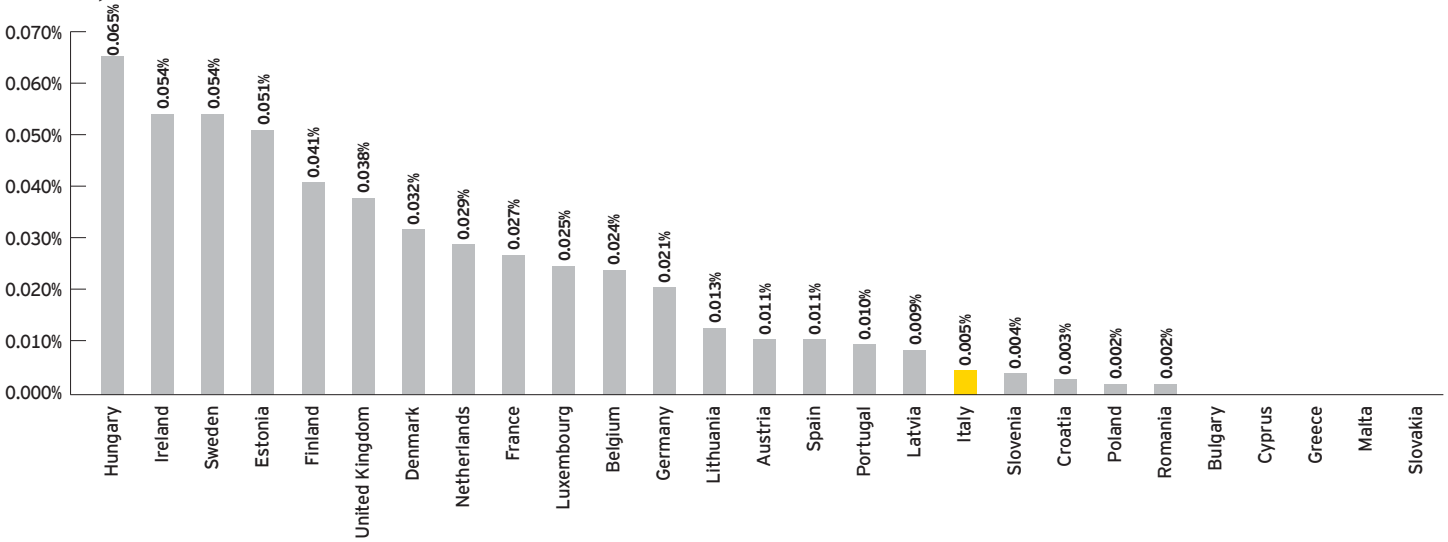
According to the National Venture Capital Association (NVCA), VC investments in the US, in 2012, amounted to $ 26.7 billion, less than 2011 totals and greater than 2010. The total number of venture-backed companies exceeds 3,000, with an increasing proportion of the investment dollars (53%) going to Californian companies. Although biotechnology was the second largest sector, receiving 15.4% of total investment, after software (31%), the combined share of VC investment in life sciences went from 33% in 2009 to 26% in 2012.[6]

On this side of the Ocean, according to the European Venture Capital Association (EVCA), the overall amount of venture capital invested in European companies in 2012, totalled € 3.2 billion.

While the number of venture-backed companies remained stable (2,900), aggregate funding in Europe was down (-14%) compared with the previous year, and markedly down (-53%) compared with the height of the financial boom (€ 6.3 billion in 2008). Given continuing uncertainties in the Eurozone in particular, it is perhaps not surprising that overall business sentiment

Figure 7.4

Venture capital investment in EU (% of GDP)

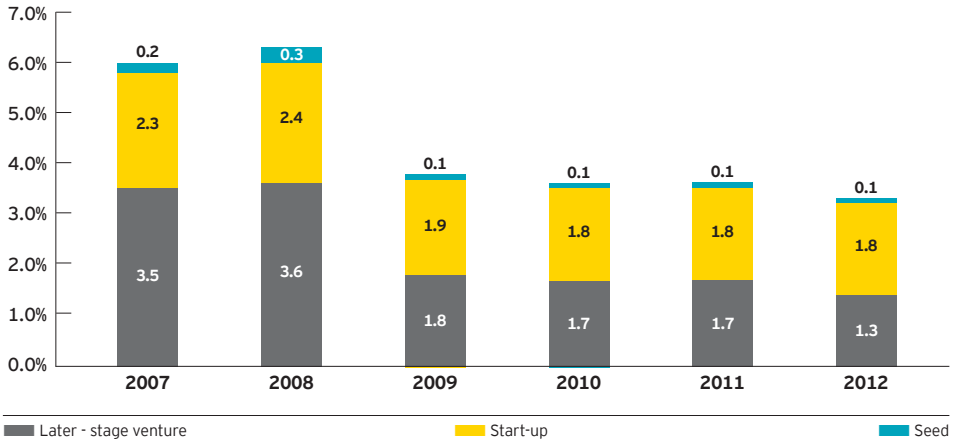


has not favoured investment in higher-risk/higher-reward opportunities.

Looking at investment on a country-by-country basis scaled to GDP (Figure 7.4), the UK, Sweden and Ireland continue to perform well, though less well than in 2011. Finland and Denmark, previously among the leaders, have dropped back. Estonia (0.051%) has climbed to be almost on a par with Ireland and Sweden (0.054% each) and pulled ahead of the UK (down from 0.045% to 0.038%); this performance may reflect broader economic changes, including labour market flexibility. However, the standout performer in venture investment was Hungary: already above the EU average in 2011 at 0.040% of GDP, it rose to 0.065% in 2012. It is probable that Hungary is beginning to see the benefit of a € 0.15 billion allocation, aimed at improving access to capital for SMEs in start-up and growth phases, of which 80% has been made available to the New Hungary Venture Capital Programme.[7]

Figure 7.5

Venture Capital investment in Europe by stage focus (2007-2012)



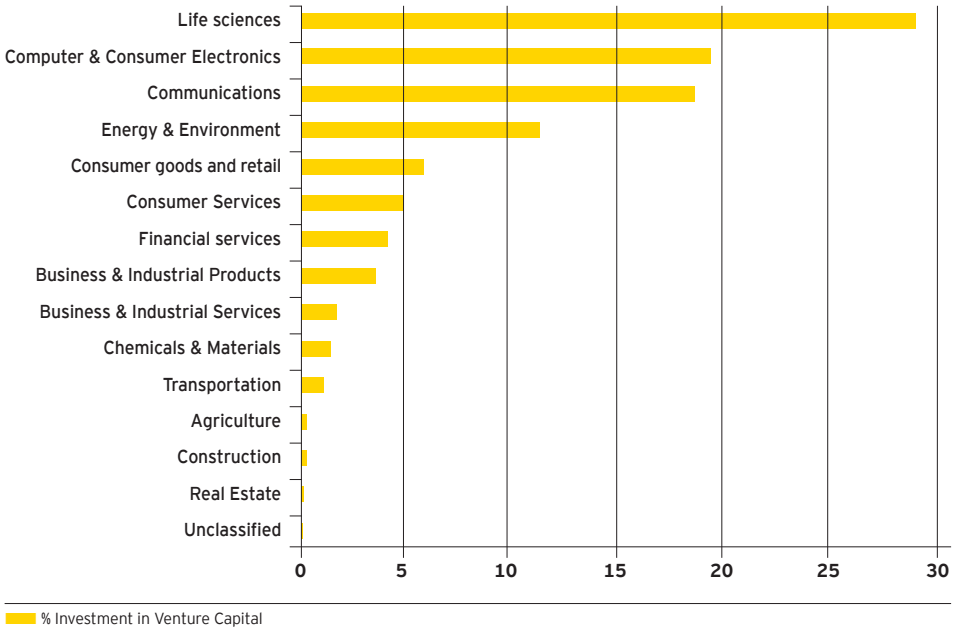
Looking at the European VC investments by stage focus in the 2007-2012 historical perspective, we are seeing a clear increase in the share of start-up stage ventures, which currently account for 56% of VC activity, compared to 35% in 2007. Conversely, the share of later-stage investments decreased from 58% in 2007, to 40.6% in 2012 (Figure 7.5).[8]

6. Source: National Venture Capital Association (NVCA)
7. Source: European Commission - Venture Capital
8. Source: European Private Equity and Venture Capital Association (EVCA)

The financing perspective

Figure 7.6

Venture Capital investments by sector – available EU countries data (2012)



In fact, 2012, too, confirmed the encouraging trend noted last year of innovative firms and research-based sectors receiving the major share of venture investment, thereby assisting the rebalancing European economies. The top sectors for investment continued to be life sciences (28.4%), computer and consumer electronics (19%), communications (18%) and energy and environment, which together accounted for nearly 77% of all venture investment (Figure 7.6).[7]

However, a potential threat remains with the high cash requirements of life science companies in particular. With the decline in 2007-2012 of later-stage funding, a cause of concern is the ability of the venture industry to maintain support for companies in these sectors, which often require successive tranches of investment

VC&PE activities in Italy: prospects for the biotech industry

After a weak recovery in 2012, the Italian private equity and venture capital market remained positive during first semester 2013 with an increase in the number and value of investments.

The Italian Private Equity and Venture Capital Association (AIFI), which collects six-monthly data on PE and VC investor activity in Italy, recorded 161 new transactions in first semester 2013. This was 10% more than the same period in the previous year and amounted to € 1,407 million, a 62% increase in value.

The majority were buyouts with € 923 million invested, up by 80% over the same semester in 2012, followed by expansion measures at € 415 million (+64%).

The early stage segment grew by 18% over first semester 2012 and, with 65 investments, ranked first ahead of the 64 expansion transactions (+19%).
More specifically, early stage transactions in high-tech sectors accounted for 69% of the total, demonstrating once again that investments in innovation drive the highest number of seed agreements or start ups.

Divestments of shareholdings totalled 65 (+48%) while, based on historical purchase price, the divested value increased from € 141 million to € 1,106 million (+683%). If the types of exit are considered in terms of figures and amounts, transfers to industrial partners took the lion's share (respectively 37% and 34% of the total).

As a result of funds activity in the healthcare sector during first semester 2013, good end-of-year results are expected, with a promising pickup in private equity activity and an overall increase in transactions and early stage activities.

While 2012 was exceptionally good, with large-scale transactions such as Kedrion, Lima Corporate, Bellco, Euticals, Izo and Labomar bringing the amount invested to € 355 million, a number of important agreements

over an extended period before realizing the commercial potential of their R&D.

This is particularly true for biotech companies where the incubation time from start-up to IPO or acquisition has increased from five years to about nine. For VC funds that are usually on a 10-year life cycle where the fund expects to cash out 10 years after starting, investments with an average nine-year timeline on returns create a problem. As a result, many VC funds prefer to invest in sectors with more rapid payoffs.

These numbers partly explain a significant trend in the last few years where more funding is coming from major pharmaceutical companies and less from VCs. The problem is that pharmaceutical companies are not typically as interested in early platform technologies and that, for them, "early stage" usually means a company right around the stage of filing an IND, which is the first step to getting approval for human testing of a new drug compound.

According to Ed Mathers, partner at New Enterprise Associate (NEA), one of the world's largest venture capital firms, pharma companies will eventually have to come back for innovative technology at some point since they have reduced their R&D capabilities in recent years. Further supporting this observation is the fact that about 50% of compounds currently in clinical trials are originated outside large pharma companies. Certainly, small biotechs are necessary to fill the pipeline with new innovative therapeutics, and will thus be the industry to keep the biotech environment fertile.

Based on the 2012 merger and acquisition data from the Swiss-based firm HBM Healthcare Investments, VC investors received 3.5 times their investment upon exit, in upfront payments alone.

This is a record and huge improvement over the less than two-fold return seen on upfront payments from 2005 to 2007. According to David Thomas, Director of Industry Research & Analysis at the Biotechnology Industry Organization (BIO) in Washington D.C., this might be the beginning of enticing more VCs to get off the sidelines and come back to biotech.

As already observed, a number of policy recommendations were made at the European level, as it is increasingly clear that the market is not providing the scale of investment that companies need. A number of governments have already taken specific action in favor of VC funding, ranging from tax exemption of capital gains arising from investments in innovative enterprises (Belgium, France, the Netherlands), to the development of subsidized loan programs that originate from matching funds, in which government intervention guarantees or limits the risk of the private investor (France).

While diverting public resources to the venture market in times of economic constraint continues to be a challenge, venture funding properly directed is an essential instrument in developing the new, growth industries of the future. The focus of funds on industries with high growth potential such as life sciences, computing, communications and energy provides some basis for optimism that, despite the decline in funding, the economic impact of those investments that are being made could be significant.

were signed in first semester 2013, among which the Charterhouse Capital Partners buyout of DOC Generici.

Over the past ten years, venture capital investments in biotech companies have risen significantly, demonstrating the interest that Italian operators hold in one of industry's most innovative sectors. After the peak reached in 2006, with 32 transactions totalling € 252 million, investments were impacted by market turbulence after the 2007 financial crisis. It was only in 2012 that hopes of a real turnaround finally returned when 35 transactions worth € 355 million were posted.

First semester 2013 results - with 18 transactions standing at € 36 million – seem to be promising, and investments in a very strategic sector for the country are expected to stabilize further in 2014.

However, there is still a great deal that can and must be done. On the one hand, make the financial community more aware of the potential of biotech companies. On the other, unfreeze the market by promoting the collection of new financial resources with special tax incentives, or ease divestments in shareholdings held by funds by simplifying M&A and IPO transactions. This will free resources for new investments and trigger new funds collection.

International benchmarking

Though Italian pure biotech companies are on average modestly capitalized, they were able to provide the business community with several true success stories, endorsing their attractiveness for rewarding venture opportunities. Besides being the expression of the results that may arise from the fruitful synergy of entrepreneurial skills, forward-looking investments and scientific expertise, these stories also remind us that there is much more we can do in order to fully exploit the innovation potential of biotechnology in Italy.

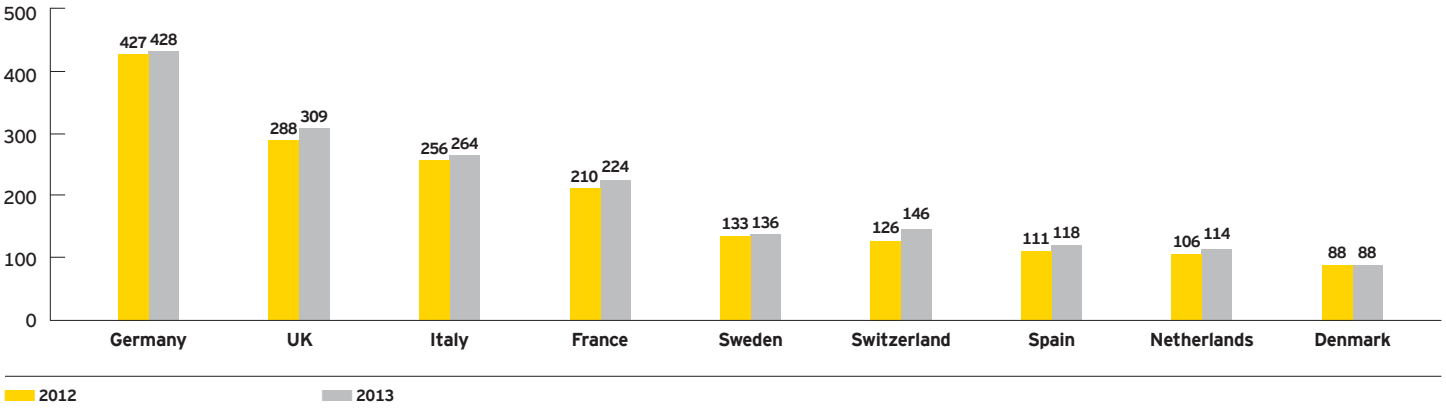
The 2014 Report, as a tradition, ends with an analysis of the key financial indicators that characterise the biotech sector in the main European countries. This comparison also allows us to ascertain where the Italian biotech companies stand, and what they are doing in order to cope with the current European scenario.

This benchmark was made possible also thanks to the data annually collected and published by EY Global Biotechnology Centre, in order to portray the state of the sector at an international level. The comparison of the Italian data with the ones presented in the "Beyond Borders" report is made possible because of the use of the same EY definition of "biotech company".

The Italian biotech industry is showing a slight increase in terms of number of companies compared with the previous year. In fact this trend is confirmed by the data presented below, which clearly show an increase in the number of pure biotech companies: from 256 in 2012 to 264 in 2013.

Figure 8.1

Number of pure biotech companies in the main European countries (Source: EY)



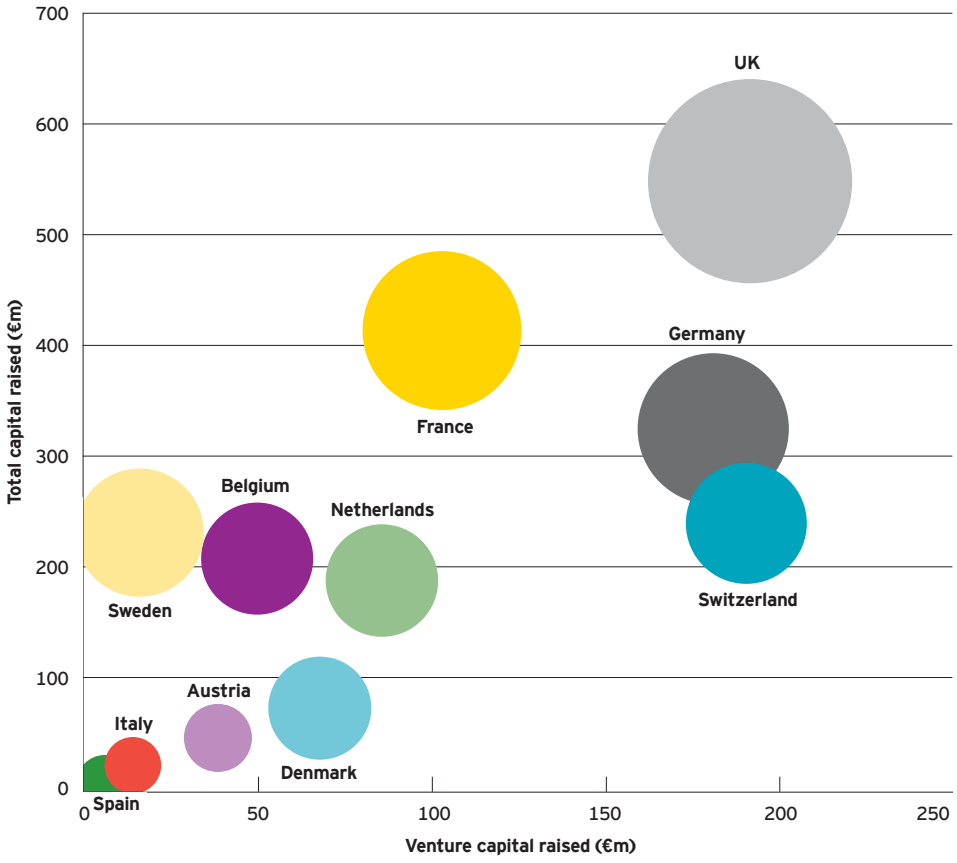
As regards the European scenario, the situation varies depending on the country: UK, France and Switzerland seem to be the only countries showing a considerable growth; Germany, Spain, Italy and The Netherlands are marginally growing, while no European country seems to show a decrease compared to the previous year. (Figure 8.1).

Figure 8.2 shows that Italy is far from the other countries in Europe in terms of VC development. In particular, we can notice that northern-European countries are much more attractive for venture capitalists. Specifically, as in the 2013 report, UK confirms to be the first venture capital collector in Europe, while Germany, Switzerland and France are followers. Italy and Spain are, on the other hand, at the very bottom of this ranking.

Based on the results of our survey, 14% of the pure biotech companies in our sample seek co-development, while about 6% pursue out-licensing deals. This draws our attention on an alternative way to develop the business, particularly when venture money is scarcely available. For pure biotech companies, strategic alliances become a potential solution for fund raising and for growth.

Figure 8.2

Capital raised by European countries in 2013. Size of bubbles shows number of financings per country
(Source: EY)



International benchmarking

Figure 8.3 compares the overall values of the strategic alliance agreements reached by the European pure biotech companies, namely with pure companies and with pharmaceutical companies, for the years 2011, 2012 and 2013.
What has emerged from 2013 is a recovery of the potential value of alliances in the industry, driven by the agreements between big-pharma and biotech companies. The value of the deals between biotech companies shows a strong increase, comparing the 2013 outcomes to the past. Overall, the total number of deals is decreasing: if in 2012 the total amount of the deals were 47, in 2013 the number was 43.

However, based on our analysis, 55% of the Italian pure biotech companies consider a strategic alliance to be an achievable option for next year, which is a lower percentage than the 78% originating from the answers of the companies of the entire sample (not just the pure biotech ones).

In order to raise money, companies may also look at an IPO on the public markets, although the amount of capital they can possibly raise is influenced by markets' conditions and by the macroeconomic scenario as a whole.

This explains the considerable number of biotech IPOs in Europe between 2005 (26) and 2006 (25) as well as the fact that in recent years, the number of public offerings has declined considerably. Compared to last year, when the number of IPOs in Europe stood at 3, 2013 looked more promising with 7 IPOs being successfully closed.

In year 2013 the potential value of Mergers and Acquisitions (M&A) between biotech companies has also increased, following 2012 in which, on the contrary, we had seen a dramatic reduction in the number of deals, compared to 2010 and 2011.

The 2013 market shows a significant growth in terms of number of offers and of total amount involved. On the one hand, there is a huge increase in the potential value of the biotech-biotech deals, and on the other even the transactions between large pharmaceutical companies and biotech companies show better results. As a matter of fact, both the total amount (approximately € 15 billion) and the number of deals (20) have increased significantly.

This trend is also confirmed by our survey: compared to 2012, the number of M&A transactions concluded by the companies in our sample increased from 2% to 9 %. However, probably due to the many uncertainties of the current economic scenario, M&A remains an unlikely (30%) or even very unlikely (40%) option for most of the companies surveyed.

Figure 8.3

Number of deals and potential values of alliances in the biotech industry in Europe. Values in millions of Euros (Source: EY)

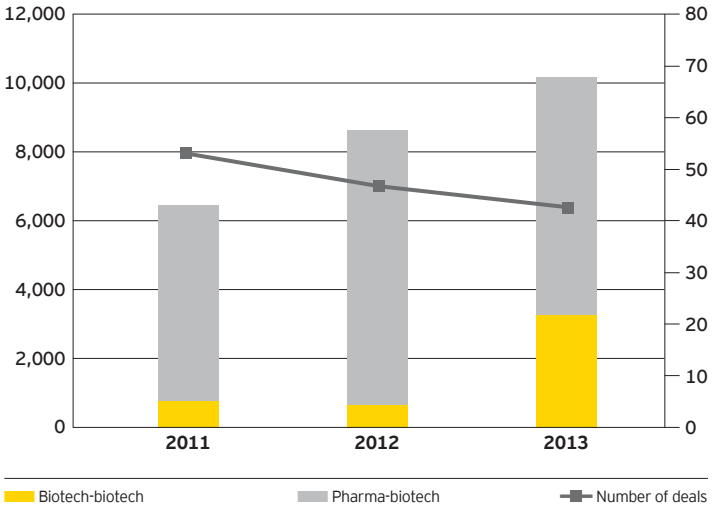
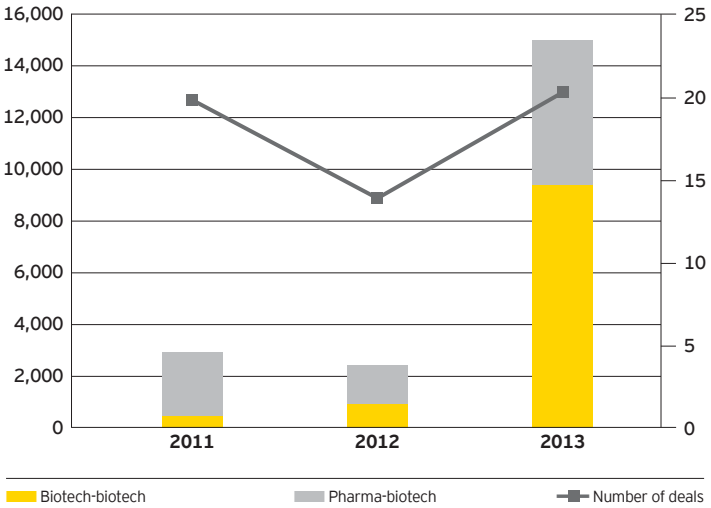


Figure 8.4

Number of deals and potential values of M&A transactions in the biotech industry in Europe. Values in millions of Euros (Source: EY)



International benchmarking

Table 8.1

Selected biotech alliances, deals and M&A in Italy (Source: EY)

Company 1		Company 2		Description of of the deal
Name	Country	Name	Country	
ADIENNE Pharma & Biotech S.r.l.	IT	Medical Need Europe AB	SE	ADIENNE Pharma & Biotech, an Italy-based pharmaceutical and biotechnology company, has signed an exclusive distribution agreement with Medical Need Europe AB, under which Medical Need will market and sell ADIENNE's Tepadina™ (thiotepa) in Denmark, Finland, Iceland, Norway and Sweden. Tepadina™ was approved as an orphan drug in the EU through an EMA centralized procedure in March 2010. The product holds a broad indication as conditioning therapy, in combination with other products or radiotherapy, in connection with hematopoietic stem cell transplantations (HSCT) and in high dose chemotherapy with HSCT support for the treatment of solid tumours, in both adults and children.
Philogen S.p.A.	IT	Pfizer Inc.	US	Philogen has entered into a worldwide license agreement with Pfizer for Dekavil, a novel investigational therapy for autoimmune diseases. Pfizer retains exclusive rights to market any products that may be developed as a result of the collaboration. Philogen will receive an upfront payment and will be eligible to receive milestone and royalty payments. Currently in phase I clinical testing, Dekavil has the potential to become a first-in-class therapy for autoimmune diseases. Pfizer plans to explore the activity of Dekavil in Inflammatory Bowel Disease in addition to Philogen's on-going clinical program for Dekavil in Rheumatoid Arthritis.
Toscana Biomarkers S.r.l.	IT	AMAR Immunodiagnostics plc	IND	A new ELISA kit for the diagnosis of rheumatoid arthritis will be produced and commercialized thanks to the collaboration between Toscana Biomarkers and AMAR Immunodiagnostics. The two companies have recently signed a license and supply agreement that follows the fruitful cooperation started about one year ago. According to this agreement, AMAR Immunodiagnostics will produce and commercialize in India an ELISA kit based on citrullinated peptides developed, patented and produced by Toscana Biomarkers, a research and development company dedicated to the discovery and validation of new tests for diagnosis and follow-up of autoimmune diseases. The kit is intended to detect anti citrullinated protein antibodies (called ACPA) in patients' sera. ACPA determination, which allows differentiating rheumatoid arthritis from other acute and chronic arthritis, even in the early stages of disease, has recently become one of the most important tests for diagnostic laboratories.
Versalis S.p.A.	IT	Yulex corporation	USA	Versalis, a global leader in elastomers and a subsidiary of the Italian based multinational group Eni, and Yulex Corporation, an agricultural-based biomaterials company, have entered into a strategic partnership to manufacture guayule-based biorubber materials, and will launch an industrial production complex in Southern Europe. The partnership will cover the entire manufacturing chain from crop science to biorubber extraction, to the construction of a biomass power station. Versalis will manufacture materials for various applications: after an initial focus on consumer and medical specialty markets, The partnership will leverage Yulex's core competencies including crop science and biorubber extraction technologies, to boost Versalis' bio-based portfolio. The investment will include an ambitious research project to develop technologies targeting the tire industry.
Nerviano Medical Sciences S.r.l.	IT	Les Laboratoires Servier S.A.S.	FR	Nerviano Medical Sciences and Servier announced a collaboration and worldwide license agreement to further develop and commercialize first-in-class Nerviano compounds inhibiting the protein kinase TTK/MPS1. A key regulator of mitosis, TTK/MPS1 is aberrantly overexpressed in a wide range of tumours and represents a promising target in oncology. Terms of the collaboration include an upfront fee of € 8 million and a potential for up to € 100 million in option fees, clinical and regulatory milestones in addition to royalties for the sale of licensed products. Under the terms of the agreement, Nerviano will complete the preclinical development of the lead candidate drug and, if Servier exercises the option, Servier will bear all development and commercialization costs. Nerviano will continue to support Servier for the early clinical development and the supply of the licensed product.
Okairos AG	CH - IT	GlaxoSmithKline (GSK)	UK	In order to further expand its vaccines platform technology expertise, GlaxoSmithKline (GSK) has acquired Okairos AG for € 250 million in cash. Although incorporated in CH, Okairos is an Italian clinical-stage biopharmaceutical company, spun out from Merck in 2007, which has developed a novel vaccine platform technology that is expected to play an important role in GSK's development of new prophylactic vaccines as well as new classes of therapeutic vaccines. Okairos' technology complements GSK's existing vaccine technology and expertise, and will enable GSK to continue its work developing the next generation of vaccines.
Silicon Biosystems Inc.	US - IT	PGXL Technologies LLC	US	PGXL Technologies and Silicon Biosystems Inc. announced a collaborative partnership to make the highly regarded Silicon Biosystems DEPArray technology available through PGXL Technologies. The PGXL programme will allow clinical researchers and pharma sponsors to obtain the level of data fidelity and resolution needed in cancer biomarker discovery and translational research. PGXL Technologies is the sister company of PGXL Laboratories, a global leader in the clinical application of pharmacogenetic and molecular diagnostic testing for personalized medicine. In October 2013, the National Cancer

Company 1		Company 2		Description of of the deal
Name	Country	Name	Country	
				Institute (NCI) has selected PGXL Technologies as one of four recipients of funding for development of circulating tumour cell (CTC) isolation technologies that enable downstream molecular analysis of single cells. PGXL Technologies will leverage Silicon Biosystem's DEPArray™ technology to help meet the goals of the NCI contract.
Silicon Biosystems S.p.A.	IT	Menarini Group S.r.l.	IT	The Menarini Group has acquired Silicon Biosystems, a provider of specialized molecular and cellular biology technologies capable of recovering and analysing tumour cells from blood samples. Silicon Biosystems' DEPArray™ and Ampli1™ genomic analysis technologies are being used in clinical research to advance the development of cancer diagnostics and accelerate the age of precision medicine through personalized therapies. Financial terms of the acquisition were not disclosed.
Nerviano Medical Sciences S.r.l.	IT	Ignyta Inc.	US	Nerviano Medical Sciences has signed a license agreement with Ignyta, granting the American biotech company exclusive global development and marketing rights to RXDX-101 (a tyrosine kinase inhibitor directed to the TrkA, ROS1 and ALK proteins, in clinical development in molecularly defined patient populations for the treatment of solid tumours) and RXDX-102 (a tyrosine kinase inhibitor directed to the Trk family tyrosine kinase receptors, TrkA, TrkB and TrkC, which is currently in preclinical development for the treatment of multiple cancers). Under the terms of the agreement, Ignyta will assume sole responsibility for global development and commercialization of RXDX-101 and RXDX-102. Nerviano will be entitled to receive certain upfront and milestone payments, as well as tiered royalty payments on future net sales of RXDX-101 and RXDX-102.
Bio3 Research S.r.l.	IT	Xediton Pharmaceuticals Inc.	CA	Bio3 Research has granted Xediton Pharmaceuticals an exclusive license to market its dietary supplement BiocysanTM in Canada. Bio3 Research will be also responsible for the supply of the finished product. BiocysanTM is a dietary supplement, based on oral L-Cysteine, for individuals who are at risk of developing severe anaemia, via re-establishing GSH levels in the blood.
EOS (Ethical Oncology Science) S.p.A.	IT	Clovis Oncology Inc.	US	Sofinnova Partners, an independent venture capital firm based in Paris, announced the sale of portfolio company Ethical Oncology Science (EOS), an emerging biopharmaceutical company based in Milan, developing novel targeted medicines to treat cancer, to Clovis Oncology for up to $ 420 million (€ 310M). Under the terms of the agreement, Clovis has acquired EOS for an up-front payment of $ 200 million, which includes $ 190 million in Clovis common stock (3,713,731 shares) and $ 10 million in cash. Clovis will pay an additional $ 65 million in cash upon the initial approval of lucitanib by the FDA. Pursuant to a license agreement that EOS signed with Servier in 2012, Clovis is entitled to receive up to € 350 million (approximately $ 470 million) upon the achievement of development and commercial milestones, as well as royalties on sales of lucitanib in the Servier territories. Clovis will also pay the EOS shareholders up to an additional € 115 million in cash upon the receipt by Clovis of certain of the milestone payments pursuant to this license agreement.
MolMed S.p.A. (MLM.MI)	IT	GlaxoSmithKline (GSK)	UK	MolMed has entered into an agreement with GlaxoSmithKline (GSK), under which MolMed will be responsible for the manufacture of GSK's investigational gene therapy for compassionate use in patients with Adenosine Deaminase Deficiency - Severe Combined Immune Deficiency (ADA-SCID). MolMed previously produced, on behalf of Telethon, the investigational gene therapy where the correct form of the ADA gene is inserted into the patients' own bone marrow derived stem cells. GSK is now continuing the clinical development of the ADA-SCID gene therapy in collaboration with the San Raffaele Telethon Institute for Gene Therapy (HSR-TIGET), from which GSK has in-licensed the rights to develop and commercialize the therapy.
Nicox S.A.. (NYSE Euronext Paris: COX)	FR - IT	Eupharmed S.r.l.	IT	Nicox will acquire 100% of the shares of Eupharmed, a privately-held Italian ophthalmic company, for € 3.5 million in newly issued Nicox shares, plus a potential, additional earn-out payment linked to the achievement of certain business objectives. The acquisition provides Nicox with an established sales and marketing platform in Italy together with a broad portfolio of eye care products. Eupharmed had sales of € 3.6 million in 2012, and is expected to achieve full-year sales of approximately € 3.9 million in 2013. The acquisition is part of Nicox's strategy to establish sales infrastructure in the five major European markets and in the United States.
Gentium S.p.A. (Nasdaq:GENT)	IT	Jazz Pharmaceuticals plc (Nasdaq:JAZZ)	IRL	Jazz Pharmaceuticals and Gentium announced that they have entered into a definitive agreement pursuant to which a subsidiary of Jazz Pharmaceuticals will make a cash tender offer of $57 per share for all outstanding Gentium ordinary shares and American Depository Shares, in a transaction that is valued at approximately $1 billion. In October 2013, the European Commission granted Gentium the marketing authorization for the company's lead product DefidelioTM (defibrotide), for the treatment of severe hepatic veno-occlusive disease (VOD).

When the synergy of entrepreneurial skills, forward-looking investments and scientific expertise makes a success story

Figure 8.5

2013 Venture Capital investment in biotech – global
(Source: EY)

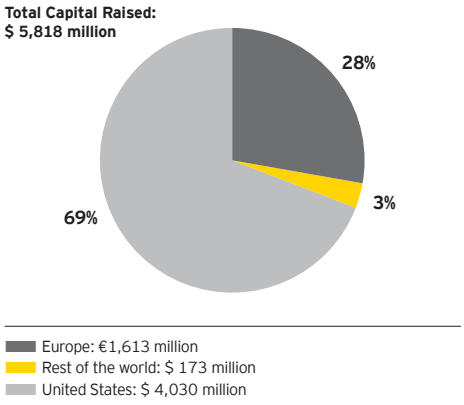
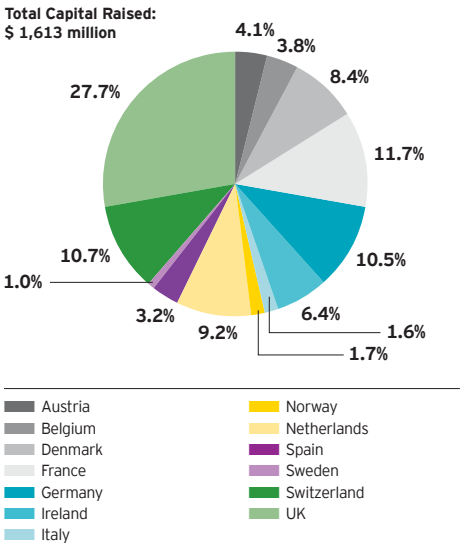


Figure 8.6

2013 Venture Capital investment in biotech – Europe
(Source: EY)



An internal analysis of the 2013 financial data relating to venture investments in biotechnology, (Figure: 8.5), highlights once again the gap between United States and Europe. Out of a global investment of $ 5.8 billion, approximately 69% of the resources went to US biotech companies ($ 4.03 billion), while only 28% to European biotech firms ($ 1.613 billion).

Focusing on the European figures alone, Italy is lagging far behind compared to the other European countries: Italian biotech companies have in fact picked up only 1.6% of the total VC investment in Europe, compared to 27.7% in UK, 11.7% in France, 10.5% in Germany, 9.2% in the Netherlands, 8.4% in Denmark, or even to 4.1% in Austria, 3.8% in Belgium and 3.2% in Spain (Figure 8.6).

The emphasis placed by the European legislator on the importance of the development of a strong and dynamic Venture Capital market, as a key prerequisite for the growth and stability of the entire economic system, was already highlighted in the previous chapters of the present report.

Similarly, we also made the point that the weakness and heterogeneity of the European reality is also attributable to differences in the industrial texture of the EU Countries, the diversity of the policies adopted by the individual member States in order support and attract venture investments, as well as the heterogeneity itself of the intermediaries and financial instruments involved.

As a matter of fact, the VC&PE market is still underdeveloped in Italy, compared to what happens in other European economies, and the re-launching of the national industrial system will largely depend on the local capacity to increase the pool investors, not only with the funds, but also with the expertise that is necessary to support the creation and growth of new innovative start-ups and entrepreneurial initiatives.

This is even more true in the case of biotech companies, although we have had a number of true and significant success stories in the course of 2013, endorsing the attractiveness of the Italian biotech industry for fruitful venture opportunities.

Reference is made to the cases of those companies that managed to exploit the results of their basic research activities through considerable development capabilities, and that have been able to create shareholder value by bringing their innovative technologies and products to the market.

As well as being the expression of the outstanding results that may arise from the fruitful synergy of entrepreneurial skills, forward-looking investments and scientific expertise, these stories also remind us that there is much more we can do in order to fully exploit the innovation potential of Italian biotechnologies.

A number of these deals are a clear sign of the quality of Italian academic research. This is the case of the Tigem (a Telethon Institute) collaborative research agreement with Shire, in late 2012, related to new therapies for lysosomal storage and neurodegenerative diseases, which allowed the Italian institute

five years financial support for its research activities, with a licencing option for future clinical developments.

In a similar framework, this is also the case of MolMed, a mid-ninety academic spin-off that has grown today into a medium enterprise, listed on the Italian Stock Exchange. Recently, MolMed has entered into an agreement with GlaxoSmithKline (GSK), and will be responsible for the manufacturing of GSK's investigational gene therapy for compassionate use in patients with ADA-SCID, previously produced on behalf of Telethon. GSK is now continuing the clinical development of the ADA-SCID gene therapy in collaboration with the San Raffaele Telethon Institute for Gene Therapy (HSR-TIGET), from which GSK has in-licensed development and commercialisation rights.

From a business angle, it is also worth mentioning the recent venture (Hit Discovery Constance GmbH) founded by Axxam, a leading Italian provider of discovery services, with two other key partners such as Lead Discovery Center (Dortmund/Germany) and Centre for Drug Design and Discovery (CD3, KULeuven, Leuven/Belgium). The new company is based in Constance (Germany) and will make use of the already established equipment and know-how of the former Takeda/Nycomed/Altana research site. Combined with Axxam`s already established HTS discovery platforms, HDC represent one of the largest screening hubs worldwide.

In a an M&A perspective, a number of significant transactions occurred in 2013, starting from the acquisition of Okairos, an Italian clinical-stage biopharmaceutical company, by GSK for € 250 million in cash. Spun-out from Merck in 2007, Okairos had raised more than € 23 million from venture funds and obtained public grants for € 25 million. In a relative short time, the company developed a novel prophylactic and therapeutic vaccine platform technology which complements GSK's existing vaccine technology and expertise.

In September 2013, Silicon Biosystems, an innovative Italian diagnostics company, was acquired by the Menarini Group. The genomic analysis technologies developed by Silicon BioSystems are being used in clinical research to advance the development of cancer diagnostics and accelerate the age of precision medicine through personalized therapies, and will contribute to Menarini's pharmaceutical and biotechnology programmes in oncology.

In November last year, Ethical Oncology Science (EOS), an emerging biopharmaceutical company developing novel targeted medicines to treat cancer, was acquired by Clovis Oncology for up to $420 million (€310m). EOS had already raised € 25 million capital, and signed an upfront € 45 million license agreement with Servier on its lead compound lucitanib (E-3810). Significantly, in terms of funding repeat entrepreneurs, Sofinnova had already backed the company's founders in Novuspharma, a spin off from Hoffmann La Roche that went public in Italy in 2000, and was then successfully sold to CTI, a Nasdaq listed company.

An additional milestone is also the cash tender offer from Jazz Pharmaceuticals for Gentium, an Italian manufacturing and development biopharmaceutical company, listed on the Nasdaq, in transaction that is valued at approximately $ 1 billion. Said offer, which was announced in December 2013, follows marketing authorization for the company's lead product defibrotide (the first product resulting from the research activity of an Italian pure biotech company to reach the market), for the treatment of severe hepatic veno-occlusive disease (VOD), in October. Gentium's shares have been increasing up to 600% since January 2013.

A number of commercial deals are also noteworthy, including the worldwide license agreement between Philogen and Pfizer for Dekavil, a novel investigational therapy for autoimmune diseases, and the five year agreement between DiaSorin, a global leader for in vitro diagnostics listed on the FTSE MBI Index, and Hoffmann La Roche, to allow the connectivity of the LIAISON XL System developed by the Italian multinational Group, to the Roche Cobas 8100TM automated workflow series.

If in a global world such as the biotech industry, scientific results overcome geographic frontiers, the quality of Italian research also seems to be behind the success of many foreign companies. This is the case of Intercept, the New York-based biotech which rose almost fourfold on January 9, 2014 after the company announced that a trial for a new liver disease drug combating non-alcoholic steatohepatitis (NASH) was stopped early after the primary endpoint of the trial was met. As a matter of fact, Intercept's science originated at the University of Perugia, and a significant owner of its stock is Genextra, an Italian biopharma investment company created in 2004 by a group of prominent Italian entrepreneurs and financial institutions, in partnership with leading scientists from the European Institute of Oncology (IEO).

Once again, the recent history of the Italian biotech sector is a proof of the excellence of our research, as well as of the outstanding capacity of our firms to transform innovation into valuable products and enterprise value, taking advantage from experienced entrepreneurs, managers and scientists.

Methodology

The 2014 Italian Biotechnology Report uses the same EY methodology consolidated over the last four years. In doing so, we were not only able to analyse the financial trends in the 2012-2013 period, together with the articulated reality of biotechnology in Italy, but also to compare the data with those drawn from other studies on the biotech sector conducted internationally by EY. Consequently, the decision to entrust the writing of this report once again to EY was crucial not only to increase the time frame of the analysis, but also to ensure the highest methodological consistency with previous studies.

Also in the 2014 report, reference is made to 2013 for all the general information about the companies under consideration, with the exception of economic-financial data that refer more to the accounting year 2012.

Similarly to what was already done in the previous reports, companies within the sample have been split into two main types:

- Companies that "use modern biological techniques to develop products or services for the treatment of humans or animals, agricultural productivity, renewable resources, industrial production and environmental protection", and whose core business falls among these activities, defined as "pure biotech" according to the definition adopted by EY;
- Enterprises that, according to the OECD definition, use "at least one biotechnological method to produce goods or services, or research and development in the biotech field," and with a smaller share of their economic activities related to biotechnology, defined as "other biotech". For the purpose of our analysis, "other biotech" includes the Italian pharmaceutical companies, the subsidiaries of multinational companies based in Italy and "other Italian biotech", such as CRO (Contract Research Organisation) and other companies not related to the above types.

As usual, the companies of the sample were classified according to the application area in which they operate (Table 9.1)

The data we compiled and analysed were primarily collected by means of the questionnaire sent by Assobiotec, in cooperation with Farmindustria, to the companies in the sector. Once again, this approach allowed us to access information not normally available from public

Table 9.1

Biotech companies: definition of the sectors of application

	Definition
Pure biotech	Companies whose core business activities are exclusively related to biotechnology
Other Italian biotech	Other biotech companies that use at least one biotechnological method to produce goods and services to carry out research in the biotech field, without this being the core business of the firm
Red biotech	Biotechnology applied to human health: use of modern biotechnological methods for the development of therapeutic products, tissue engineering, vaccines, drug delivery technology, methods of molecular diagnostics, drug discovery activities and cosmetics
Green biotech	Agro-food biotechnology: use of modern biotechnological methods for the production of transgenic plants with applications in food, chemical, manufacturing, molecular pharming (pharmaceutical production in plants), tests for the detection of ingredients or contaminants in food
White biotech	Industrial biotechnology: use of modern biotechnological methods for production and processing of chemicals, materials and fuel, including technology for environmental bioremediation
GPET	Genomics, Proteomics and Enabling Technologies: methods and techniques of genomics (investigation of the structure and function of genes) and proteomics (analysis of protein expression, structure, post-translational modifications, interactions and function), bioinformatics technologies, bio-chips and other bio-related tools, biopharmaceutical productions, etc.
Multi-core	Companies that operate in at least two of the application areas mentioned above

sources. For the companies who did not reply to the questionnaire, the information was gathered by consulting balance sheets and corporate websites, as well as the international database of EY. We identified 422 companies that carried out activities in coherence with the definition of biotech company that we have adopted (Table 9.2).

Of 35 new companies that we identified, 7 were actually set up in 2012, while the other 28 were identified thanks to our market screening ability and added to the 2013 sample, while 4 firms were excluded, not being properly included last year; these changes are intended to avoid distortions in the comparison phase, because of different sampling. In 2012, the firms no longer active in the field were 19, due to bankruptcy or liquidation.

As regards red biotech, Table 9.3 defines the different application fields composing the sector. For the therapeutics pipeline, the information comes directly from the companies or thanks to Assobiotec screening of public sources.

With reference to new entries, in the 2013 Report we considered it appropriate to provide an overview of the innovation landscape, and we requested the contribution of the BioTTasa project team. BioTTasa is a project co-financed by the Ministry of Economic Development notice of call RIDITT, which aims at developing a broad spectrum of technology transfer initiatives, including patent licenses, research contracts and business creation in the field of biotechnologies, starting from those developed by the CNR laboratories in the following areas: Diagnostics and development of innovative drugs, Gene therapy, Biosensors in the field of food and environment, Biodiversity and Bioenergetics and Research Services.

Table 9.2

Results of data collection: comparison of the 2012 Report, 2013 Report, and 2014 Report with reference to target companies and companies analysed *

	2012 Report	2013 Report	2014 Report
Sample*	394	407	422
- Questionnaires received	155	155	142
- Information from external sources	239	252	280
No information	232	283	253
New companies	54	48	35
- Set up the previous year	21	34	28

* *The table shows the biotech data in our possession at the date of report publication*

Table 9.3

Red biotech: application fields

Application field	Description
Therapeutic	Drugs or other therapeutic approaches, such as gene or cell-based therapies, including: - biologicals: recombinant proteins, monoclonal antibodies, products based on nucleic acid technology and cell therapy - low molecular weight compounds (small molecules): pharmaceutical products which are developed, tested, or identified by means of screening methods based on biotechnology - Advanced Therapy products: gene therapy, cell therapy and tissue engineering
Vaccines	Biological preparations for prophylaxis and treatment
Drug delivery	Technologies to convey the drugs to a specific site through optimization of their absorption and their distribution (advanced materials, liposomes, antibodies, cell therapy, etc.)
Molecular diagnostics	Tests and methods based on DNA/RNA for the diagnosis, prognosis and detection of any predispositions to specific diseases and for the analysis of pathogenic mechanisms
Drug discovery	Synthesis, optimization and characterization of drug candidates, assay development, screening and validation activities on medicinal products

Appendix

Companies with R&D activities in Italy

- A.A.A. - Advanced Accelerator Application
- AAT - Advanced Analytical Technologies
- A.T. Grade
- Ab Analitica
- Abbvie
- Abiel
- Aboca
- Accelera
- Actelion Pharmaceuticals Italia
- Actygea
- Adienne
- Advanced Biotech Italia
- Agrifutur
- Agritest
- Agroils Technologies
- Agrolabo
- Alexion Pharma Italy
- Alfa Biotech
- Algain Energy
- Algares
- Alicebiosources
- Allergan
- Alltox
- Also Biotech
- Altergon Italia
- Ambrosia Lab
- Amgen
- Anabasis
- Analisi & Controlli
- Anallergo
- Ananas Nanotech
- Angelini
- Apavadis Biotechnologies
- Aptalis Pharma
- Aptenia
- Aptuit
- Apuliabiotech
- Archimede R&D
- Ardis
- Areta International
- Arintha Biotech
- Arterra Bioscience
- Asoltech
- Associated Drug Designers
- Avantea
- Axxam
- B&C Biotech
- Bayer
- BBA Biotech
- BCS Biotech
- Beta Renewables
- BGT Italia Biogenomic Yechnology
- Bict
- Bio Fab Research
- Bio Flag
- Bio Genetix
- Bio Hi-Tech
- Bio3 Research
- Bioaesis
- Bioagro
- Bioanalisi Trentina
- Biocell Center
- Bioci Di Ciaiolo Carlo
- Biocomlab
- Biodermol
- Biodigitalvalley
- Bioecopest
- Biofer
- Biofordrug
- Biogen Idec Italia
- Biogenera
- Bio-Ker
- Biolife Italiana
- Bioman
- Biomarin Europe
- Biomat
- Biomatica
- Biomedical Research
- Biomedical Tissues
- Biomerieux Italia
- Biomicroshear
- Bionat Italia
- Bionucleon
- Bio-On
- Bioops
- Biopaint
- Biopox
- Bioprogress Biotech
- Bio-Rad Laboratories
- Biorep
- Biorimedia
- Biorna
- Biosearch Ambiente
- Biosistema
- Biosoilexpert
- Biosphere
- Biostrands
- Biosuma
- Biosynt
- Biotecgen
- Biotech 4
- Bioteck
- Biotest Italia
- Biotrack
- Biouniversa
- Biounivet
- Bluegreen Biotech
- Bluesod Lab
- Bmr Genomics
- Boehringer Ingelheim Italia
- Bouty Healthcare
- Bracco Imaging
- Bristol-Myers Squibb
- Bsa Ambiente
- Btm Biological Tools For Mediterranean Agricolture
- Byflow
- Colosseum Combinatorial Chemistry Centre For Technology
- C5-6 Italy
- Cage Chemicals
- Callimaco
- Cbm Scrl
- Ccs Aosta
- Ceinge Biotecnologie Avanzate
- Celgene
- Celldynamics
- Cereplast
- Charles River Laboratories Italia
- Chemi
- Chemtex Italia
- Chiesi Farmaceutici
- Chorisis
- Chrono Benessere
- Clonit
- Cogep
- Congenia
- Cosmo Pharmaceuticals
- Costantino E C.
- Cpc Biotech
- Creabilis Therapeutics
- Crs4
- Crucell
- Cryolab
- CSL Behring
- Cti
- Cutech
- Cyanagen
- Cyanine Technologies
- Cyathus Exquirere Italia
- Dac
- Dalton Biotecnologie
- Delos Ricerche
- Derming
- Di.V.A.L.
- Dia.Pro Diagnostic Bioprobes
- Diasorin
- Diatech
- Diatheva
- Diesse Diagnostica Senese
- Diesse Ricerche
- Dna Analytica
- Dompé
- DSM Biosolution
- Ecobioservices And Research
- Ecoil
- Ecotechsystems
- Elan Pharma Italia
- Eli Lilly Italia
- Eos
- Ephoran Multi Imaging Solutions
- Epic
- Epigen Technologies
- Epinova Biotech
- Epitech
- Eridania-Sadam
- Erydel
- Espikem
- Eugenomics
- Euroclone
- Eurosen
- Eurospital
- Eurovix
- Euticals
- Exenia Group
- Exosomics Siena
- Experteam
- Explera
- Explora
- Externautics
- Fabbrica Italiana Sintetici
- Fase1
- Fatro
- Fedra Lab
- Fem2 - Ambiente
- Ferrari Biotech
- Fidia Advanced Biopolymers
- Finceramica Faenza
- Fly Life
- Food Research Innovation
- Fotosintetica & Microbiologica
- G&Life
- Galileo Research
- Geistlich Biomaterials Italia
- Geltis Biotech
- Gemiblab
- Genechron
- Genedia
- Genespin
- Geneticlab
- Genomix4life
- Genomnia
- Genovax
- Gentium

- Gentoxchem
- Genzyme
- Gexnano
- Gilead Sciences Italia
- Gio.Eco
- Giotto Biotech
- Glaxosmithkline
- Glyconova
- Gnosis
- Godiagnostics
- Grape
- Green Lab
- Greenceutics
- Grifols Italia
- Hmgbiotech
- Ho.P.E.
- Holostem Terapie Avanzate
- Hpf Nutraceutics
- Hygeia Lab
- Idrabel Italia
- Iga Technology Services
- Inbios
- Incura
- Indena
- Innovate Biotechnology
- Integrated Systems Engineering
- Intercept Italia
- Intermune
- International Plant Analysis And Diagnostics
- Iom Ricerca
- Ipsen
- Isagro
- Isb Ion Source & Biotechnologies
- Isogem
- Istituto Biochimico Italiano Giovanni Lorenzini
- Istituto Di Ricerche Biomediche Antoine Marxer
- I.R.B. Istituto Di Ricerche Biotecnologiche
- Italfarmaco
- Janssen-Cilag
- Kayser Italia
- Kedrion
- Kemotech
- Kither Biotech
- Kos Genetic
- Kron Morelli
- Ktedogen
- Laboratorio Genoma
- Lea Nanotech
- Life And Device
- Life Line Lab
- Lipinutragen
- Lofarma
- Mater Biotech
- Matric Europa
- Matrica
- Mavi Sud
- Med & Food C.Q.S.
- Medestea Research & Production
- Mediapharma
- Mediteknology
- Menarini Biotech
- Merck Serono
- Meristema
- Metapontum Agrobios
- Mbs
- Micro4you
- Microbiotec
- Microbo
- Microgenomics
- Micron Research Service
- Millipore
- Mindseeds Laboratories
- Mismed
- Molecular Biotechnology
- Molmed
- Molteni Therapeutics
- Murotherapy
- Mybasol
- Mybatec
- Myrmex
- N.T.I.
- Naicons Scrl
- Nano4bio
- Nanomaterials.It
- Nanomed Labs
- Nanomed3d
- Nanosurfaces
- Nanovector
- Narvalus
- Natimab Therapeutics
- Naxospharma
- Nealys
- Need Pharmaceuticals
- Nerviano Medical Sciences
- Neuheart
- Neuroscienze Pharmaness
- Neuro-Zone
- Next Genomics
- Nexthera
- Ngb Genetics
- Nicox Research Institute
- Nobil Bio Ricerche
- Noray Bioinformatics
- Notopharm
- Novagit
- Novamont
- Novartis Vaccines And Diagnostics
- Novartis
- Novo Nordisk
- Noxamet
- Nurex
- Nutraceutica
- Nutrigene
- Officina Biotecnologica
- Okairos
- Oncoxx
- Ophera
- P.A.N. Piante Acqua Natura
- Personal Genomics
- Pfizer Italia
- Pharmago
- Pharmadiagen
- Pharmeste
- Philogen
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- Phytoremedial
- Pincell
- Plantechno
- Plasmore
- Polymed
- Prigen
- Primm
- Probiotical
- Procelltech
- Progefarm
- Promis Biotech
- Proteotech
- Proxentia
- Raresplice
- Ravano Green Power
- Recordati Industria Chimica & Farmaceutica
- Relivia
- Remembrane
- Research And Innovation
- Resindion
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- Rigenerand
- Roche Società Unipersonale
- Rotalactis
- Rottapharm Biotech
- Sacace Biotecnologies
- Sacom
- Safan Bioninformatics
- Salentec
- Sanofi
- Sclavo Diagnostics International
- Serge Genomics
- Setlance
- Shire Italia
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- Sigma-Tau Industrie Farmaceutiche Riunite
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- Tecan Italia
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- Tecna Lab
- Tectronik
- Tethis
- Teva Italia
- Therabor Pharmaceuticals
- Tib Molbiol
- Tissuelab
- Toma Advanced Biomedical Assays
- Top
- Tor
- Toscana Biomarkers
- Transactiva
- Trustech
- Turval Biotechnologies
- Tydockpharma
- Ucb Pharma
- Ufpeptides
- Versalis
- Vetogene
- Vetspin
- Virostatics
- Vismederi
- Vivabiocell
- Wetware Concept
- Wezen Biopharmaceuticals
- Xeptagen
- Ylichron

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Art direction:
In Pagina sas, Saronno (VA)

Print:
Elledue, Milan

Milan, February 2014

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