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Italian Biotechnology Report

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Alessandro Sidoli
President of Assobiotec

The 2011 edition of the "Italian Biotechnology Report" by Assobiotec and Ernst & Young, in cooperation with Farmindustria and ICE, shows that the Italian biotech industry has responded positively to the difficult international economic situation by confirming the growth and consolidation trend which has characterized this field over the last decade. This is of major importance for Assobiotec, the national association for the development of biotechnology - celebrating the 25th anniversary of its foundation this year - that represents companies and technological and scientific parks operating in Italy in the various sectors of Life Sciences.

Over the last few years, biotechnology in Italy has become an established industrial reality in all fields of application, including human health, agro-food, and industry. The path has been difficult, but even so the biotech sector has progressed enormously, resulting in well-earned respect on an international level - an unimaginable achievement just a few years ago. Our biotech companies show that they are remarkably capable of maximizing investments in terms of value creation, that they can count on absolutely competitive scientific excellence and on the presence of an important link with academic research and, most of all, that they are still driven by the spirit of initiative that characterizes so many successful stories of Italian entrepreneurs. These are the reasons that explain the significant growth rate of biotech also in our country.

Human health (red biotech) is certainly the most representative and developed sector: our companies have a solid pipeline of highly innovative drugs and diagnostics resulting in a constantly increasing number of R&D products. This high level of excellence is also shown by the increased number of orphan drug designations obtained by new drugs for the treatment of rare diseases, a field in which the Italian red biotech companies play a major role, especially due to the qualified contribution of our academic research which produces the highest number of scientific publications in this field.

At the same time, the growth in terms of number and turnover of companies applying new biotech methods in the agro-food (green biotech) and industrial (white biotech) fields further confirms the pervasive potential of these technologies and their extraordinary involvement in the successful development of models that are based on biodiversity and eco-sustainability. Furthermore, the application of nanotechnology to biology and biochemistry (nanobiotechnology) will have an extraordinary impact in terms of scientific and technological development not only in the fields of medicine and diagnostics, but also in the green and white biotech sectors.

Although Italian biotech is characterized by recognized scientific excellence and a high degree of dynamism, it still needs a rigorous framework of economic, financial and fiscal interventions to foster research and innovation, and adequate capitals to support the very high long-term investments typically required in this field. Such strategies have already been successfully implemented by several European governments, competing with each other in making massive investments, attracting excellence and resources and building synergies.

We hope that Italy, too, will establish a specific development strategy to help create an increasingly solid and meaningful entrepreneurial and industrial network. Adequate and consistent regulations are needed, which should take into account all the specificities of this field, to ensure the best allocation of resources and favor new investments in order to reinforce the competitiveness of the whole Italian research and innovation system.

This is an important objective on which our Association, together with the companies, the entrepreneurs and the managers of the entire biotech sector, will continue to work tenaciously and enthusiastically, convinced as we are that Italy deserves to and can compete in one of the key sectors for the re-launch of economy and employment, as well as for the quality of life for future generations.

Sergio Dompé
President of Farmindustria

Biotech Research and Revolution: the Growing Role of Italy

Biotechnology is offering a radical revolution for human health today. Companies and R&D investments are constantly growing, accounting for 90% of the overall biotech turnover

The figures confirm that "Red biotech" is driving biotechnology in Italy.

There are 246 companies, mainly small in size, contributing for the most part to research projects with 237 products in the development phase, many of which for the treatment of cancer, neurological and autoimmune diseases, and accounting for more than 30% of the total clinical trials conducted in our country.

These research activities of "pure biotech" companies are focused on the initial phases of product development. Eighty-six percent of the projects are in the discovery phase and almost 80% in the preclinical phase, thus fueling innovation by pharmaceutical companies which play a crucial role in the clinical development of drugs. Indeed, these companies support almost 70% of the R&D investments in biotechnology for human health.

The pharmaceutical industry is thus showing its intent to enhance biotech potential and participate in the "network", in response to the changes in supply and demand on an international level.
The degree of specialization is increasing and the knowledge required is more and more diversified and complex. Indeed, real changes today result from partnerships. Scientific discoveries stem less and less often from a single "brain", but result from the cooperation between universities, public and private research centers and companies.

The capability of developing a leadership in a specific field and of introducing it into the international network of excellence is the vital success factor. Nothing else.

Particularly in the biotech field, this new research model offers important growth opportunities for small academic start-ups and spin-offs, which often provide the technological transfer for implementing projects that will be developed by larger companies.

Over 75% of the products and projects developed in Italy are classified as "first in class" and more than 80% have been granted at least one patent, thus confirming the high degree of innovation of the system.

And this is not all. Italy is to the fore in the field of rare diseases as it is demonstrated by the highest specialization index in terms of publications in this area as compared to the overall Life Sciences.

These diseases, of which 80% are of genetic origin, receive most of the contributions for their treatment from the biotech field.

In particular, a survey conducted by Farmindustria shows that 30 companies are developing 67 projects, 63 of which related to molecules that have already been designated as orphan drugs and the remaining 4 for which the designation is pending. Almost 60% of the cases are in an advanced investigational phase. All these projects have a therapeutic application in the treatment of cancer diseases (48%), blood and hematopoietic organ diseases (14%), metabolism and digestive system disorders (10%).

However, we should not feel satisfied with what we have achieved so far, for a holt would involve rapidly loosing ground in the global competition; indeed, Italy has still much to do to catch up with other countries which have shown the ability or the will to invest more during the last twenty years. The companies' capability of innovation and, in fact, the possibility for them to thrive are at stake.

In order to further encourage the presence of the pharmaceutical industry, it is crucial to have policies capable of exploiting its potential through R&D incentives, as well as a stable regulation framework and competitive conditions with the main European countries.
Moreover, we should not neglect the sensitive aspects related to intellectual property. In particular, we should not run the risk of hi-tech productions migrating to foreign countries. This would be a loss we cannot afford.

Umberto Vattani
President of ICE

Global Partnership for Innovation and Competitiveness: the Biotech Industry in Italy and the Role of ICE

This Report on the state-of-the-art of biotechnology in Italy is now considered one of the most authoritative tools for in-depth analysis and dissemination of Italian excellence in such a strategic sector of our economy.

The present edition of the Report has widened the scope of the analysis to include some new topics: from innovative therapies and diagnostics, which are traditional strengths of the Italian biotech field, to other technologies, including nutraceutics, biomass, biomaterials, nanobiotechnology and regenerative medicine. This new methodological approach provides a wider framework which emphasizes the positioning of the Italian biotech industry within the European scenario by analyzing the strengths which differentiate it from its competitors.

The Report will be widely disseminated as usual by ICE, not only at the main international conventions in the field and in the dedicated section of our specialized portal biotechinitaly.com, but also through the activity of assistance and information which is carried out by our offices, 365 days a year, with the aim of supporting the Italian companies operating on the world markets.

In the current international economic scenario, which is characterized by strong growth, even the most innovative SMEs, such as those working in the biotech sector, need assistance and guidance, especially on emerging markets that are the richest in opportunities but also the most difficult to operate in.

In this context, it is crucial for the re-launch of competitiveness of our companies to search for new forms of cooperation on an international level, since the challenge of innovation can only be taken up if the related costs and risks are shared with a network of global partners.

The shift of the world economic barycenter toward Eastern countries opens new opportunities for Italian biotech companies that dare scouting different markets from the traditional ones, i.e., Europe and the United States. It is also our institute's task to make the initial contacts easier by providing a high-profile presentation of the Italian sector, as described in this Report.

Offering international investors deeper knowledge of the technological vocations of our companies can facilitate the development of new scientific projects within contexts of great interest, including the treatment of rare diseases, or environmental and cultural legacy protection.

At a time when obtaining public and private financial support for applied research is very difficult, we are convinced that it is more than ever necessary to make the potential applications of the Made in Italy technological innovation known to our international counterparts, for example by way of informative tools such as this Report.

Executive Summary

The 2011 edition of the Italian Biotechnology Report, besides including the main data on the entire sector for 2010, also contains an analysis of its evolutionary trends in relation to those aspects emerging from and outlined by the previous report, together with an in-depth benchmarking between the Italian market and those of the main European countries.

Italian biotech shows continuous growth and competitiveness on a European level

Despite continuous difficulties in the economic situation, the Italian biotech industry showed a growing trend in 2010. At the end of the year, 375 Italian companies were identified as being engaged in research and development activities; of these, 221 fall under the definition of "pure biotech" companies as outlined by the Ernst & Young Center for international studies in biotechnology. This figure is twice as significant: on the one hand, Italy is the third country in Europe, following Germany (403) and the United Kingdom (275), in terms of number of dedicated companies, and on the other hand it is the European country with the highest growth in the number of pure biotech companies (+2.8% compared to the 2010 Report).
Therefore, the Italian companies have successfully and effectively coped with the financial crisis unlike other countries, such as the United Kingdom, which reported a negative growth (-3.2 %) in the number of companies compared to 2009.

Italian biotech companies look to diversification

Out of the 375 identified companies, 246 operate in the human health sector and of these, 185 on an exclusive basis. As outlined in the 2010 Report, the driving role of "red biotech" allows Italy to be aligned with the average of the main European countries, where 70% of biotech companies operate in this segment. Conversely, with regard to other application fields of biotechnology, the dedicated companies operating in the "green biotech" field are 49, those in the "white biotech" 21, those in the GPET (Genomics, Proteomics, and Enabling Technologies) 41, while 79 companies have activities in more than one application field ("multi-core"); this involves a significantly larger share, growing from 6% in 2010 to 21% this year. Therefore, an increasing number of Italian biotech companies are clearly pursuing diversification in more than one application field by building on the expertise developed within their field of origin.
The weight of multi-core companies increases when we consider pure biotech companies alone, with a percentage as high as 24%.
Lastly, the size of companies remains a peculiar feature of this sector, with 75% of companies falling under the "micro" (less than 10 employees) and "small" (less than 50 employees) categories.

The increasing role of science parks and incubators for pure biotech

The analysis of the location of companies operating in the biotech field clearly shows that most of them have independent headquarters (56%). However, if we look

at pure biotech companies alone, this figure is significantly lower (44%). Indeed, in the pure biotech cluster, almost half of the companies are located next to science parks and incubators, with an increase from 44% in 2009 to 49% in 2010.
The increase in the number of companies located within this type of facilities is explained by the opportunity to share services for cost containment purposes, especially in the start-up phase, and to access specific technical and managerial expertise.

R&D turnover and investments of pure biotech companies are growing

The economic and financial analysis shows that the overall turnover for the biotech sector in Italy is € 7.4 billion, with an increase of 6% as compared to last year. The pharmaceutical companies account for 84% of the total, of which 16% are pure biotech companies. This growing trend specifically applies to the pure biotech segment, with a turnover of about € 1.18 billion, and a growth of 12%, as compared to the 2010 Report.

With regard to R&D investments, it is estimated that in 2009 biotech companies made an overall investment of about € 1.76 billion, with an increase of 2.5% as compared to 2008. About 70% of cumulative data are accounted for pharmaceutical companies.
Of note, however, the increase in R&D investments by pure biotech companies is substantially in line with the increase in their business, accounting for 11%, for a total of € 533 million, equal to 45% of their turnover.

The focus on research by pure biotech companies is also demonstrated by the high proportion of employees dedicated to R&D activities. As shown in our survey, pure biotech companies have on average one employee dedicated to R&D activities every 2.7 employees, as compared to a 1:10 ratio in the other companies of the biotech field. Within the pure biotech cluster, the companies with the highest number of R&D employees, in proportion to the total number of employees, are those operating in the field of nanobiotechnology, where more than half of the employees are engaged in research activities.

The rich pipeline of Italian pure biotech companies

The Italian biotech pipeline totals 237 products for therapeutic use, of which 82 in preclinical phase, 30 in Phase I, 67 in Phase II and 58 in Phase III of clinical development. The research activities of the Italian pharmaceutical companies have contributed for 32 products, most of which are still in preclinical phase or in the initial clinical trial phases, while 79 products, most of which in late-stage development, are in the portfolio of the Italian affiliates of multinational companies .

Despite limited cash flow, the number of products being developed and clinical trials conducted by Italian pure biotech companies reflects a rather stable trend, thus indirectly confirming their capability to create value by maximizing the financial resources available.

With 64 products in preclinical phase and 60 in clinical development phase, of which 21 in Phase I, 26 in Phase II and 13 in Phase III, pure biotech companies are the true promise for the entire sector.

Although no product has been marketed yet, it is clear that these companies are rapidly filling a time gap which is exclusively due to the fact that most of them are relatively young, if we consider the period of time (10 -12 years) which is necessary to complete the development of a new molecule today.

The high level of excellence achieved by our pure biotech companies is also demonstrated by the significant increase (+10%) in the number of orphan drug designations obtained by the European and the U.S. regulatory authorities in the field of rare diseases, and by their dynamism in the field of advanced therapies where, among a total of 19 projects being clinically developed, 2 protocols of cell therapy have already reached Phase III. As far as the pharmaceutical industry is concerned, this is mainly involved in the more advanced phases of clinical development, indirectly confirming the excellence of the Italian centers for clinical trials, especially in oncology and neurology.

The high quality of Italian research

Although our country ranks 13th in terms of R&D investments in proportion to GDP (1.2%), Italian research ranks among the best in terms of quality, with a trend indicating a steady growth.

In fact, Italy is one of the top three countries worldwide in the number of publications per researcher (0.41), and among the first ten countries in terms of citations per scientific article. These are the most appropriate parameters to assess the quantitative and qualitative efficiency of our scientists.

Another significant measure of the Italian research output is the number of patents: as shown by an Ernst & Young analysis, Italy ranks third in Europe with 1.4 patents per 1000 researchers, following Germany (2.4) and France (1.8).

Financing

Access to financial support is a priority issue for most of our biotech companies, especially those in the initial phase of development. On an international level, the difficult economic situation which began in 2008 has resulted in a huge decline in the funds available for the whole sector even if, over the last two years, the financing trend has been constantly growing, suggesting a rapid return to the pre-crisis situation.
In 2010, € 2,532 million were collected in Europe, 52% of which from Private Equity capital increases, 40% by Venture Capital operators and 7% through IPOs.

With regard to Italian biotech companies, 2010 showed a 27% increase in the volume collected from Venture Capital, Private Equity and IPO investments in respect to 2009, with investments accounting for € 72 million. Conversely, there has been a significant decline in grants, from 62% in 2008 to 50% in 2009, substantially due to the reduction (7%) of public funds allocated to research, on a national level.

The main future perspective: strategic alliances for growth

According to the experts, the perspectives of the biotech sector will be largely positive again, with a strong growth trend regarding both profits and investments. Indeed, most of the companies have stable or growing turnover forecasts, and do not intend to reduce the workforce, but rather to increase it in order to maintain a rich and competitive pipeline of projects.
After all, the biotech market is still widely unexplored and, as such, it remains attractive for new investments. However, in order to support its development, it is crucial that the players in this sector either look for external investors, or create alliances among themselves in order to reach the critical mass which is necessary for competitive growth.
The interviews carried out show that Italian biotech companies are looking for new and alternative financing sources.
In fact, 27% of the companies included in the sample will try to strengthen their corporate structure through Private Equity or Venture Capital investments in the next two years.
However, the real challenge today is to pursue and establish strategic alliances in order to shift from the size of a small start-up to that of a consolidated company with a critical mass, in terms

of available technologies and financial resources that would justify and support the necessary development investments. This is why 18% of the companies which were interviewed stated that alliances are the winning option to guarantee competitiveness on the market.

Success factors and challenges

According to the companies interviewed, success in biotechnology is closely linked to specialization in selected fields of pharmacology, including oncology, neurology and infectious diseases, as well as to progress in Advanced Therapies and the subsequent development of customized therapeutic models.
Similarly, the genetic improvement of plant varieties or the control of origin and quality in food, as well as bioremediation methods and production of biomass energy, are the basis for promising applications in the agro-food and industrial fields, respectively.
Moreover, an essential condition for biotechnology to really mirror the expansion of life sciences in Italy is to define a precise development policy for the whole sector that should be based on strategic, systematic and coordinated structural interventions within a predictable and stable overall framework. This would be a major display of consistency for a country which beliefs in innovation as the key to occupational and economic development.

The System of Biotech Companies in Italy

Italian biotech is rapidly consolidating. The number of companies, their turnover and their commitment in R&D are increasing. Most companies operate within the field of biotechnology applied to human health, followed by those which are active in the agro-food and industrial fields. A strong trend towards diversification is emerging, with an increasing number of companies capable of exploiting the expertise acquired in the field of origin to the new application fields. This dynamic and challenging reality fuels a market that is still mostly unexplored and particularly attractive for new investments.

Introduction

At the end of 2010, 375 companies investing in Research & Development in the biotech field in Italy were identified. Our analysis shows that Italian biotech is continuously strengthening and consolidating according to three different perspectives:

- the growth of turnover from biotech products and services, increasing by 6%;
- the incidence of R&D investments on biotech turnover, growing from 25% to 28%;
- the number of companies operating in several application fields, which has almost doubled.

The segmentation of the companies by type (Figure 2.1) shows that 59% (221 units) of the sample is made up of "pure biotech" companies whose core business is exclusively related to biotechnology, and the remaining 41% is made up of companies which do not fall under the definition of pure biotech ("other biotech"). The latter include foreign capital companies and national companies that fall under the

Figure 2.1

Analysis by type of business
(Source: Ernst & Young)

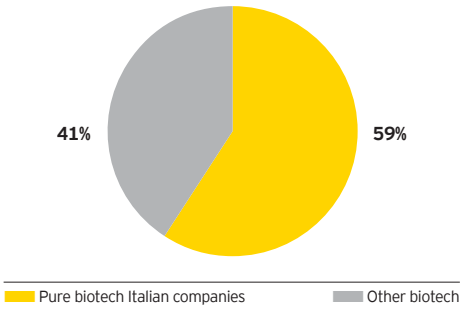


Table 2.1

Pure biotech Italian companies: key data
(Source: Ernst & Young)

Pure biotech	2010 Report	2011 Report
Number of companies	215*	221
Total turnover	€1,056 million	€1,184 million
Total R&D investments	€483 million	€533 million
Total number of employees	2.050	2.248

** The companies evaluated were 215 and not 187 (2010 Report) since, in order to compare data from the two reports (2010 and 2011), the data of the 2010 Report were integrated by adding a number of companies which were only identified this year in relation to the increase of the sample size (see chapter on Methodology)*

OECD definition of biotech companies (including CROs, mixed consortium companies or companies which do not come within the above categories).

The sample composition shows that the ratio between pure biotech and other biotech companies is basically stable as compared to the 2010 Report, when the latter accounted for 41% of the total.

The situation of the pure biotech cluster is developing both in terms of turnover and investments as well as in terms of workforce in the R&D field (Table 2.1). Table 2.1 shows the key data concerning pure biotech companies, comparing 2010 values to 2011 figures. Taking into consideration that different sample sizes were used in the two different time periods, it was deemed appropriate to include further data in the 2010 Report in order to allow for a more homogenous comparison. Therefore, we added some data concerning companies which were already operating within the biotech field, but which could be identified only this year thanks to improved analytical skills.

Analysis by sector

An initial classification of the companies operating within the biotechnology sector was made by application field (Figure 2.2). This analysis highlights that about half of the companies taken into consideration (49% of the sample - 185 units) operate exclusively in the red biotech field. The remaining 51% is made of 12% (41 units) of companies which deal with GPET (Genomics, Proteomics, and Enabling Technologies), while 13% are the so-called green biotech companies (49 units), 5% are white biotech companies (21 units) and the remaining 21% (79 units) are companies operating within more than one application field ("multi-core").

Figure 2.3 shows that the distribution of companies by application field has slightly changed as compared to the 2010 Report. The change is mainly due to the increase in the number of companies falling under the multi-core cluster; this indicates that biotech companies are engaged in diversification within several application fields, by exploiting the expertise developed in the field of origin. Since the number of newborn companies is limited, it is possible to assume that several GPET and red biotech companies have expanded their businesses thus becoming multi-core companies.

Figure 2.2

Analysis by application field
(Source: Ernst & Young)

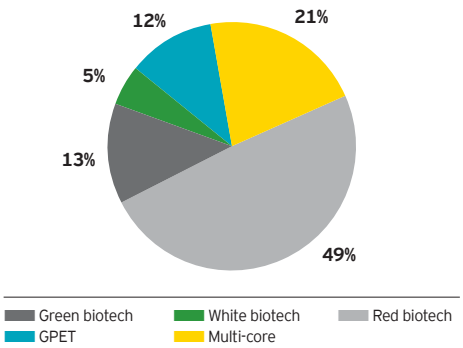


Figure 2.3

Analysis by application field, comparison between years 2009 and 2010 (Source: Ernst & Young)

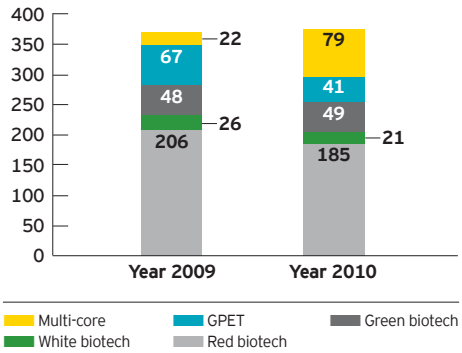


Figure 2.4

Italian pure biotech companies: analysis by application field (Source: Ernst & Young)

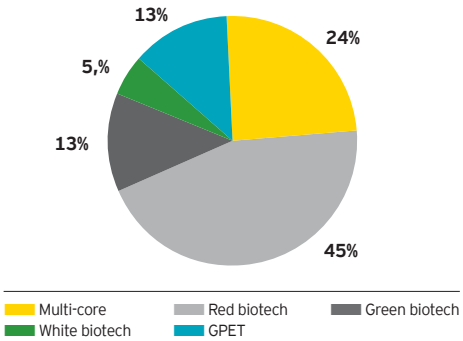
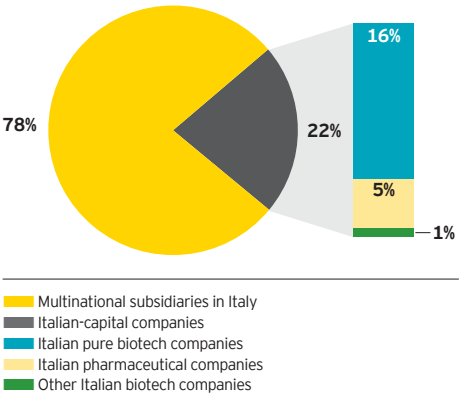


Figure 2.5

Italian-capital companies: turnover analysis by type (Source: Ernst & Young)



Analysis by type

The trend of biotech companies towards diversifying their activities in different application fields is even more striking if we focus on pure biotech companies alone. Indeed, within this segment the multi-core percentage increases from 21% to 24%, mostly due to the companies operating within the red biotech and the green biotech fields (Figure 2.4).

The analysis of the Italian biotech cluster from an economic and financial point of view shows that 2009 was characterized by a 6% increase in the total turnover, which accounts for € 7.4 billion. Also pure biotech company contribution increased reaching approximately 16%, with a turnover of € 1.18 billion. The segment that contributed most to the total turnover from biotech products and services is that of the multinational subsidiaries in Italy (78%) (Figure 2.5).
This analysis by size shows that the big companies with more than 250 employees (12% of the sample) yield 78% of the overall turnover, while the micro companies (45%) produce almost 10% of the turnover (Figure 2.6 - 2.7).

Comparison with the 2010 sample shows an increase in the percentage of micro and small companies; this is due to the fact that a very high number of companies of this size, all together accounting for 78% (Figure 2.8), were added to the sample.

When we consider the pure biotech companies alone, the percentage of micro companies reaches 58% (Figure 2.9).

Academic spin-off companies are business ventures stemming from the academic environment or from research institutions set up by a group of scientists who leave the organization to which they belong in order to start an independent enterprise. Their purpose is to make the best of the expertise and research activities developed within their organization of origin, with which they usually maintain a strong business relationship.

On the other hand, industrial spin-offs usually develop specific projects generated within the industrial environment in a new entrepreneurial and autonomous perspective, and can be "individual", when they are set up by one or more people who decide to leave an organization in order to start an autonomous activity,

Figure 2.6

Analysis by size (Source: Ernst & Young)

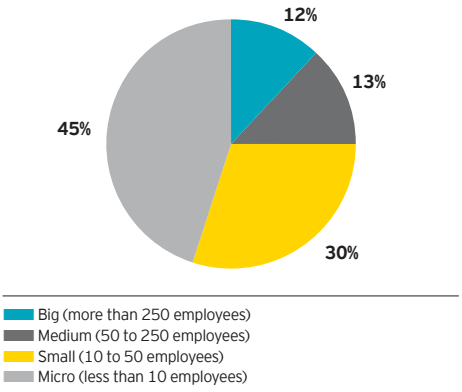


Figure 2.7

Analysis of the 2009 turnover by size (Source: Ernst & Young)

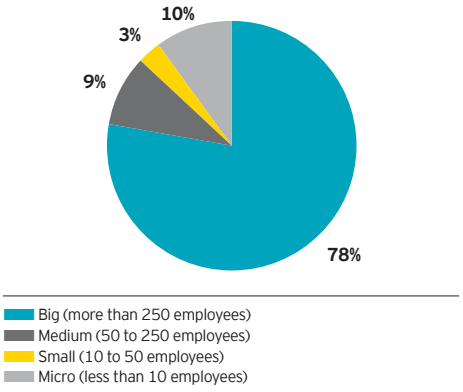
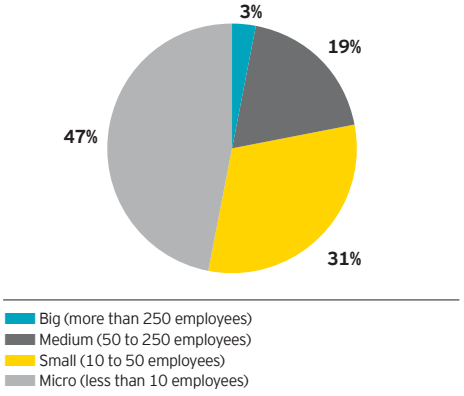


Figure 2.8

Companies added to the sample: analysis by size (Source: Ernst & Young)



or "corporate", when a specific branch of activity of the parent company is transferred to a new and independent unit. Industrial spin-offs usually have a higher degree of specialization and job sharing, as compared to the parent company, and they often contribute to accelerating the processes of re-organization of more complex structures.
Finally, industrial spin-outs are generated by the "split" of a division into a separate activity implemented by a company. Industrial "spin-outs", unlike spin-offs, acquire full rights on the assets and the intellectual property of the parent organization.

With regard to their origin, the Italian biotech companies are mainly set up as start-up companies (37%) or as academic spin-off companies (20%) (Figure 2.10). If we consider the 6 companies which were established last year, they mainly stemmed from academic spin-offs (50%).
With regard to their geographic location (Figure 2.11), biotech companies are mainly concentrated in the North of Italy. Lombardy is the region which hosts the highest number of companies (129 units) and, along with Piedmont (37), Veneto (31), Latium (30), Tuscany (30) and Emilia Romagna (26), accounts for 75% of biotech companies operating in Italy.
Six companies were founded during the last two years and they are located in Latium (2), Lombardy (1), Sardinia (1), Emilia Romagna (1) and Campania (1).

Thirteen percent of the sample (51 companies) is hosted in at least one of

Figure 2.11

Analysis by geographic distribution
(Source: Ernst & Young)

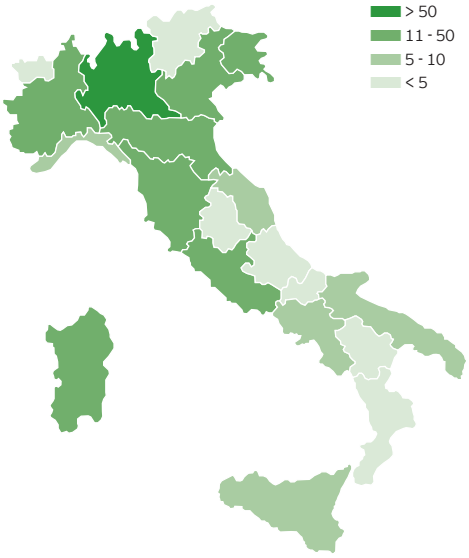


Figure 2.9

Italian pure biotech companies: analysis by size
(Source: Ernst & Young)

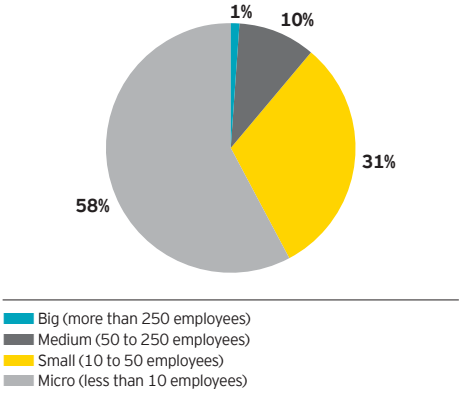


Figure 2.10

Analysis by origin
(Source: Ernst & Young)

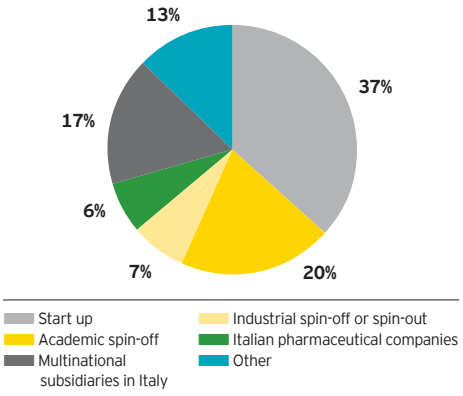


Figure 2.12

Analysis by region, with regard to Objective 1 (EU structural funds) (Source: Ernst & Young)

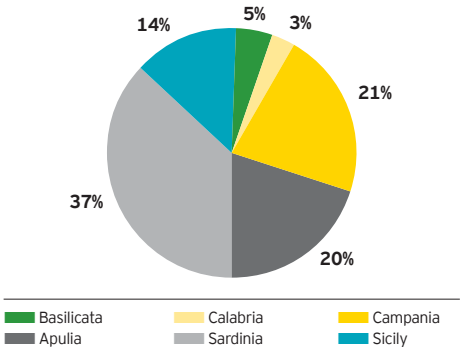
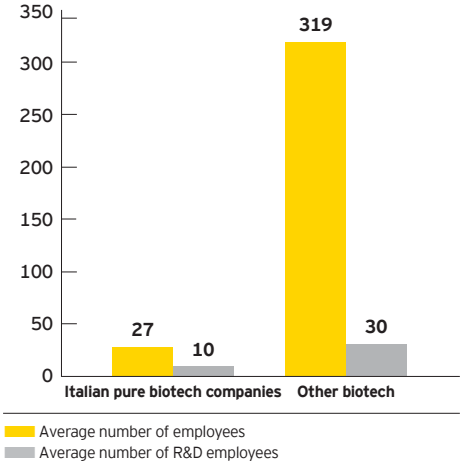


Figure 2.13

Average number of total employees and R&D employees (Source: Ernst & Young)



the regions falling under Objective 1 that is the first main Objective of the Structural Funds which are managed by the European Union in order to finance several development projects in Member States, and which currently account for 37.5% of the overall EU budget.
The main objectives for these funds are the following: reduction of regional disparities in terms of wealth and well-being (Objective 1); increase of competitiveness and employment (Objective 2); support to cross-border cooperation (Objective 3).

Objective 1 covers regions which are considered to be lagging behind in terms of development, i.e., whose GDP per capita is below 75% of the EU average. In Italy, the regions covered are: Basilicata, Calabria, Campania, Puglia, Sardinia, Sicily and Molise (the only region whose support is transitory). The total number of sites identified in these regions (65) is actually higher than the number specified in Figure 2.11, since some companies also have secondary sites in other regions different from those in which their headquarters are located.
On the whole, the headquarters are distributed as follows: 37% are located in Sardinia, 21% in Campania, 20% in Puglia, 14% in Sicily, 5% in Basilicata and 3% in Calabria (Figure 2.12).

Also this year, consistently with the 2010 Report, we do confirm that most of the companies have an independent headquarter (55%), followed by those located within a science park or an incubator (34%), and then by those located near universities, clinical centers and research institutions (11%).

The average number of employees is highly variable, if we consider the different types of businesses carried out by the biotech companies operating in Italy (Figure 2.13).This number ranges from 27 employees, for the pure biotech companies, to 319 employees, for all the other biotech companies.
This last data, on the other hand, presents significant lack of homogeneity within the sample since it ranges from companies with small units to companies with over 100 employees.

In comparison to the 2010 Report, the number of employees of the other biotech companies has decreased remarkably due to the fact that this year the sample includes a higher number of micro companies.

Figure 2.14

Other biotech: employees' distribution (Source: Ernst & Young)

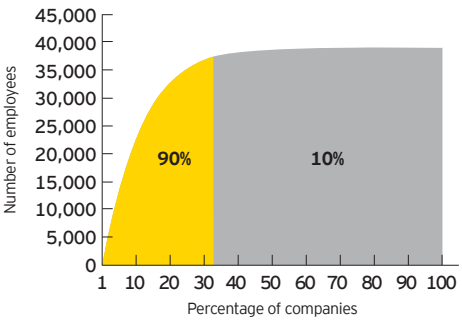


Figure 2.15

Analysis of R&D employees (Source: Ernst & Young)

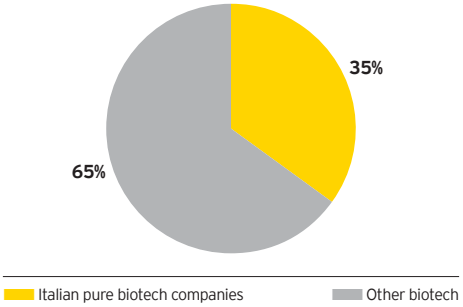


Figure 2.16

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

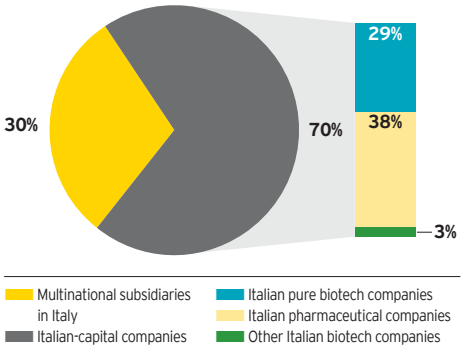


Figure 2.14 shows that 90% of employees of the other biotech companies are included in the 32% of companies making up the sample. This highlights the fact that the other biotech cluster is made up of a small number of big companies and a high number of small and micro companies. The pure biotech cluster is more homogenous since 12 companies alone (5.5% of the cluster) have more than 100 employees. The analysis of these data further highlights the difference between the number of total employees and that of R&D employees. Indeed, pure biotech companies employ one R&D employee every 2.7 employees, while for the other biotech companies this ratio is one R&D employee every 10 employees.
The projection of the average number of employees working in the companies of the sample that have not provided these data results in an estimation of 6,399 R&D employees, of whom approximately 35% are employed in pure biotech companies (Figure 2.15).

When we consider R&D investments in the biotech field, we notice that, in most cases, they are generated by the Italian pharmaceutical companies cluster (38%), followed by pure biotech companies (29%), multinational subsidiaries in Italy (30%) and other biotech companies (3%) (Figure 2.16).

Moreover, 20% of the research activity is outsourced to third parties (Figure 2.17) in line with data of the previous Report.

Figure 2.18 shows a comparison of the 2008 results with the 2009 results.
As further detailed in Chapter 10, the 2010 and the 2011 reports actually refer

to the 2008 and the 2009 turnover data, respectively, as we deemed appropriate to take into consideration the latest accounting periods for which complete balance sheet information was available.

In the 2010 Report, 75% of the companies had a positive balance sheet; this percentage rises up to 78% in the 2011 Report. Although pure biotech companies remain below the average, with 63% of companies with a positive balance sheet, they do show a slightly positive trend in comparison with the 2010 Report, differently from the other biotech segment which shows the higher increase in terms of number of companies at loss. Figure 2.19 shows that more than 86% of pure biotech companies expect their profits to remain stable as compared to 2009, and only 3.3% assume that they will be decreasing. The most optimistic segment, in terms of 2010 profits, seems to be the one including the Italian subsidiaries of multinational companies: as many as 29% of these believe that the 2010 profits will be growing.

The biotech field is extremely challenging and fuels a market largely unexplored as yet and thus very appealing investment wise. The interviews made to companies

Figure 2.17

Italian pure biotech companies: analysis of R&D investments (Source: Ernst & Young)

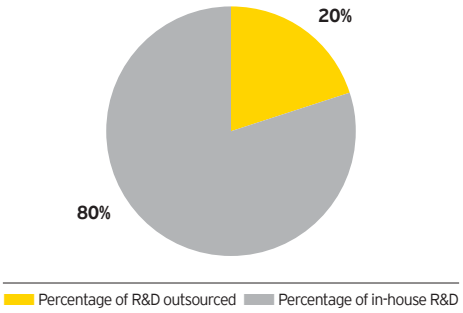


Figure 2.19

Estimated profits for 2010
(Source: Ernst & Young)

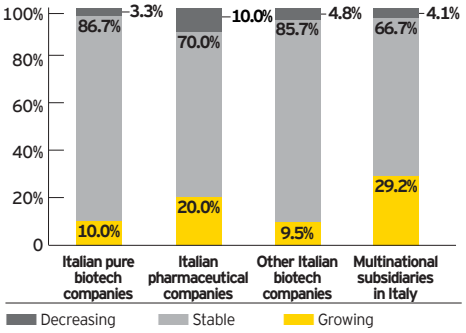


Figure 2.18

Analysis of the net financial results, 2008 vs. 2009
(Source: Ernst & Young)

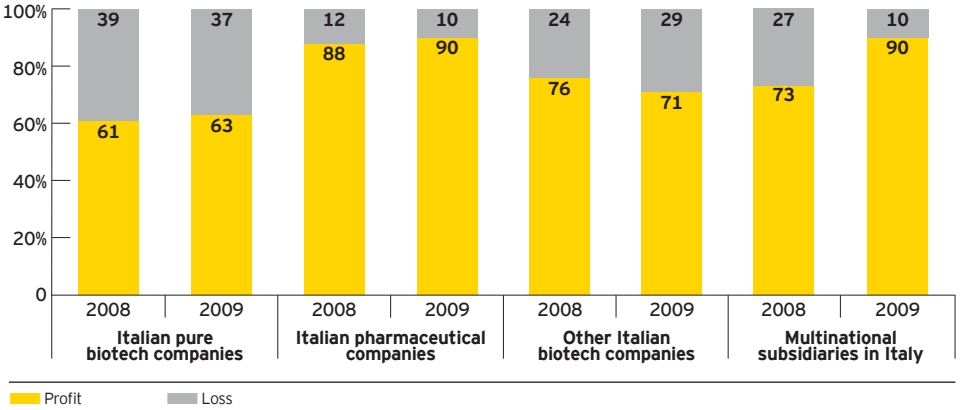


Table 2.2

Analysis of the main reactions to the challenges deriving from the economic crisis (Source: Ernst & Young)

Challenges (%)	Increasing operating efficiency	Seeking alternative sources of capital	Layoffs	Reducing items in development product pipeline	New business models	Seeking alliances opportunities	Seeking M&A opportunities
Already implemented in 2010	64.8%	25.8%	14.3%	12.1%	30.6%	24.5%	3.8%
Very likely in 2011	17.6%	33.3%	10.0%	3.0%	19.4%	41.5%	13.2%
Likely in 2011	14.3%	28.0%	5.7%	10.6%	26.4%	29.3%	15.1%
Unlikely in 2011	2.2%	7.5%	34.3%	40.9%	15.3%	2.8%	37.7%
Very unlikely in 2011	1.1%	5.4%	35.7%	33.4%	8.3%	1.9%	30.2%
Total	100%	100%	100%	100%	100%	100%	100%

that have been operating in this field for years show that they plan to seek new and alternative financial sources, as well as to establish alliances aimed at better addressing the opportunities that may arise in the short and medium term (Table 2.2).

This commitment is also confirmed by their intention to increase rather than reduce their workforce, as well as to maintain a rich and competitive project pipeline. As confirmed by most of the companies which were interviewed, the new market opportunities indirectly imply the possibility to seek and to implement new business models, i.e., providing a number of services against payment.
The grant of licenses on proprietary products or technologies is still a priority for most of the companies which were interviewed, notwithstanding that a good percentage of these intends to acquire patents from other companies and to exploit them for production purposes (Table 2.3).

Table 2.3

Analysis of future developments (Source: Ernst & Young)

Future development (%)	Increase number of employees	Decrease number of employees	Inlicense a product or technology	Outlicense a product or technology	Seek alliance opportunities	Acquire another company	Be acquired by another company	Merge with another company	Move into a new business segment
Very likely	33.3%	2.2%	15.6%	16.5%	33.6%	2,4%	3.6%	3.5%	1.2%
Likely	41.4%	11.4%	31.1%	58.2%	59.8%	14.8%	26.5%	31.4%	17.9%
Unlikely	17.1%	50.0%	28.9%	18.7%	6.6%	30.9%	43.4%	41.9%	46.4%
Very unlikely	8.2%	36.4%	24.4%	6.6%	0.0%	51.9%	26.5%	23.2%	34.5%
Total	100%	100%	100%	100%	100%	100%	100%	100%	100%

Research in Italy

Biotechnology is a research-based activity and requires the continuous support of appropriate funds in order to turn ideas into concrete projects. In the meantime, biotechnology is a strategic area for the development of Knowledge Economy, where Italy is well equipped to compete on the international stage and deserves a favorable scenario in order to increase investments and research.

Research and innovation is the key to the world of what is possible though unknown. Without them, no country has a future. This equation is always valid, for everybody in every field, especially in the biotechnology area, and this has been highlighted recently by the U.S. President "When we fail to invest in research, we fail to invest in the future." (Obama, 21/9/10). Consistently with this declaration, President Obama has announced an increase in R&D investments by 3% of the U.S. GDP.

The share of GDP invested in R&D is one of the most used indicators to compare the innovation propensity of different countries. Based on this indicator, Italy appears to tail the most advanced countries: in 2009, the ratio between R&D investments and GDP was 1.2%: very much lower when compared to that of the other main European countries, and less than half lower when compared to the U.S. data.

However, it should be highlighted that the innovation capability and the positioning of an economic system within the competitive international arena are affected by a number of factors. Although synthetic indicators (the R&D/GDP ratio or number of R&D employees/ number of total employees) provide a "macro" indication of a country's average innovation engagement, they do not account for the innovation capability of each specific sector.

With regard to Italy, the average parameter is deeply influenced by the composition of the industrial fabric which is characterized by a higher percentage of workforces in the traditional "Made in Italy" fields (which are, by definition, less research-intensive) and by companies which are smaller in size and usually attract proportionally lower R&D investments.

When we look at the indicator of the ratio between R&D employees and total employees in the manufacturing industry, considering a total value of 100 for Italy, the main EU countries have on average a value of 239. But if we apply the parameters indicating companies' research activity to the industrial structure of other countries, the gap is considerably reduced: Italy goes from 100 to 218 (Figure 3.1).

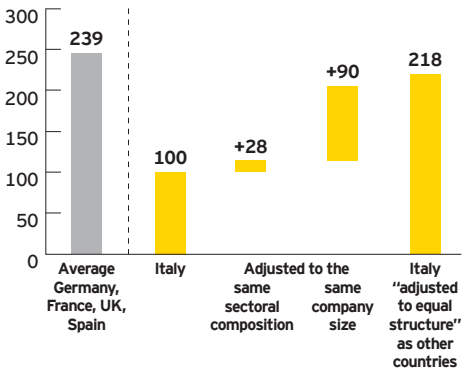
This shows that the gap in terms of average data does not indicate that Italian companies are less engaged in R&D compared to Europe, but only that the number of companies conducting research is lower and that Italian research is absolutely competitive on the international level.

In conclusion, in order to increase the growth capability of the whole economic system, it is certainly necessary to improve its research content, even if in Italy there are some sectors capable of competing in the field of knowledge economy, including biotechnology and life sciences.

These are the fields that need more support, especially in light of the evolution of the innovation processes involving the main hi-tech sectors today.

Figure 3.1

Percentage of R&D employees on total employees (Italian Index=100) (Source: Eurostat estimates)



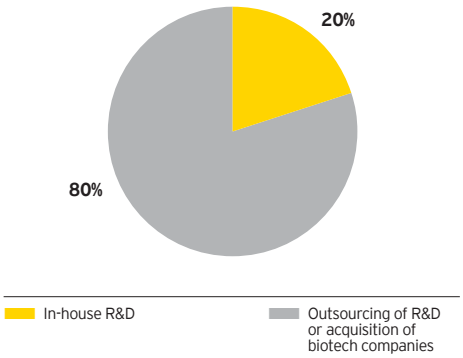
The biotech revolution in the R&D organization: opportunities for pharmaceutical companies in Italy

A survey conducted on the main international pharmaceutical groups shows that today 80% of the most efficient innovation is carried out outside company facilities, through the acquisition of small projects which are conceived within small biotech companies or centers of excellence, and that only in 20% of the cases are produced by the big corporate research laboratories (Figure 3.2).

These figures reveal a paradigm shift, caused by a deep change in both the demand and supply of innovation on an international level.

Figure 3.2

Origin of innovation
(Source: Ernst & Young)



In fact, the demand for new drugs increases and changes, since on the one hand pharmaceutical companies need to enrich their pipeline, while on the other, the type of innovation required is different and increasingly addressed to unsatisfied needs, thus shifting the focus towards more targeted therapies, related to individual characteristics and therefore more effective.

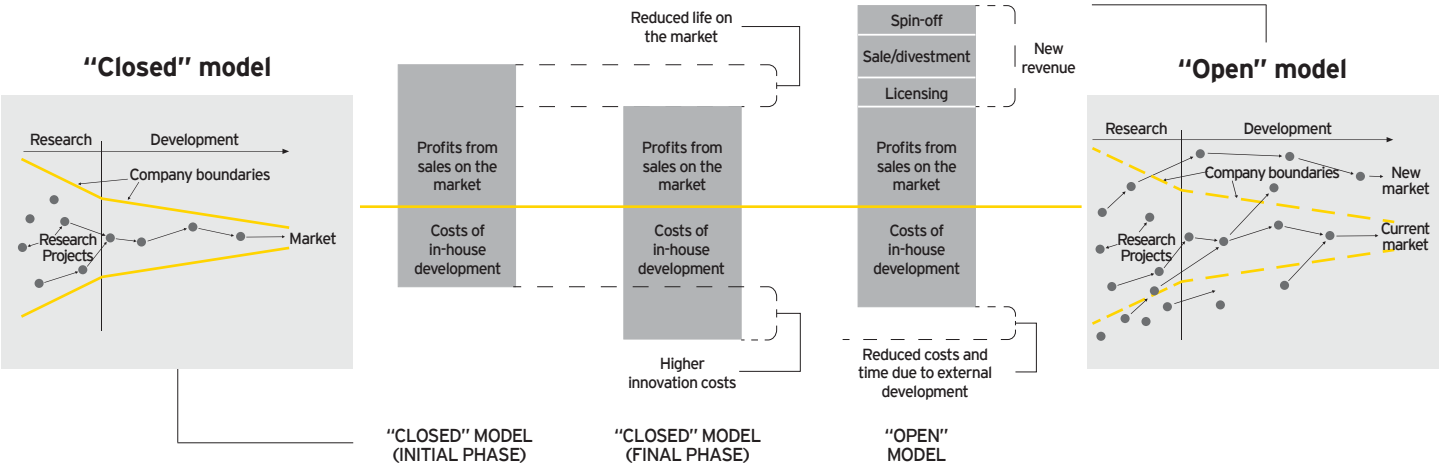
At the same time, a number of supply shocks - such as an increase in the investments needed to make an innovative drug available (currently higher than a billion euro) and a reduction in the profitability of this sector - make it necessary to optimize the lengthy R&D process.

Moreover, the dissemination of new technologies - especially those related to molecular biology - allows both to explore new frontiers (e.g., personalized medicine) and to improve the efficiency of the entire development process, whose costs currently exceed 50% of the overall R&D costs.

All these events bring about a real "revolution", wherein the level of specialization increases and the skills

Figure 3.3

Switch from a close model to an open model of innovation (Source: OECD)



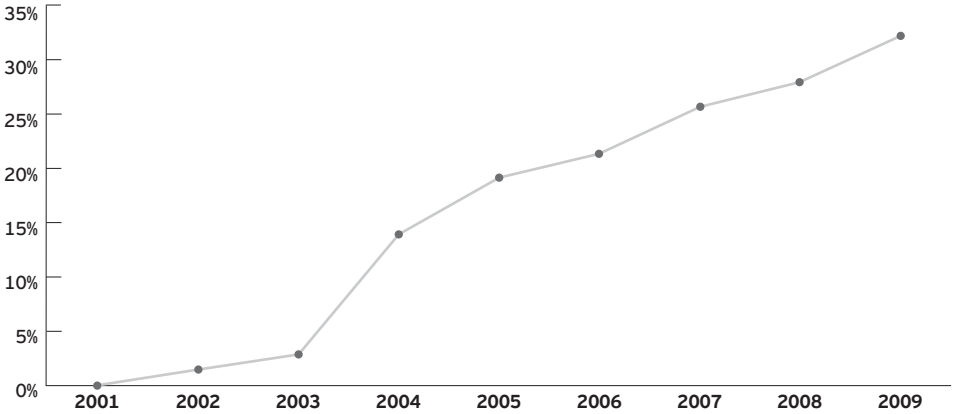
required multiply and become more complex, involving interdisciplinary processes and synergies between different companies.

For this reason the discovery of an innovative product goes beyond corporate boundaries and is developed in partnership with other entities, also because single companies - even large ones - rarely have the necessary resources to competitively follow all the steps of the research process; therefore, research tends to develop via a co-operation between different subjects linked through an innovative network.

An open-innovation organization gives added-value to SME innovation, since success is not essentially produced by the critical mass, but by the ability to develop a leadership in a specific skill and introduce it within the network of international excellence (Figure 3.3). This trend results in the organization of large companies' R&D structures into flexible and specialized units, reinforcing "Search & Development" or "Research Hunting" work to discover innovative ideas that can just be developed with the knowledge and resources that only large companies can deploy, although in cooperation with external entities such as SMEs, universities, and centers of excellence.

Figure 3.4

Percentage of clinical trials on biotech products, Italy
(Source: The National Monitoring Center for Clinical Trials)

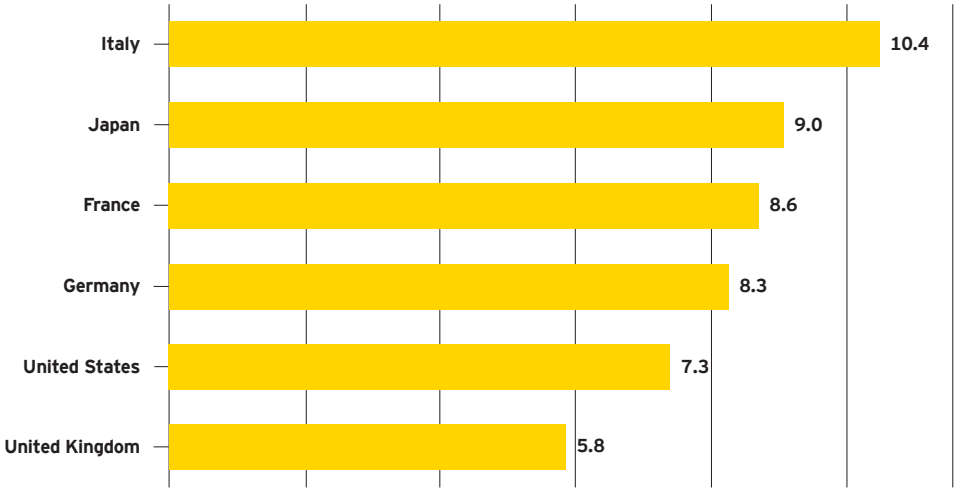


The Italian system can exploit considerable opportunities in this "marketplace of ideas" by emphasizing the value of its excellence in different fields including: the traditional high-quality production, the specialization in biomedical R&D, the quality of researchers (among the main factors of attractiveness mentioned by foreign companies working in Italy), an increasing number of innovative SMEs, the excellence of various public centers.

The increased number of clinical trials confirms the quality of skills available in our country and can also be very important for industrial growth. Data issued by the

Figure 3.5

Specialization index referred to publications on rare diseases (% of Life Science publications in 2000-2008) (Source: CERM)



National Monitoring Center for Clinical Trials show that the studies on biotechnology products and biologicals have tripled over the last five years (from 85 to 235), also increasing their percentage over the total number, which is currently higher than 30% (Figure 3.4).

The drug development investigational phase, which is the equivalent of pre-competitive development in other sectors, is a crucial step for the growth of the entire pharma-biotech industry, and can also be a competitiveness factor for the country. More efficient processes, for example those characterizing Translational Research, can improve the transfer of laboratory results to new applications and products.

Therefore, the links between pharmaceutical companies, biotech SMEs, public and private centers of excellence, both in basic research and technology transfer, are the drivers of innovation in life sciences, where investments should be made in order to increase the value of an expertise already existing in Italy. An example of this is the Milan cluster, which ranks among the best in the world in the field of oncology and rare diseases; these research fields involve groups of patients with very specific diseases and for this reason can prove to be an extremely interesting area for future development.

Italy can play a major role in this area, as the incidence of publications in life sciences over the total number of publications shows: 10.4% in our country compared to 9% in Japan, 8.6% in France, 8.3% in Germany (Figure 3.5).

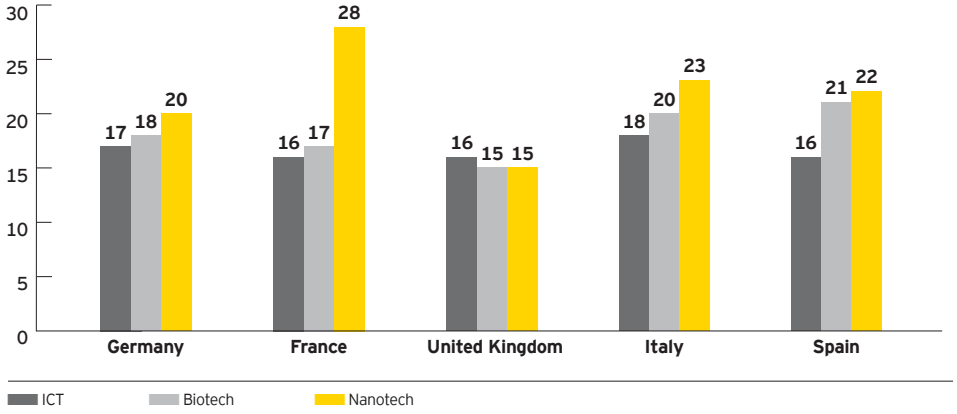
Another interesting element for assessing the potential return of research activities of a given country in terms of application outputs, as well as to quantify its innovation capability, is the rate of success of patent applications.
Figure 3.6 reports the rate of success of patent applications filed with the EPO (European Patent Office) in the biotech field. Among the main European countries, Italy has one of the highest rates of success (20,1%) and, within biotech patents, a much higher rate than the EU average (17.6%).

The outputs of research process in the biotech sector in terms of scientific publications can be analyzed by using the number of the so-called Highly Cited Researchers (HCR) as an indicator, i.e., the authors who have been mostly cited in scientific publications over the last 10 years. A global analysis shows that Italy ranks tenth by absolute number of HCR in publications in the biotech sector.

In terms of biotech patents - accounting for about 3% of the total patents filed in Italy - it is possible to carry out another

Figure 3.6

Success rate of patent applications in the biotech field, 2009
(Source: "Annual Report on innovation 2010" - COTEC)



analysis by using as indicator the number of patents in proportion to the number of researchers in the country.
Figure 3.7 shows that Italy, as in the field of scientific research in general, is not affected by its disadvantageous position in terms of investments and technological skills.
Also from a wider time perspective, we can observe no significant changes with regard to Italy, France and Spain, compared to a strong decrease for Germany and the United Kingdom.
The results of the analysis of the questionnaires sent to biotech companies for the preparation of this Report are discussed in the box "Biotechnology patent activity in Italy".

Lastly, with regard to financing, Italian biotech companies access three main types of sources: institutional programs, charities and risk capital that will be analyzed at length in Chapter 8.
Institutional programs can be distinguished from a geographical point of view into international, European and Italian programs.

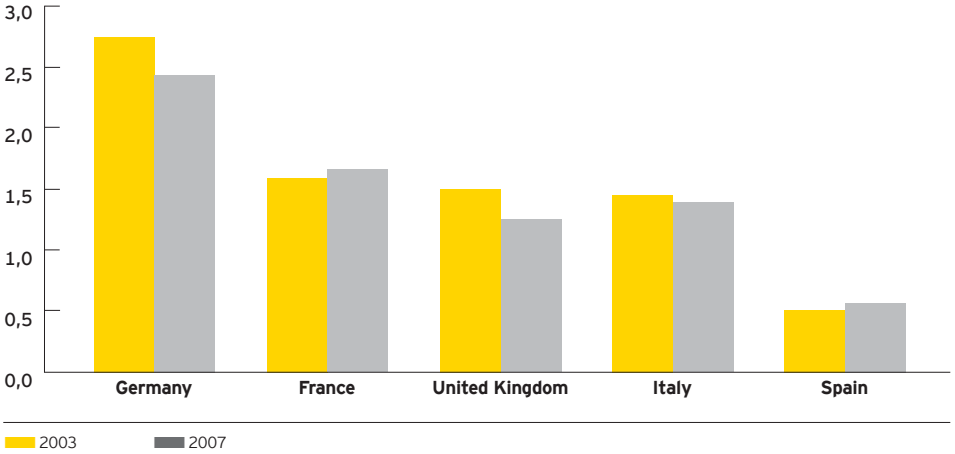
The most important international program is certainly that organized by the "National Institutes of Health" (NIH), the state agency of the Department for Health and Human Services of the United States. With 36 billion dollars per year, the NIH is the biggest investor in biomedical research in the world. An internal study shows that for every dollar invested, NIH funding produces 3.11 dollars in terms of economic growth.

Within Europe, the main financing program for Italian biotech companies is the 7th Framework Program, and in particular the call for proposals under the FP7-KBBE (Food-agriculture, fisheries, biotechnology). Italian participation in the KBBE, which was closed on 14 January with a budget of about € 190 million, was on the whole positive. Italy ranks first in terms of number of financing proposals (55), second in terms of projects which actually received funds (35 out of 55) and third in terms of coordinated and financed proposals (7 out of 55).
The participants were mainly private companies (38%), followed by universities (28%), research bodies (20%), public centers (5%) and others (9%).

On a national level, companies can access various regional and national calls for

Figure 3.7

Number of biotech patents per 1000 researchers (Source: Ernst & Young)



proposals, including those organized by MIUR (Ministry of Education, University and Research), or by MISE (Ministry of Economic Development). For further information on regional calls, see Chapter 8.

Charities are the main alternative sources to government funding programs, even if their role is institutionally restricted to the support of non-profit research. In Italy, the main foundations allocating funds to biotech research are AIRC (Associazione Italiana per la Ricerca sul Cancro) whose objective is the raising of funds for furthering cancer research as well as the management of educational campaigns, and Telethon whose main objective is the development of new therapeutic approaches for the treatment of muscular dystrophy and other genetic diseases.

The Fundamental Role of Scientific and Technological Parks in the Development of the Italian Biotech Industry

Today the Scientific and Technological Parks (STP) system contributes significantly to the development of competitive environments on the territory, and to the creation and growth of the small biotech companies which make up most of the Italian scenario.

The location of a company within a STP is often the only possible choice for starting up a new company whose "core business" is in the field of research and development; within the park, the new company can find both technological platforms and skills, as well as a number of opportunities in terms of complementary cooperation with other companies or research groups.

From this point of view, the role of STPs goes beyond the institutional one of promoting and coordinating R&D activities within the research and industrial world. The parks support the transfer of innovation knowledge and expertise, the synergic use of resources, the optimization of the research and development potential scattered over their area of action; they propose themselves as mediators between the demand for knowledge by companies and the offer of technological and scientific innovation by universities and public and private research centers.

For their role of mediation in the technology transfer process, the parks hold a privileged position since they can monitor events in the world of both small and large biotech companies. Therefore, STPs are a reservoir of expertise and information which is then extremely useful when companies engaged in the research and development of new products with biotechnological content must face common issues and are exposed to international competition.

All strategies and actions of the Italian biotech parks are driven by the Commissione Tecnica Unitaria (CTU) on Biotechnology, the working team within which the experts from Assobiotec (the National Association for the Development of Biotechnology set up within Confindustria-Federchimica) and those of the Associazione dei Parchi Scientifici e Tecnologici Italiani (APSTI) work together in pursuit of common objectives. This effort is needed to coordinate the activities carried out by the Italian BioParks, a community of 15 scientific and technological parks operating within the field of biotechnology applied to the human health, agro-food and industry sectors.

One of the most important short-term objectives is the implementation of the Carta dei Servizi Biotech (Biotech Services Charter), which will provide the Italian scientist with all information relating to the expertise and technological platforms (laboratory equipment and tools, unconventional analysis services) which are available within each science park in Italy. Moreover, together with offering a location, the STP network is able to provide assistance by means of "seed financing", needed to support the activities of new companies during their early years, and allowing them access from the beginning to a national and international network of operators.

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Biotechnology patent activity in Italy

Finalized agreements

It is known that in the field of biotechnology cooperation agreements concerning innovation activities, both at the beginning and at the end of the process - from research to commercialization activities - are a vital element affecting companies' competitiveness. Over the 2006-2009 period, the 81 companies that completed the section of the questionnaire proposed by Assobiotec concerning patents, signed 414 deals overall, that is, an average of 1.3 agreements per company per year. During the same period, 25 companies, little less than a third, signed no agreements. In 2010, the overall number of signed agreements was 304, with an annual average of 4.6 deals which is so clearly higher than that of the period 2006-2009 (Figure 3.8). In terms of frequency distribution, although the number of companies not signing any agreements has remained stable and that of companies having signed only one agreement has declined, there has been an over 100% increase in the number of companies signing more than ten deals. Therefore, we may conclude that the increase in the average number of signed agreements is due to the increase in the activities carried out by the 10/15 most active companies, rather than to an increase in the activities of the 45/50 less active ones.

Patents portfolio

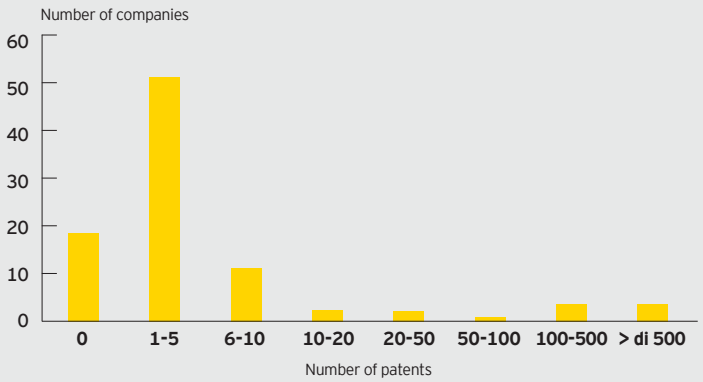
With regard to the number of active patents (i.e., already granted) held at present by the companies answering this item of the questionnaire (n=98), the average is 110, the highest number in the sample being 5,218. In all, the companies of the sample hold 10,766 patents. However, the situation is not homogeneous. There are 18 companies which have no patent compared to 51 companies which have less than five, and a few companies which have a relatively high number of patents. In particular, 10 companies have more than 100 patents, and three of them have more than a thousand (Figure 3.9). A further question was aimed at discovering for how many of the patents among those included in the companies' portfolio, the inventors were researchers employed in Public Research Bodies (PRB). In such cases the patents do not belong to the PRB, but to the companies, with the

Figure 3.8

Analysis of the annual average number of deals (n=81) (Source: Ernst & Young)

Figure 3.9

Analysis of patent portfolio (n=98) (Source: Ernst & Young)



involvement of at least one public researcher among the inventors; presumably these patents were obtained through research contracts according to art. 66 (i.e., research activities carried out by a PRB with private funds and according to specific requests) or by means of private consultancy activities carried out by public scientists (i.e., the PRB actually allows its employees to provide scientific consultancy services based on a specific contract). Notably, in 31% of more than 10,000 active patents PRB scientists are indicated as inventors; this confirms that public research makes a substantial contribution to innovation by private companies.
Regardless of the importance of the contribution of public researchers in obtaining these patents (it would be necessary to verify the numerical incidence of public researchers compared to others and, even so, we would not obtain the precise evidence of the individual contribution), this is certainly an important sign of how public and private research are closely related in this field.
More precisely, there are more than 30 companies for which more than 75% of the patents include at least one PRB scientist among the inventors. Presumably, these companies are academic spin-offs in which researchers from university are included by definition among the inventors of patents owned by the companies.
Only for 13 companies, no public researcher is reported among the inventors of patents owned (Figure 3.10). Again with regard to the overall patent portfolio, (in this case considering 35 complete answers), 55% of the patents are reported to be Italian, 31% European, 9% U.S. and 5% were filed in other countries (Figure 3.11).

Innovation activity

During the 2006-2008 period, the 65 companies that answered a specific question on the patents filed, declared to have obtained 1,930 patents; that is equal to an annual average of about 10 patents per company. In particular, 38% of the companies have not obtained any patent and 51% have obtained less than 10 patents (Figure 3.12). The average figure (about 10 patents) have been obtained thanks to a small number of companies which have filed a high number of patents. In particular, four of the companies included in the sample have obtained more than 200 patents from 2006 to 2008, the highest number being over 700 patents.

In 2009 only (with 54 responders), the average of patents granted was 11.3, slightly higher than in the 2006-2009

Figure 3.10

Analysis of patents co-authored with PRB (n=54)
(Source: Ernst & Young)

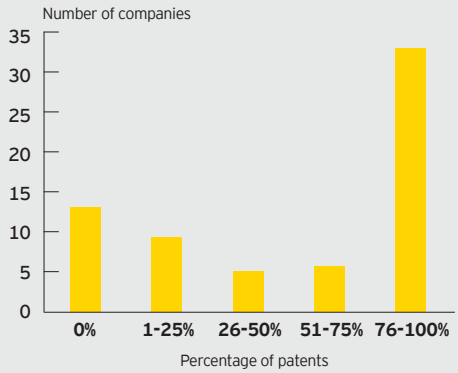


Figure 3.11

Analysis of patents by region of application filing (n=35)
(Source: Ernst & Young)

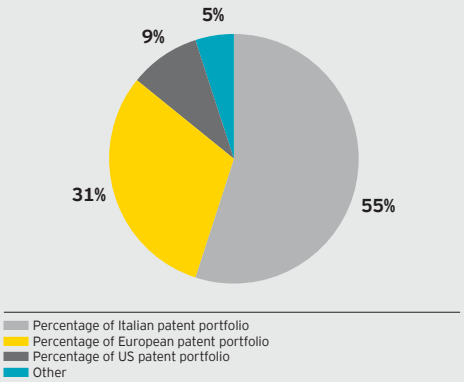


Figure 3.12

Percentage of companies by number of patents granted, 2006-2008 (n=65)
(Source: Ernst & Young)

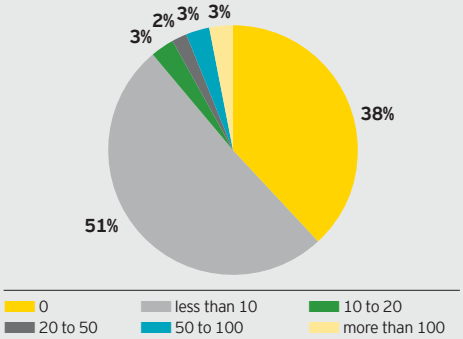
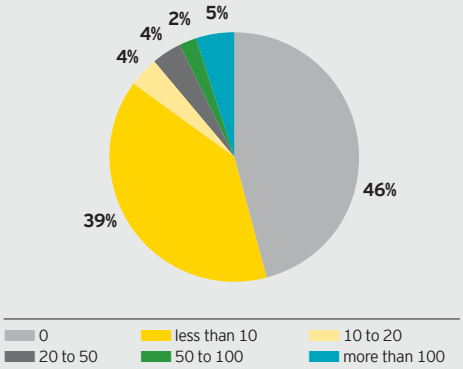


Figure 3.13

Percentage of companies by number of patents granted, 2009 (n=54)
(Source: Ernst & Young)



period, for a total of 608 patents. When compared to the previous period, the percentage of companies not having obtained any patent has increased, just like the percentage of companies which have obtained a high number of patents, more than 10 (Figure 3.13).

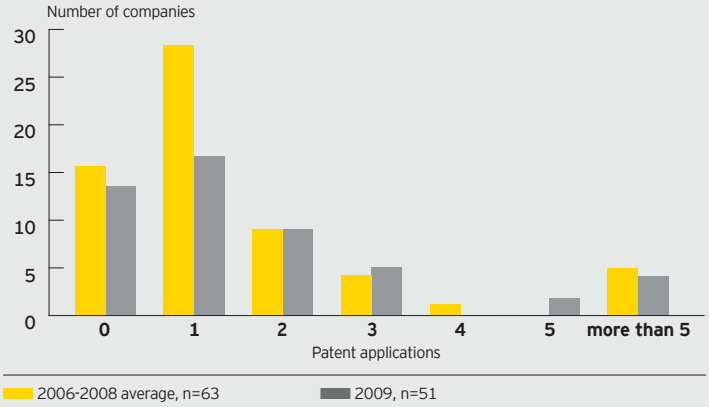
With regard to the applications for new patents, during the 2006-2008 period, the 63 companies that answered this specific question filed a total of 360 patent applications, i.e., an annual average of 1.9 per company.

About half of the companies have filed one patent application and about a quarter have filed no applications.
In 2009 (n=51), the average number of patent applications filed was 2.5 and, as such, slightly higher, with 126 total applications (Figure 3.14).

The Full Time Equivalent (FTE) employees dedicated to the management of Intellectual Property (IP) within the companies has increased from 1.13 (based on a sample of 53 responding companies) in the 2006-2008 period, to 1.24 FTE in 2009 (based on a sample of 46 responding companies).

Figure 3.14

Analysis of the annual average number of patent applications filed (n=51)
(Source: Ernst & Young)



Therefore, there was only a minor change. In the 2006-2008 period, 28% of the companies did not have any employees dedicated to IP while 56% had only one employee dedicated to this activity. The highest number of FTE employees dedicated to IP, over this period, was seven.
In 2009, 33% of the companies did not have any employee dedicated to IP, while 46% had one employee only.
This means that the slight increase in the number of employees dedicated to IP was concentrated within the companies which already had some dedicated employees. The highest number of FTE employees dedicated to IP in 2009 was eight.
With regard to the annual spending for the management of intellectual property, the percentage distribution of companies is reported in the Figures 3.15 e 3.16.
No important changes have occurred during the period 2006-2008 and in 2009. Actually, a third of the companies spend little or nothing for IP, another third spend between 10 and € 50 thousand and a third spend more than € 50 thousand.

In the 2006-2008 period, 30 of the 44 companies that completed the questionnaire stated they had not obtained any patent licenses by PRB, 9 obtained only one license, 2 obtained two patents, 1 obtained four licenses, 1 obtained five licenses and 1 obtained six (Figure 3.17).
In 2009 only, 32 out of 37 respondent companies did not obtain any patent license by PRB, 4 companies obtained one, and one company obtained two. Considering the different period of time, the trend seems to be stable (Figure 3.18).
With regard to the number of research agreements signed with PRBs, compared to the 2006-2008 period, in 2009 a higher percentage of companies signed at least one research agreement with PRBs. The "active" companies go from 58% to 64% of the total.

Figure 3.15

Annual intellectual property spending, 2006-2008 (n=59). (Values in thousands of Euros)
(Source: Ernst & Young)

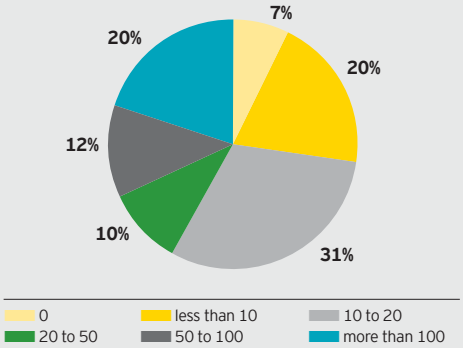


Figure 3.16

Annual intellectual property spending, 2009 (n=53). (Values in thousands of Euros) (Source: Ernst & Young)

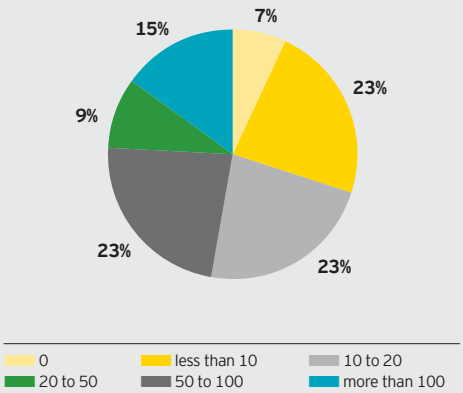


Figure 3.17

Analysis of research agreements with PRB by amount, 2006-2008 (n=45). (Values in thousands of Euros)
(Source: Ernst & Young)

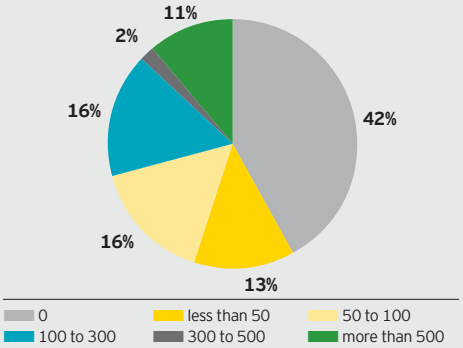
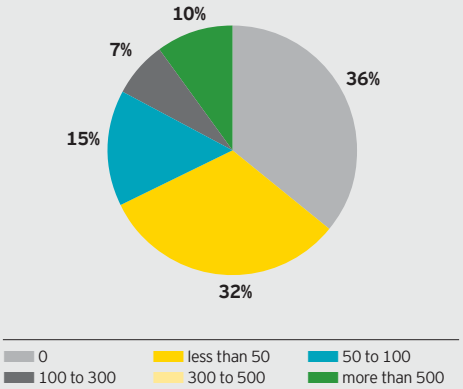


Figure 3.18

Analysis of research agreements with PRB, by amount, 2009 (n=41). (Values in thousands of Euros)
(Source: Ernst & Young)

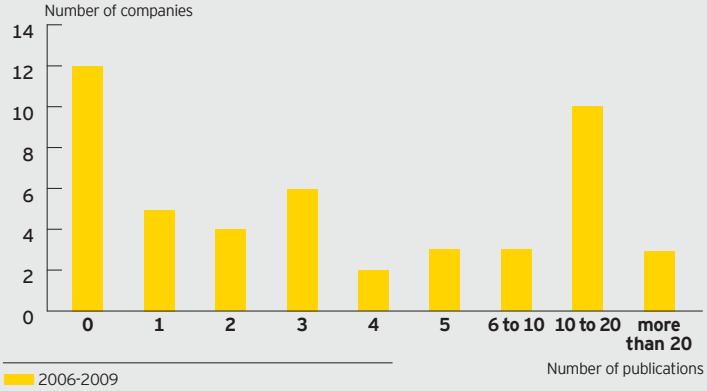


In particular, the number of companies signing agreements for an amount lower than € 50 thousand has increased, indicating that the overall increase in the number of "active" companies is mainly due to companies which sign deals for a rather limited value.

Finally, during the 2006-2009 period, the total number of scientific publications, which are co-authored by scientists belonging to the companies participating in our survey together with scientist which are employed in PRBs, was 356 (46 responding companies), i.e., about eight publications per company (Figure 3.19).

Figure 3.19

Analysis of scientific publications co-authored by PRB scientists
(Source: Ernst & Young)



Red Biotech

As the leading segment of Italian biotechnology, red biotech accounts for 96% of the overall turnover, and shows a constant increase both in terms of number of companies and volume of R&D investments Most of the companies involved are small, originating from start-ups and industrial or academic spin-offs. These companies grow in synergy with pharmaceutical companies and fuel a pipeline of 237 innovative products stemming from the network of life sciences in Italy.

General introduction

The most important segment of the biotech field is that related to human health (red biotech), both in terms of number of companies and employees, as well as volume of R&D investments and turnover.
Table 4.1 shows that, compared to the 2010 Report, the red biotech turnover and R&D investments have grown by 2% and 6%, respectively. Conversely, the number of R&D employees has substantially remained unchanged, even if a higher number of companies were included in the sample; however, this trend is not generalized since, as we shall see, the number of pure biotech companies R&D employees has increased.
Red biotech accounts for about 96% of the overall biotech turnover in Italy, showing a growth when compared to the 92% value of the 2010 Report. Its application fields include five main segments:

- therapeutics: development of gene- or cell-based drugs and therapies, where the following categories of products are included:
  - biologicals developed, tested or discovered by means of screening biotech methods;
  - low molecular weight molecules based on nucleic acid technology and on cell therapy;
- tissue engineering: biological substitutes for reconstruction or replacement of tissues and organs, obtained by using stem cells, new biomaterials and growth factors;
- vaccines for prophylaxis and treatment;
- drug delivery: technology used as vehicles for drugs to reach a specific site by optimizing their absorption and distribution (e.g., advanced materials, liposomes, antibodies, cell therapy);
- molecular diagnostics: DNA/RNA-based tests and methods for the diagnosis, prognosis and identification of any predispositions to specific diseases, and for the analysis of pathogenic mechanisms;
- drug discovery: synthesis, optimization and characterization of drug candidates, assay development and screening, validation activities on medicinal products.

Table 4.1

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

Red Biotech	2010 Report		2011 Report	
	Total	Pure biotech	Total	Pure biotech
Number of companies	243	138	246	141
Total biotech turnover	€7,010 million	€930 million	€7,157 million	€1,056 million
R&D investments	€1,580 million	€379 million	€1,679 million	€453 million
Total R&D employees	5,489	1,490	5,587	1,687

The companies operating in the red biotech field are 246 (about 66% of the total 375 companies included in the

sample): 185 of them are exclusively focused on red biotech, while the remaining 61 are also active in the other fields of application, and therefore are so-called "multi-core" (Figure 4.1). Overall, our analysis included 31 additional red biotech companies, as compared to the 2010 Report. Of these, 2 were set up during last year; 18 were already active in this field, but were identified thanks to a deeper analysis of the biotech market; 11 were already included in the sample of the 2010 Report, but extended their activities to red biotech only last year.
Among these 31 companies, there are 24 dedicated and 7 multi-core companies: this is a significant number when considering that, in the 2010 Report, only a 9% of red biotech companies were multi-core. As anticipated in Chapter 2, there is a clear marked trend towards diversification, with an increasing number of companies able to employ the expertise acquired in the field of origin in new fields of application.

In terms of type of company, the sample distribution is very similar to that of the 2010 Report (Figure 4.2). Most of the sample (57%) is made up of companies falling under the pure biotech category. The remaining 43% is mainly made of multinational subsidiaries in Italy (19%) and other Italian biotech companies (14%). However, it is clear that the multinational subsidiaries, although only a fifth of the sample, account for most (79%) of the overall turnover (Figure 4.3).

The share of biotech turnover of the Italian pharmaceutical companies account for 6%, with a 3% growth compared to the

Figure 4.1

Red biotech companies: analysis by application field
(Source: Ernst & Young)

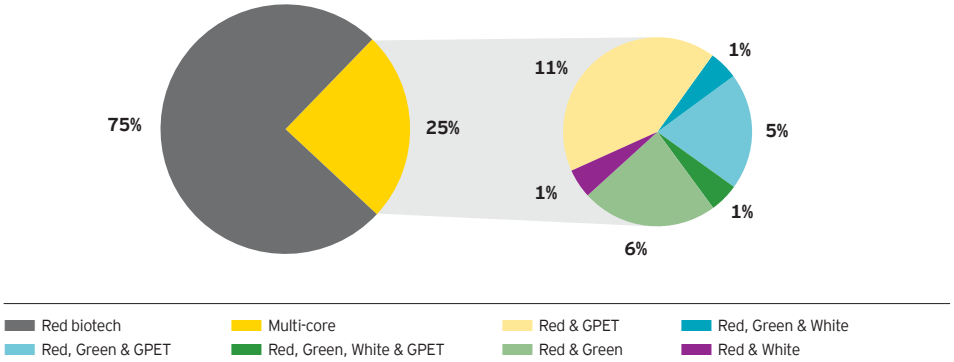


Figure 4.2

Red biotech companies: analysis by type (Source: Ernst & Young)

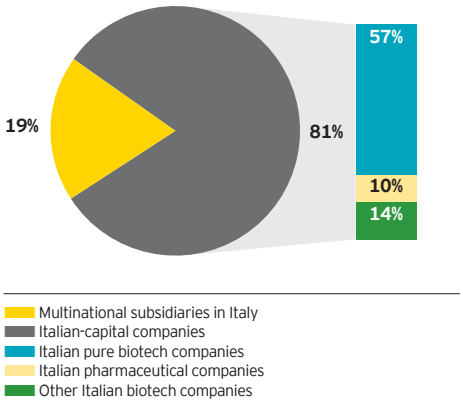


Figure 4.3

Red biotech companies: analysis of the 2009 turnover by type (Source: Ernst & Young)

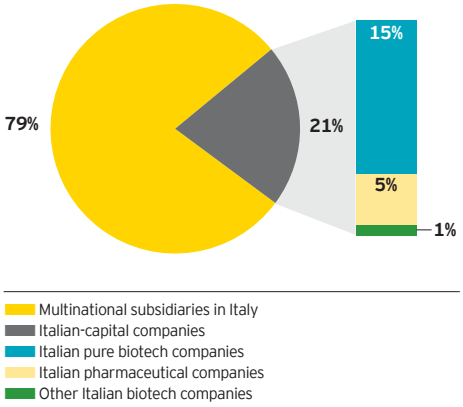
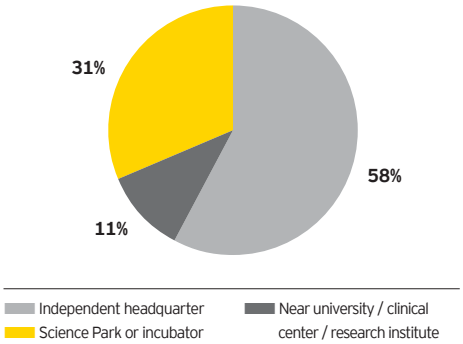


Figure 4.5

Red biotech companies: analysis by location (Source: Ernst & Young)



2010 Report; therefore, it is possible to conclude that the Italian pharmaceutical companies are starting to exploit the potential offered by the biotech market. These companies are differentiating their pipelines towards biotech products and financing the relevant R&D activities by using the profits resulting from their traditional pharmaceutical business.

The geographic distribution of the companies operating in the human health area is highly concentrated, with almost 40% of red biotech companies located in Lombardy (Figure 4.4). Moreover, Lombardy and Latium show a great industrial vocation, with the presence of 72% of all the multinational subsidiaries in Italy. Piedmont and Sardinia report instead a strong prevalence of science parks and incubators: approximately 80% of the biotech companies hosted in these two regions are based within these facilities. Overall, the companies located near science parks and incubators have increased by 4% compared to the 2010 Report (Figure 4.5).

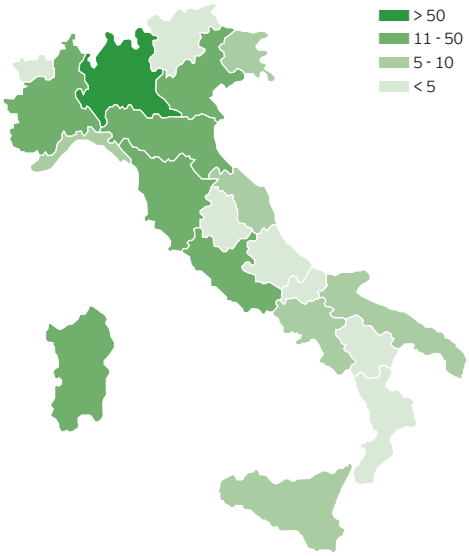
Most of the companies (36%) operating in the red biotech field were founded as start-ups (Figure 4.6). With respect to last year, it is possible to notice a slight increase (1%) in the number of companies originating from academic spin-offs, due to the fact that some companies already existing last year were not taken into consideration in the 2010 Report.

The segmentation of companies by number of employees shows that a large majority (71%) have less then 50 employees (Figure 4.7). Therefore, they are classified as micro or small companies.

As far as the analysis of the main investments made by the companies included in the sample is concerned, particular attention should be focused

Figure 4.4

Red biotech companies: analysis by geographic location (Source: Ernst & Young)



upon R&D investments: in 2009 about € 1,680 million, which account for the 23% of the entire biotech sector, were invested in red biotech activities.
Although accounting for only 10% of the companies operating in the red biotech field, the Italian pharmaceutical companies support 42% of R&D investments in this specific area (Figure 4.8), in addition to the contribution by multinational subsidiaries which accounts for 29%.
These R&D investment volumes confirm that red biotech companies are more engaged in research activities than in manufacturing and sales, and that they are particularly active in the development of biologicals, where about 40% of the sample is currently operating (Figure 4.9).

The analysis of financing sources shows that today companies usually resort to public contributions on a regional, government, European or even international level, as well as to VC/PE and debt (Figure 4.10). It should

Figure 4.6

Red biotech companies: analysis by origin (Source: Ernst & Young)

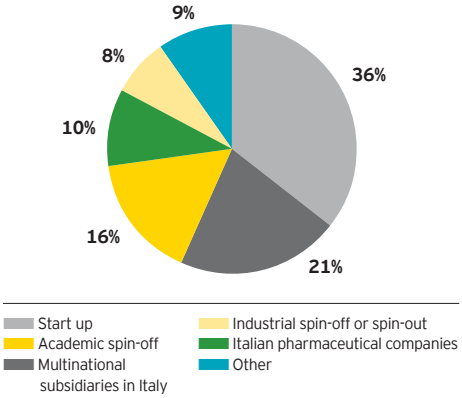


Figure 4.7

Red biotech companies: analysis by size (Source: Ernst & Young)

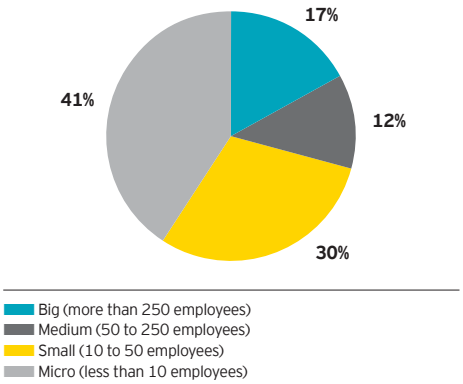
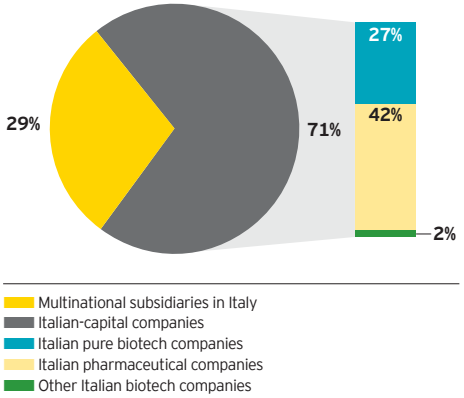


Figure 4.8

Red biotech companies: analysis of R&D investments by type (Source: Ernst & Young)



be specified that this feature is closely linked to the pure biotech segment, as pharmaceutical companies most commonly rely on self-financing.

The above described situation will probably change in the next two years, especially regarding pure biotech companies that have clearly stated their intention of turning increasingly to strategic alliances and partnerships, rather than debt. These alliances may also include co-development of products and technologies in the investigational phase, co-marketing of products and technologies in the commercialization phase, or even Mergers & Acquisitions (M&A).

As already highlighted in the 2010 Report, on a national level the cooperation between companies and third parties concerns primarily the involvement of universities; in more than half of the red biotech companies, joint projects with academic research groups have been developed. Again with regard to the 2010 Report, there is an increasing trend towards setting up international co-operations, in particular (33% of the cases) with universities and other foreign companies.

Figure 4.9

Percentage of red biotech companies focused on R&D, production and sales (Source: Ernst & Young)

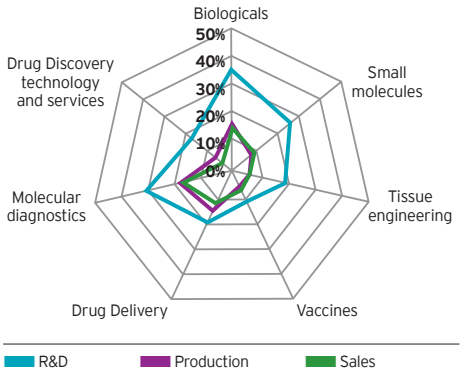
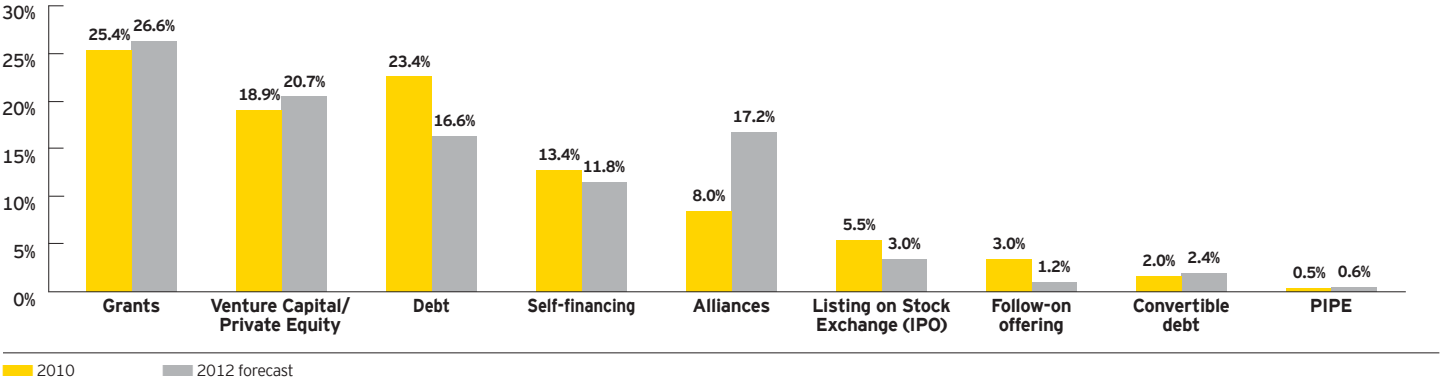


Figure 4.10

Red biotech companies: analysis of financing sources (Source: Ernst & Young)



Benefits of Integrated Research in Drug Discovery and Development

Strategic Outsourcing is now considered the most cost-effective strategy for the international pharmaceutical R&D.
The most efficient model of outsourced research is via fully integrated multidisciplinary teams, working together to deliver comprehensive development plans which do address and optimize all the aspects concerning drug development, in every single phase.
This approach is fully embodied by the "one-stop-shop" model adopted by the Aptuit Verona Research Centre that is now part of Aptuit, a fully integrated pharmaceutical services company, focused on Contract Research, Contract Development & Contract Manufacturing for pharmaceutical and biotechnology companies.
The range of expertise and experience present in Verona are provided as an integrated service and include: target biology, pharmacology, medicinal and computational chemistry, safety assessment, chemical development, analytical chemistry, pharmaceutical development, bioanalysis, drug metabolism and pharmacokinetics and clinical sciences.
The platform activities are combined with a close functional integration between preclinical and clinical disciplines, with risk evaluation and reduction enhancing the development prospects from the very beginning of the project, as well as the generation, protection and safeguarding of intellectual property and the preparation of quality documentation and regulatory submission.

"Quality by Design"

Quality by Design allows for the analysis of risk associated with the active ingredient and final product production processes and to obtain a series of advantages including:

- *cost savings*
- *reduced timelines for completion of all development phases and registration of new drugs*
- *reduced environmental impact*

The "Quality by Design" approach guarantees and supports the introduction of new technologies such as continuous synthesis, allowing for greater production under controlled conditions as well as for improved monitoring of chemical associated risks compared to traditional methods.

The benefits of integrated approaches that ensure continuity between preclinical and clinical research are exemplified in Translational Medicine and Quality by Design.
Translational Medicine enhances the quality and efficiency of drug discovery and development by integrating the knowledge provided by preclinical science to the subsequent clinical development. The efficacy, safety and clinical benefit of new drugs can be evaluated earlier, whilst feedback of clinical findings to the laboratory, stimulates novel research hypotheses, implementing a "bench to bedside to bench" approach.
Another innovative approach for integrated Drug Discovery and Development is Quality by Design (QbD). The aim of QbD is to define processes which allow for a quicker, effective industrialization and approval of new chemical entities (potentially also of generic drugs) by regulators (e.g., FDA) who are encouraging adoption of this initiative.
This approach relies upon an accurate scientific evaluation of active ingredient synthesis in order to prospectively identify those parameters and variables which influence the physical chemistry and the subsequent formulation of substances for human administration. In this way the quality of the product (active ingredient or its formulation) is guaranteed not by a retrospective check, but using consistent production processes, for which critical parameters (and tolerable variability thereof) have long since been identified in the earliest phases of development.
The Aptuit Verona Research Centre plays a key role in the development of new therapeutic agents and clinical sciences in Italy, by positively stimulating the innovation and entrepreneurial spirit and the culture of applied research in a clearly strategic and important field.

Pure biotech companies

As already seen, pure biotech companies represent the numerically most significant part in the Italian biotechnology scene. This is also true within the red biotech field where pure biotech account for 57% of the whole sector. When the data from the 2010 Report were re-calculated to include the 10 already existing companies not considered before, it was possible to see a clear growth of this specific segment in terms of turnover and investments as well as number of R&D employees. Seventy percent of pure biotech companies are exclusively engaged in research activities in the field of human health (Figure 4a.1). The remaining 30% of multi-core companies operates in the red biotech field as well as in GPET and green biotech.

The analysis of geographic location shows that 72% of pure biotech companies are concentrated in five regions: Lombardy (33%), Tuscany (10%), Emilia Romagna (8%), Piedmont (11%) and Sardinia (10%), where the most important Italian science parks are sited.

An analysis of the origins of pure biotech companies operating in the red biotech field shows that most of them (54%) were set up as start-ups; about 22% originated from academic spin-offs, with a clear increase on the 15% of the 2010 Report, due to the 6 companies that already existed but were not included in the analysis at the time (Figure 4a.2).

The segmentation of companies by workforce shows that about 90% have less than 50 employees and therefore fall into the category of micro and small companies (Figure 4a.3).

Tabelle 4a.1

Italian pure biotech companies, red field: key data (Source: Ernst & Young)

Pure red biotech	2010 Report	2011 Report
Number of companies	138	141
Total biotech turnover	€930 million	€1,056 million
Total R&D investments	€379 million	€453 million
Total number of R&D employees	1,490	1,687

Figure 4a.2

Italian pure biotech companies, red field: analysis by origin (Source: Ernst & Young)

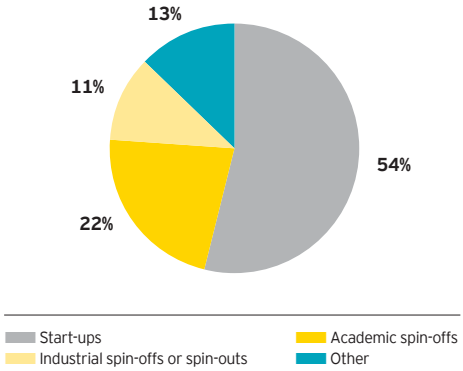


Figure 4a.1

Italian pure biotech companies, red field: analysis by application field (Source: Ernst & Young)

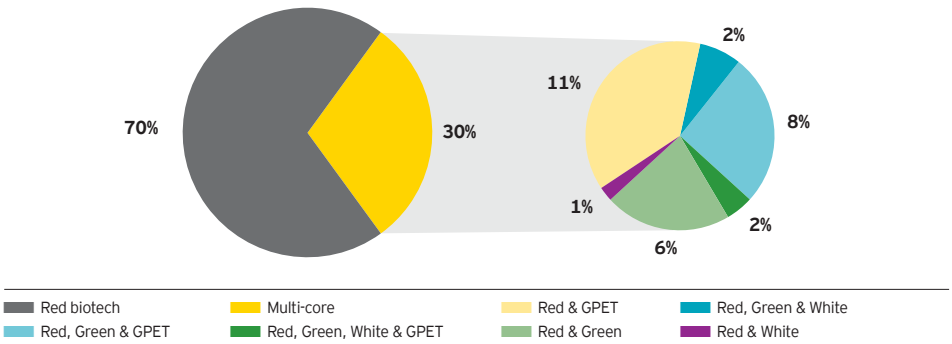
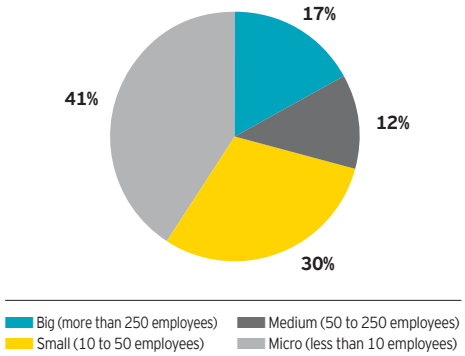


Figure 4a.3

Italian pure biotech companies, red field: analysis by size (Source: Ernst & Young)



The pure biotech companies employ approximately 1,687 people in R&D, which is 30% of the total red biotech employees. The ratio between the number of R&D employees and the number of total employees is particularly interesting: this value is much higher in the pure biotech companies, which are typically research-intensive organizations (Figure 4a.4).

The analysis of R&D investments shows that outsourced research, i.e., the share of research activities which is contracted out to universities, research centers, CROs, etc., accounts for 22% of the total (Figure 4a.5).

The analysis of financing sources is in line with that shown by the analysis of the other companies operating within the red biotech field, with predominance, both in the past and in the next two years, of government grants and VC/PE funds.

The most important type of co-operation on the national level is once again the relationship with universities, even if pure biotech companies show a greater tendency to cooperate with other companies.

With regard to the estimated 2010 turnover, pure biotech companies offer less stable perspectives, but are substantially in line with non-dedicated red biotech companies (Figure 4a.6).

In addition, pure biotech companies confirm their intention to look for new alliances, business models and capital sources, without reducing the number of projects in the pipeline and increasing the number of employees. There is a clear preference for the licensing of products and technologies to third parties instead of looking for M&A.

Figure 4a.4

Average number of total employees and R&D employees, red field (Source: Ernst & Young)

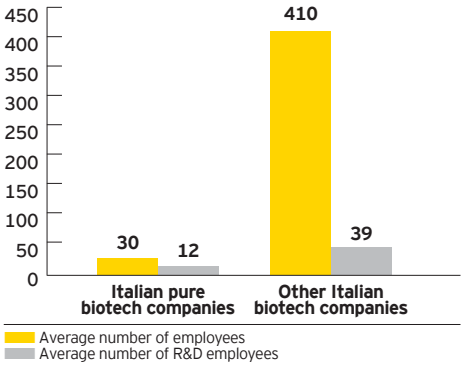


Figure 4a.5

Italian pure biotech companies, red field: analysis of R&D investments (Source: Ernst & Young)

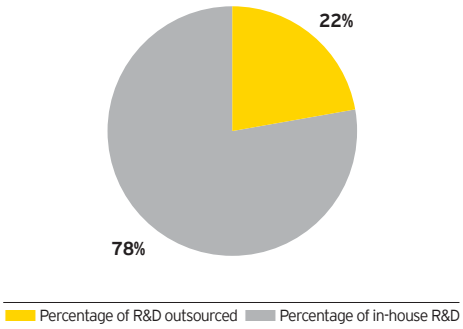
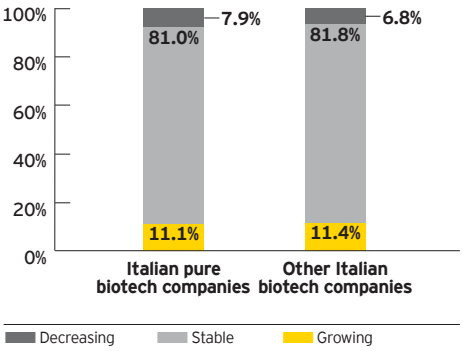


Figure 4a.6

Estimated turnover for 2010, red field (Source: Ernst & Young)



Pharmaceutical companies

This section is focused on the red biotech companies falling under the definitions of "Italian pharmaceutical companies" and "multinational subsidiaries in Italy". These two categories will be collectively referred to as "pharmaceutical companies". Table 4b.1 shows the comparison between the 2010 and 2011 data, related to this specific sample subgroup. It should be remembered that the data from the 2010 Report were modified in order to include the companies identified this year thanks to a deeper analysis.

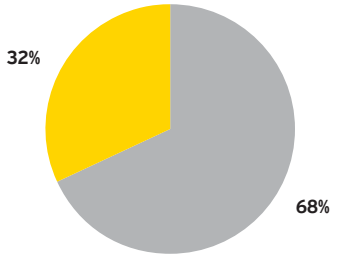
Table 4b.1

Pharmaceutical companies, red field: key data
(Source: Ernst & Young)

Pharmaceutical companies	2010 Report	2011 Report
Number of companies	69	69
Total biotech turnover	€5,780 million	€6,000 million
Total R&D investments	€1,100 million	€1,163 million
Total R&D employees	3,688	3,644

Figure 4b.1

Pharmaceutical companies, red field: analysis by origin (Source: Ernst & Young)



This comparison shows a slight increase in the biotech turnover (+4%), together with an increase in R&D investments (+6%), over last year. The analysis of the companies included in the sample shows that most of them (68%) are multinational subsidiaries in Italy and the remainder are Italian pharmaceutical companies (Figure 4b.1).

Ninety-one percent of the pharmaceutical companies operating in the biotechnology field are exclusively dedicated to red biotech (Figure 4b.2). The remaining 9% are multi-core companies which operate, for the most part, in the red and green biotech fields at the same time.

The segmentation by workforce shows that about 60% of the companies have more than 50 employees and are therefore

Figure 4b.2

Pharmaceutical companies: analysis by application field, with details concerning the multi-core companies
(Source: Ernst & Young)

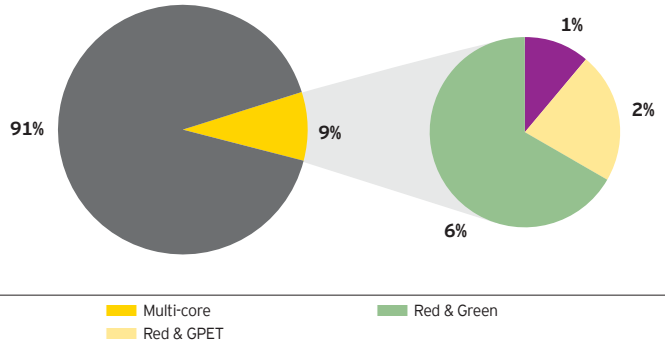


Figure 4b.3

Pharmaceutical companies, red field: analysis by size
(Source: Ernst & Young)

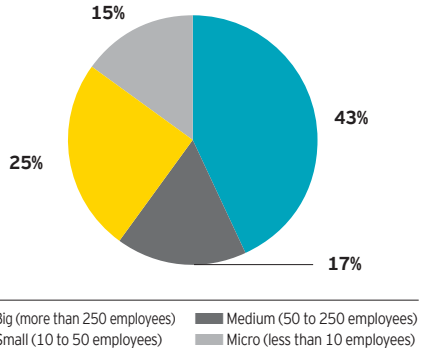
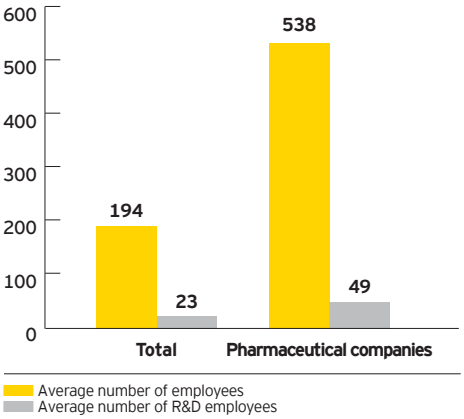


Figure 4b.4

Average number of total employees and R&D employees, red field (Source: Ernst & Young)



classified as big and medium companies (Figure 4b.3).

Pharmaceutical companies employ approximately 3,644 people in R&D, accounting for 65% of the total number of the research workers of the entire red biotech sector. Figure 4b.4 shows that the average number of employees in pharmaceutical companies is significantly higher than the total average of the whole biotech field. However, pharmaceutical companies have a much lower percentage of R&D employees compared to the total number of employees (9% versus 12% of the whole field, pure biotech companies included).

With regard to the estimated 2010 turnover, pharmaceutical companies have rather steady perspectives, with 85% of them showing stable sales, while half the remaining 15% companies forecast growth and the other half forecast a decrease in terms of turnover.

A New Hub of Excellence for the Production of Biotech Drugs in Italy

One of the major investments made by a pharmaceutical company in Italy over the last decade is that recently made by Eli Lilly Italia Spa.
Notwithstanding one of the most negative economic situations and all the issues hindering the development of this field and reducing the attractiveness of new investments in Italy, 250 million Euros were invested in the creation of a new hub of biotech excellence which will produce insulin and insulin analogs using innovative techniques.
Lilly have used their Tuscany site in Sesto Fiorentino to set up a new excellence hub for the production of innovative products, where a sophisticated technology ensures a high degree of integrated automation and computerization.
At full capacity, the plant will produce up to 120 million insulin and recombinant DNA analog cartridges to be sold both on the Italian and the international markets, with a predicted export of 90% of the total production.
Another 60 million Euro investment is forecast for the implementation of a second production line of the new plant; this confirms the strategy of the Eli Lilly group which is counting on the Italian hub as a center of excellence and reference for the production of insulin in the world.
Lilly consider the pharmaceutical industry a strategic field for the development of the Italian economic system, capable of providing an important contribution in terms of health, economic development and technological innovation, by encouraging the development of scientific and technological know-how to the benefit of the whole local industrial fabric.

But what are the factors that have played a major role in making the decision of investing in Italy? On the occasion of the inauguration of the new plant on September 25th 2009, John C. Lechleiter, CEO of Eli Lilly and Company, highlighted the following three factors that attract foreign investments to our country:

- a highly-qualified and highly-educated workforce;
- a stable and consistent regulatory framework and industrial policy. Only steady and defined rules can ensure the transparency which is needed to develop successful strategies and investment plans;
- adequate laws on patent protection which are crucial to safeguard innovation. For research-based companies the most important principle to guarantee, from a legal point of view, is a certain period of patent protection, according to the "not a day earlier, not a day later" rule;
- policies supporting innovation;
- acknowledgement of the important contribution of the biopharmaceutical field in terms of employment and economy: for each person employed in the biopharmaceutical field there are four more people employed, including partners and providers;
- the scope of the reference market: Italy is the fifth largest market in the world and its size makes it an important market for operation and competition.

Focus on Advanced Therapies

The rapid progress of biotechnology research has led to the implementation of new Advanced Therapy Medicinal Products (ATMPs), including products for gene therapy, somatic cell therapy and tissue engineering, giving rise to the need for a new classification within the category of biological medicinal products. The wide development of this field is related to the high potential of advanced therapies in the treatment of several diseases.
Unlike conventional drugs, advanced therapy products play a key and specific role in the complex physiological mechanisms and these results, with a good degree of efficacy, into the direct repair, correction or integration of the physiological and tissue functions lacking in the patient.

In Europe, advanced therapy products are acknowledged just like medicinal products and fall under the regulatory provisions concerning pharmaceutical products for human use, in terms of production, technological and scientific aspects and therapeutic indications.
Hence, their marketing authorization is granted exclusively by the European Medicines Agency (EMA).

Although to date in the world only two drugs for advanced therapies have obtained marketing authorization (ChondroCelect – TiGenix NV, the Netherlands - by EMA, and Provenge – Dendreon, USA – by FDA), during the last few years there has been a constant increase in the number of clinical trials, which also foreshadows an increase in marketed drugs in the near future.

The definition of advanced therapies includes some revolutionary biotechnology methods, which open new perspectives in the medical field:

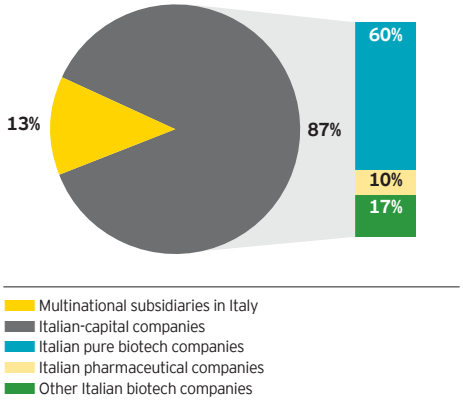
- somatic cell therapy, based on the administration of preparations containing live cells or complex parts of them, and having objectives similar to medicines;
- gene therapy, a medical technology in which DNA is used directly as a pharmaceutical substance, i.e., genes or gene fragments are introduced into the human body aiming at preventing, treating or curing a disease;
- tissue engineering, a new multidisciplinary field of biotechnology whose aim is to regenerate diseased or damaged organs and tissue by promoting overall tissue regeneration and by stimulating the reactivation of endogenous repair mechanisms.

Medicinal preparations for advanced therapies are different from those of other cell-based products that have already been used for many years, including those for blood transfusions and bone marrow transplantation, or the use of stem cells isolated from umbilical cord, tissues and organs.
In fact, before being administered to patients, the cells for advanced therapies undergo a "manipulation" or "engineering" process aiming at enhancing the donor's cells so that their new characteristics can produce a therapeutic action on the recipient's disease.

The analysis of data shows that 30 companies are engaged in research in this specific field, accounting for 12.2% of the companies operating within the red biotech field. Most of these 30 companies are pure biotech (Figure 4c.1).

Figure 4c.1

Advanced therapy companies: analysis by type
(Source: Ernst & Young)



The analyzed sample also shows that about half (49%) of these companies operate in regenerative medicine, 40% in cell therapy and 11% in gene therapy (Figure 4c.2).

The analysis by size of the companies operating within the advanced therapy field shows a certain degree of balance, with the micro cluster accounting for 39% of the sample (Figure 4c.3).

When we consider the biotech turnover, we see that the companies engaged in the AT field produce a turnover in terms of research products and services of about € 844 million (this includes the companies' total turnover and is not related to AT-related products/services only) (Figure 4c.4).

Fifty percent of the companies operating in the advanced therapy field are located in Lombardy and Emilia Romagna (Figure 4c.5).

The analysis by average number of employees working in the AT field shows that pure biotech have an average number of employees about 10 times lower than other biotech companies, and that the number of employees dedicated to R&D activities accounts for 25.4% of the total (Figure 4c.6). The average workforce in this field can be estimated to be 8,370 people, of which about 13% working at pure biotech companies.

The analysis of R&D investments shows that the 30 companies identified have invested about € 563 million.

Figure 4c.2

Advanced therapy companies: analysis by application field (Source: Ernst & Young)

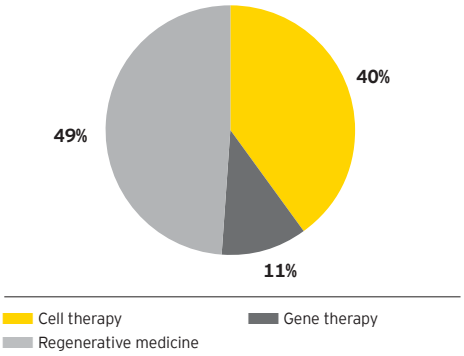


Figure 4c.3

Advanced therapy companies: analysis by size (Source: Ernst & Young)

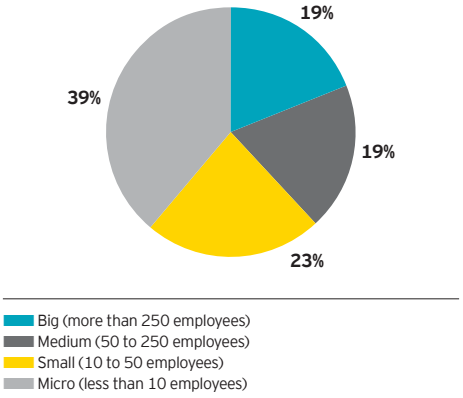


Figure 4c.4

Advanced therapy companies: analysis of the 2009 turnover by type (Source: Ernst & Young)

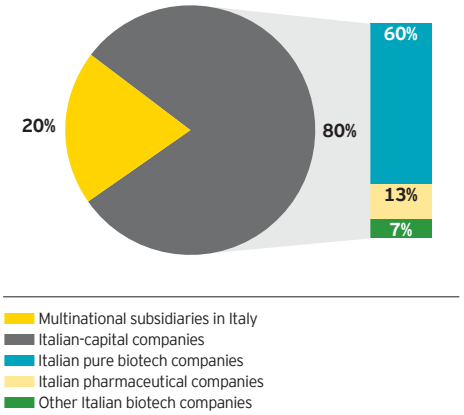


Figure 4c.5

Advanced therapy companies: analysis by geographic location (Source: Ernst & Young)

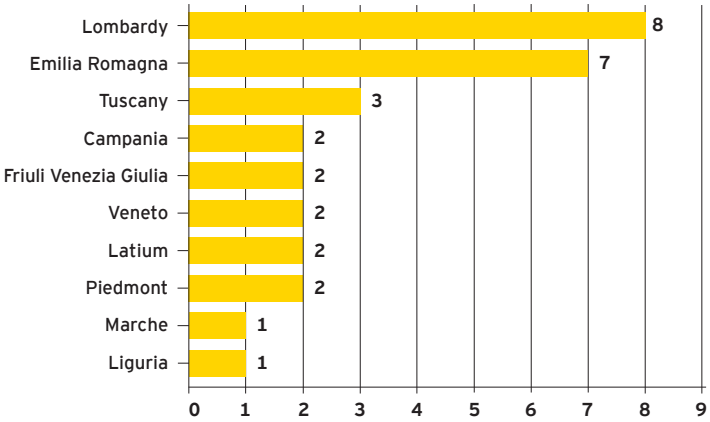
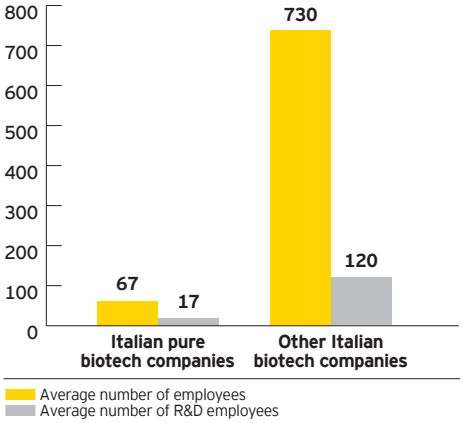


Figure 4c.6

Advanced therapy companies: average number of total employees and R&D employees (Source: Ernst & Young)



Telethon: when Strategic Management and Promotion of Excellence can attract Significant Investments

In 2010 GlaxoSmithKline plc (GSK) and Telethon Foundation - an Italian charity whose mission is to finance biomedical research for the treatment of rare genetic disease - entered into a strategic alliance for the research and development of seven rare genetic diseases through ex-vivo gene therapy approaches on hematopoietic stem cells. The alliance capitalizes on the scientific achievements of the San Raffaele Telethon Institute for Gene Therapy (HSR-TIGET).

Under the terms of the agreement, GSK gained an exclusive license to develop and commercialize an investigational therapy, currently in Phase III, for ADA Severe Combined Immune Deficiency (ADA-SCID). Furthermore, the agreement sets forth the conditions to fully develop, through milestone payments, a promising pipeline based on the lentiviral vector technology optimized at HSR-TIGET, with two ongoing trials (for Wiskott Aldrich Syndrome and metachromatic leukodystrophy) and advanced preclinical projects on beta-thalassemia, mucopolysaccharoidosis type I, globoid leukodystrophy, and chronic granulomatous disorder.

Telethon set a high strategic priority on gene therapy, as a major avenue to innovation in the development of therapies for monogenic diseases, quite early relatively to the development of this approach.

HSR-TIGET was founded in 1995 thanks to a partnership with the San Raffaele Hospital; San Raffaele and Telethon collaborate providing infrastructural and research-funding support, respectively. This logistic and conceptual integration between research laboratories and clinical activities is one of the reasons of Tiget's success.

Other elements that were pivotal in paving the way to the partnership with GSK are, mainly, a conspicuous and constant support by the funding bodies, a strategic management of research and development through a close collaboration between Telethon and the investigators at the institute and a stringent peer review-based assessment and of Tiget's science and periodic steering of its activities through expert advice.

These conditions allowed the institute to devise a long-term plan even when enthusiasm for gene therapy encountered a global setback due to some unsuccessful clinical trials, both in the United States and in France.

Strategic decisions led not only to one breakthrough achievement, such as the therapy for ADA-SCID, but to the actual development of a pipeline, fed by the institute's international leadership in the optimization of a lentiviral platform, which could eventually generate the interest of a major pharmaceutical partner.

Specifically, these decisions were represented by some fundamental recruitments – designed to integrate the best clinical and 'biotechnological' expertise and build a world-class leadership in gene therapy – the timely achievement of the necessary steps in the direction of a clinical application -such as the orphan drug designation for the gene therapy protocols and a quite onerous investment in the GMP production of vectors - and a constant balance between clinical activities and forefront research.

The Telethon-GSK partnership is exemplary of how, through strategic management and fostering of excellence, a relatively small entity can attract major international investments in Italy, in a highly competitive field, despite the extreme rarity of the studied diseases

Diagnostics

Biotechnology fully reflects the image of the development of life sciences by offering the world increasingly new tools to research and develop innovative diagnostic agents.
Modern biotech diagnostics includes diagnostic tests based on the use of DNA or protein/antibody probes, and is the field benefitting most from achievements in molecular biology and human gene sequencing areas.
New analysis techniques, derived from molecular biology, immunochemistry, genomics and nanotechnology are available today and allow diagnosing diseases until now unconceivable, while efforts are being made to fill the gap between super-advanced diagnostics and new therapeutic tools suitable to treat them.
Paradoxically, the development of advanced diagnostics underwent a strong acceleration compared to the new types of drugs needed to treat these emerging diseases; however, this is understandable since a shorter time is needed to develop and market diagnostic tools (4-5 years) than the time required to develop new drugs.

Today, in the diagnostics field a number of tools, antibodies, kits, DNA probes, chips, cell tests are available as well as animal and organ models that allow to apply them to all the possible areas of medicine. Among these, the following areas should be mentioned: prognostics, diagnostics, prediction, identification and quantification of the most adequate pharmacological treatment and the monitoring of its efficacy.

In Italy there are 64 companies operating in the diagnostics field, accounting for 26% of companies of the whole red biotech field.

The experts in this area deem that, compared to medicinal products, diagnostics may represent a possibility to enter the biotech world with lower entrepreneurial risk.
This is for two main reasons:

- the time needed for the development of diagnostic products is usually shorter than that required for the development of new drugs; the same applies to the procedure for registration and marketing authorization. With regards to the development phase, diagnostics are studied in clinical trials based on the mere analysis of laboratory samples; these studies have duration from 6 month to 2 years, while biotech drugs are tested directly on volunteers and patients in three consecutive phases which can last overall even 10 years. With regard to regulatory registration, diagnostics require the CE marking that can be obtained within 1-2 months and, therefore, the period of time needed cannot be compared to that necessary for the registration of drugs;
- the costs for the development of diagnostic products are lower, because of the more simplified clinical and regulatory phases, a high replicability of the development process starting from a single established technology, and the lower costs connected with the finalization of the registration dossier.

Of the 64 companies operating in this field, more than 80% are pure biotech companies (53) (Figure 4d.1); the remaining 17% is equally distributed between multinationals with subsidiaries in Italy and other biotech companies.

The analysis of the companies operating in the diagnostic field shows that 85% of the

Figure 4d.1

Diagnostic companies: analysis by type
(Source: Ernst & Young)

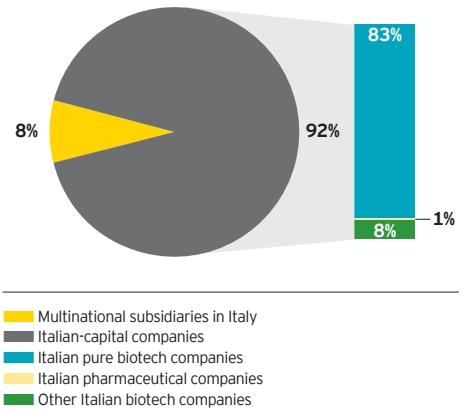


Figure 4d.2

Diagnostic companies: analysis by size
(Source: Ernst & Young)

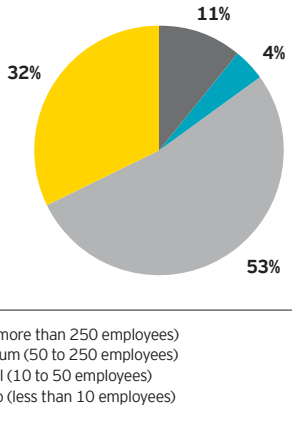


Figure 4d.3

Diagnostic companies: analysis of the 2009 turnover by type (Source: Ernst & Young)

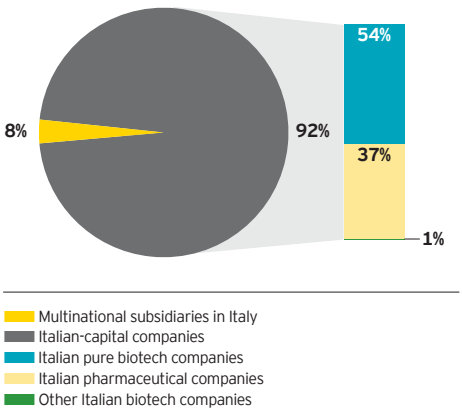
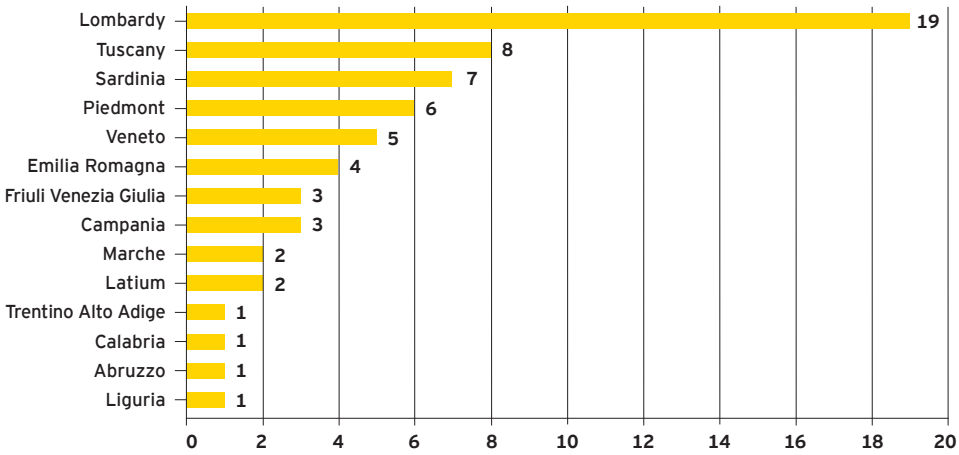


Figure 4d.4

Diagnostic companies: analysis by geographic location (Source: Ernst & Young)

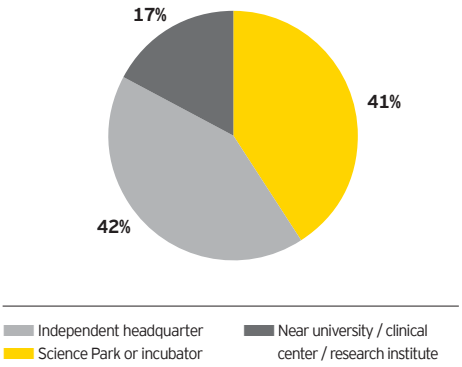


sample employ less than 50 people (Figure 4d.2), while more than 10% is made of companies which are big in size (more than 250 employees), including multinationals with subsidiaries in Italy and 2 Italian pure biotech companies.

The item which characterizes the diagnostics field most within the whole red biotech sector is the contribution of pure biotech companies to the overall turnover. With the Italian diagnostics market estimated at € 590 million (Figure 4d.3), the pure biotech companies contribute for more than half (54%) of the profits originating from the marketing of diagnostic products and kits. However, it should be highlighted that there are two main players accounting for about € 500 million of turnover alone.

Figure 4d.5

Diagnostic companies: analysis by location (Source: Ernst & Young)

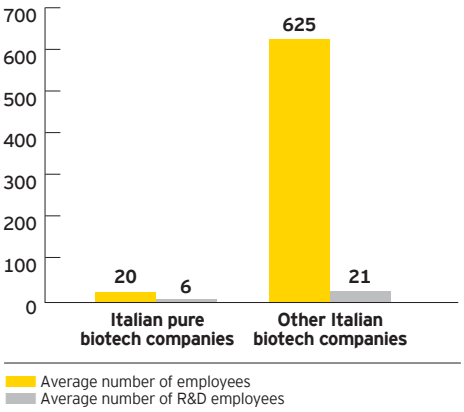


When considering the location of diagnostics companies, we see that 30% of them have headquarters in Lombardy; followed by Tuscany (13%), Sardinia (11%) and Piedmont (9%). Lombardy is once again the region offering biotech companies the highest chances for development (Figure 4d.4).
Shifting the focus from the geographic location to the type of location, a substantial balance is evident between companies with independent headquarters and those located within a science park or incubator.
Conversely, only 17% have headquarters next to universities and clinical centers (Figure 4d.5).

The number of employees working at the 64 companies identified is estimated at approximately 8,000 people, 600 of which

Figure 4d.6

Diagnostic companies: average number of total employees and R&D employees (Source: Ernst & Young)



are dedicated to R&D activities. The reason for the low ratio (7.5%) between R&D employees and total number of employees may well be that, as previously highlighted, the companies of the diagnostics field succeed in arriving quite easily on the market and, consequently, they can also develop other functions, including production, marketing and sales.

However, in most cases, pure biotech companies operating in the diagnostic field do not manage to develop an effective distribution network and they outsource all the distribution and sales activities to third parties. For this reason, considering the average number of employees in this field, pure biotech companies have an average of 20 employees, of whom about 30% dedicated to R&D (Figure 4d.6).

In other biotech companies, the percentage of personnel dedicated to R&D is drastically reduced, accounting for 3% of the total employees (625 people).

R&D investments made by companies operating in the diagnostic field are about € 180 million, accounting for 30% of the total turnover. Therefore, this figure is in line with the average of the whole biotech field, analyzed in Chapter 2.

Biotechnology for in-vitro Diagnostics

Today, the development of new generation ligand assays (Immunoassays and Nucleic Acid Assays) that are based on molecular recognition of complementary structures, must involve the integration of skills which pertain to different scientific disciplines and are not necessarily linked by a "bio" (biological, bio-chemical or bio-technological) matrix.

Until recently, the formulation of reagents (antigen, antibody or polynucleotide reagents and their biotech developments) or the technology of signals (isotopic, enzymatic, fluorescent, chemo-luminescent) represented the enabling technology for the development and improvement of ligand-based assays.

Today, following the strong demand for assay automation by users, assay integration – that is, the governance of the variables and the conditions imposed by the need for automation – is an integral part not only of the assay system development, but also of the reagent design that must be adequate both in terms of efficacy/quality of the required immunologic/molecular recognition and with regard to the conditions imposed by the hardware/software system of the instrumental component.

In this scenario, the assay's traditional architectural patterns acquire a further element of complexity: not only do bio-reagents drive the method and the assay format, but system constraints also exist (including, compressed kinetics, high consumption rates, need for calibration and repeated checks) which determine the nature and characteristics of the useful reagent.

Within this context, DiaSorin S.p.A. has set the following priorities for their research:

- development of innovative content, for niche and extensive tests, by means of massive use of engineered reagents and automated formats
- integration of analytical and industrial biotechnology with "system" disciplines such as hardware and software engineering and design control
- design and simplification, on "PCR-independent" technology, of automated molecular tests (NAT)

Based on these assumptions, DiaSorin, an Italian multinational company with more than 110 R&D employees in the world – of whom 70% in Italy – that has been operating on the in-vitro diagnostics and immunodiagnostic market for over 40 years, confirms their leading role in the innovation of reagents, as a key factor of their business model for the development of tests capable of fulfilling the most advanced clinical needs.

Therapeutics: focus on the Italian pipeline

Analysis by development phase

The Italian biotech field is dominated by companies whose activities aim at the development of highly innovative drugs. In particular, for 50 pure biotech companies evidence is available of a pipeline of projects and products. Overall, the pipeline developed by Italian pure biotech companies includes 124 products under development, of which 64 in the preclinical phase, 21 in Phase I, 26 in Phase II and 13 in Phase III. To these figures, 59 early-stage research projects, i.e., in the discovery phase, should be added (Figure 4e.1).

However, there are several drugs which have recently reached Phase III, and several others that may soon do so, taking into consideration the high number of projects which are already in an advanced phase of clinical development. In 2010 alone, 3 new drugs have entered Phase III and 2 Phase II.

For example, among the first biological products achieving Phase III there is a monoclonal antibody developed as an anticancer vaccine for the prevention of relapses in patients with ovarian cancer. The study was started in December 2006 and the initial results will be available by mid 2011.

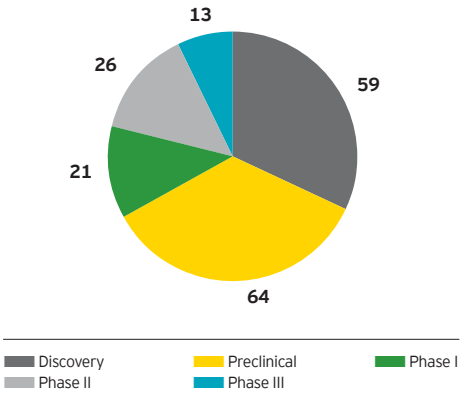
With regard to Phase II, this is generally considered a "make-or-break" phase in the development of drugs. If quite a number of Italian companies which already have molecules in Phase II are able to achieve Phase III, it is reasonable to expect that many new products will enter the market as from 2015.

On the other hand, if we take into consideration the companies falling under the wider OECD definition, the Italian biotech pipeline counts 237 products, of which 79 originate from foreign-capital companies and 158 from Italian-capital companies (124 pure biotech companies, 32 pharmaceutical companies and 2 other biotech companies) (Table 4e.1).
With regard to those companies which provided detailed information on their respective pipelines, the aforesaid definition would include, besides the already mentioned 50 Italian pure biotech companies, 10 Italian pharmaceutical companies, 15 multinational subsidiaries in Italy, and 3 Italian other biotech companies, totaling 78 companies.

Moreover (Figure 4e.2), the majority of the 32 products which originate from the Italian-capital companies research activities are still in preclinical phase or in the early phases of clinical development, while the 79 products in the portfolio of foreign-capital companies are mostly in late-stage development. Also the 2 products which originate from other biotech companies, with a multi-business focus, are still in preclinical phase.

Figure 4e.1

Italian pure biotech companies: number of products by R&D phase (Source: Assobiotec)



The detailed analysis of products in relation to their development phase shows that the role of pure biotech companies is even clearer: with the highest number of products in the preclinical development phase (64 out of 82), they are a true promise for the whole sector in the next few years.

The pharmaceutical industry in Italy is mainly involved in the more advanced phases of development, with an overall contribution to development of more

Table 4e.1

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

	Italian-capital companies				
	Pure biotech companies	Pharmaceutical companies	Other biotech companies	Foreign-capital companies	Total products
Preclinical	64	12	2	4	**82**
Phase I	21	4		5	**30**
Phase II	26	13		28	**67**
Phase III	13	3		42	**58**
Total	**124**	**32**	**2**	**79**	**237**

Figure 4e.2

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

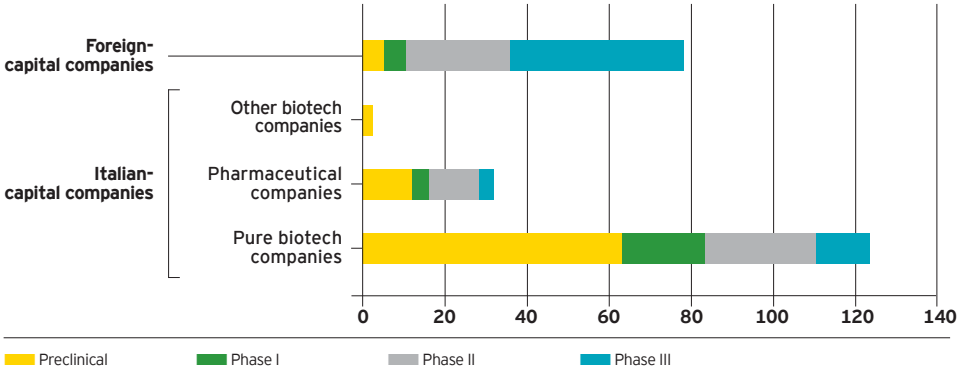
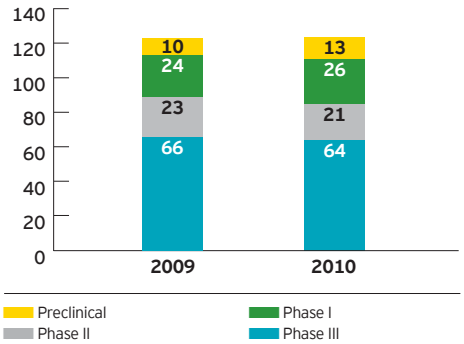


Figure 4e.3

Italian pure biotech companies: product analysis by development phase (Source: Assobiotec)



than half of the products in clinical phase. These data confirm the levels of excellence and complexity achieved by our country in the conduction of clinical trials, especially in oncology.

The above data appear even more important when we consider that the analysis was restricted to products and projects originated by R&D activities carried out mainly in Italy.

The early-stage research conducted in Italy shows that a higher number of pure biotech companies are involved (with 59 projects out of 68).
This phenomenon reflects the trend of pharmaceutical companies to outsource an increasing share of their R&D activities to companies which are smaller in size but characterized by those high levels of specialization and flexibility that are – in fact – present in the several Italian pure biotech companies stemming from academic start-ups and spin-offs.

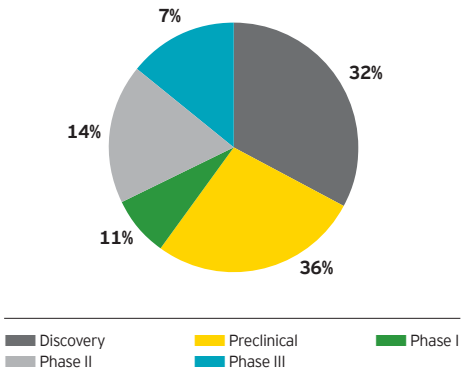
Despite limited worldwide cash flow, which also affects Italian pure biotech companies, it is still possible to highlight a basically stable trend in terms of number of investigational products and trials in Italy (Figure 4e.3).

This confirms that also in 2010 these companies have been able to create value by maximizing investments.

The segmentation of pure biotech companies by development phase shows that more than 60% of the companies are still substantially engaged in preclinical activities while, with regard to clinical development, 11% of the companies achieved Phase I, 14% Phase II and the remaining 7% has at least one Phase III product (Figure 4e.4).

Figure 4e.4

Italian pure biotech companies: analysis by most advanced drug candidate (Source: Assobiotec)



Analysis by therapeutic area

The investments of Italian companies involved in the research and development of new drugs are mainly focused in oncology (Figure 4e.5).

In particular, considering the whole R&D process and therefore including also projects in the discovery phase, the pure biotech field is very much involved in oncology (31%), in neurology (19%) and infectious disease (13%) (Figure 4e.6). On the other hand, cancer disease – since today for many of them there are no adequate therapeutic options - is the market segment that during the last few years has shown the highest growth rate.

The CNS (Central Nervous System) drug market, too, is reporting a high global growth. This trend is bound to strengthen since several neurological and degenerative diseases are directly related to the longer life expectancy and to the increased percentage of the elderly population in industrialized countries.
At this regard, it should also be highlighted that the Italian population is the oldest in the world: one in five Italians is over 65 years old, and eighty-year-olds account for 5.8% of the population – with an annual growth of 3.2%; this makes Italy an increasingly interesting scenario for those companies intending to develop and conduct clinical trials on new drugs for the treatment of age-related diseases.

With regard to pharmaceutical companies, their R&D activities are focused also on metabolic, hepatic and endocrine diseases (20% of the multinational subsidiaries in Italy), inflammatory and autoimmune diseases (14% of the Italian pharmaceutical companies), and on gastrointestinal diseases (14% of the Italian pharmaceutical companies).

Figure 4e.5

Product analysis by therapeutic area and by type of company (Source: Assobiotec)

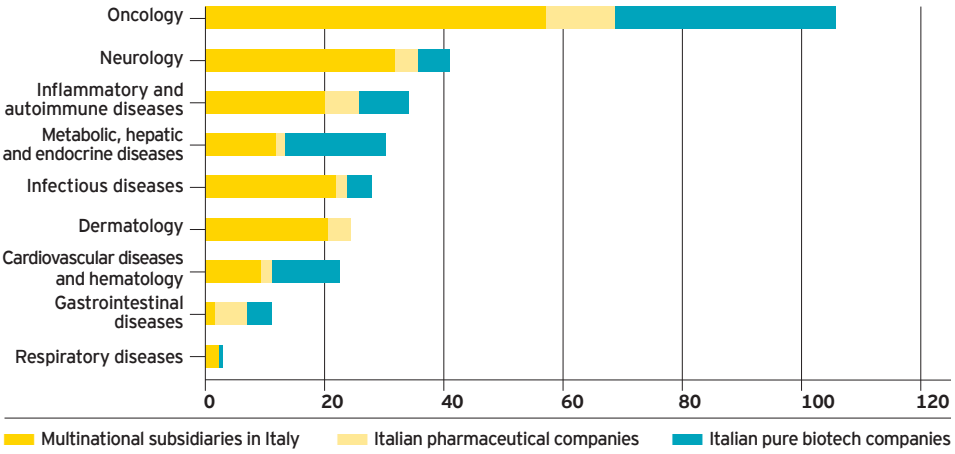


Figure 4e.6

Product analysis by development phase: (A) OECD biotech companies; (B) Italian pure biotech companies
(Source: Assobiotec)

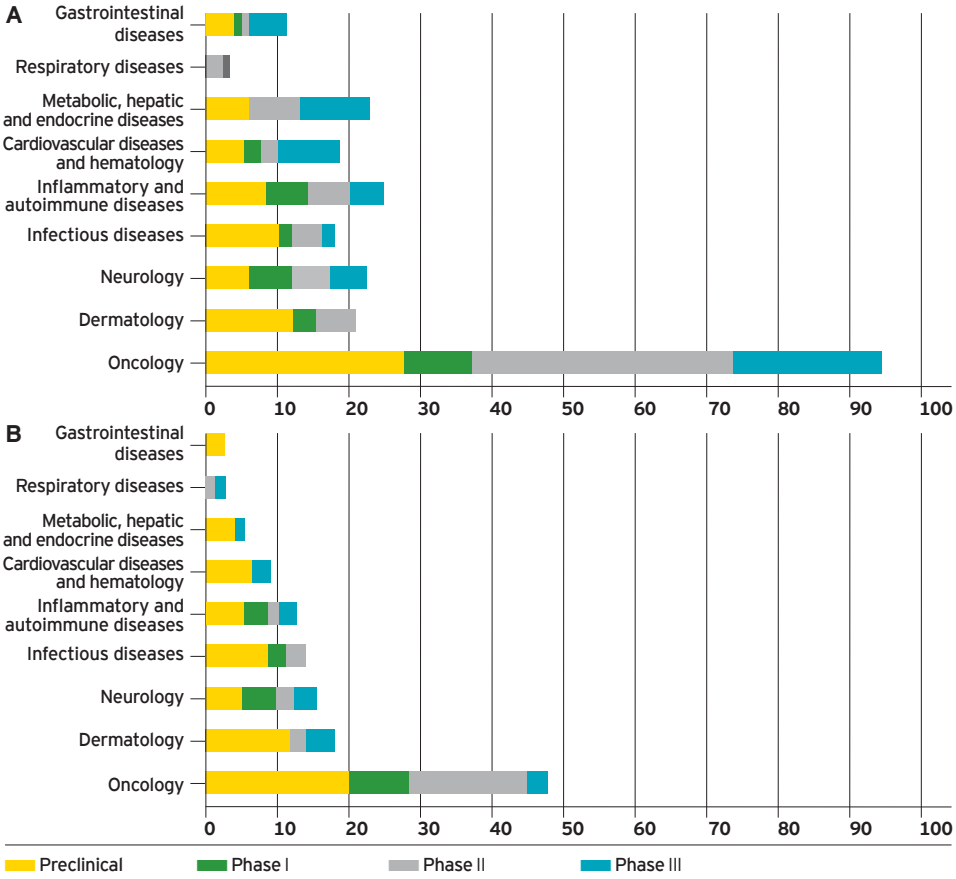


Figure 4e.7

Analysis of product candidates by type
(Source: Assobiotec)

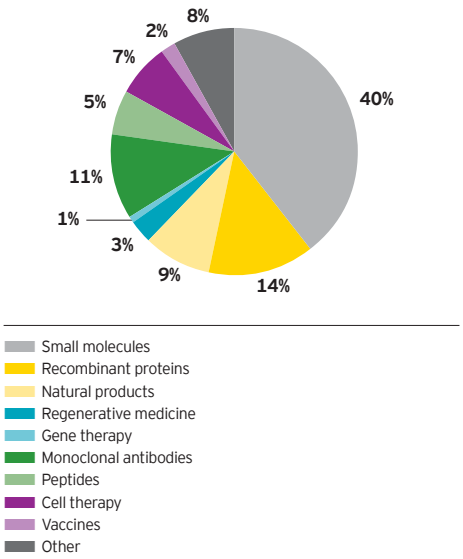
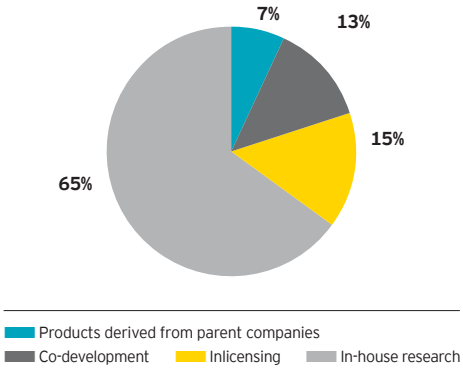


Figure 4e.8

Analysis of product candidates by origin
(Source: Assobiotec)



Among the projects in the discovery phase that, as we have seen, are originated almost exclusively by pure biotech companies, most of the investments are in the neuroscience and infectious diseases areas, where almost 50% of the projects fall. Therefore, it is reasonable to expect an increase in the products being developed in these specific therapeutic areas in the next few years.

Analysis by type of products and innovation

Overall, biologic drugs that include by definition recombinant proteins, monoclonal antibodies, as well as therapeutic agents based on nucleic acid technology and cell therapy, account for almost 40% of the Italian biotech pipeline (Figure 4e.7).

This is characterized by a strong presence of low molecular weight compounds: in fact, 40% of the drugs being developed are small molecules and have applications in oncology (11%), neurology (10%) and infectious diseases (9%).
Also monoclonal antibodies and recombinant proteins accounting for 11% and 14% of the biotechnology drug pipeline, respectively, are mainly used in the oncology area.

It is important to stress that most of the products and projects being currently developed in Italy originate from in-house research: this is true both for pure biotech companies and for the companies acknowledged being biotech according to the wider OECD definition. This further confirms the originality and solidity of Italian research, as already proven by the number and quality of scientific publications by Italian scientists.

The projects deriving from in-licensing and co-development agreements still account for a minor share of the whole pipeline; this encourages us to think that a potential closer cooperation between research and industrial development could be usefully exploited (Figure 4e.8).
The degree of system innovation is also particularly interesting. In fact, more than 75% of the products and projects carried out in Italy are classified as "First in Class", 20% fall under the "Me-too Better" category and less than 4% under the "Me-too" category. Overall, the patent coverage is also high: more than 80% of the projects and products analyzed were granted at least one patent.

Orphan Drug Designation

An increasing number of rare diseases can be treated today thanks to biotech drugs falling under the definition of orphan drugs. This is a specific area of pharmacological research where the Italian companies are particularly involved, thanks also to the contribution of our academic research which boasts the highest number of scientific publications in this area.

For example, the gene therapy protocol for the treatment of the ADA-SCID syndrome – developed in 2010 by the San Raffaele Telethon Institute for Gene Therapy (HSR-TIGET), is currently in Phase III, and GlaxoSmithKline has gained exclusive rights to its development and commercialization. The agreement on this revolutionary therapeutic approach (see the focus on Advanced Therapies) exploits the orphan drug designation received from both FDA and EMA, and is a milestone in the difficult challenge against some rare genetic diseases that up to now had aroused little interest by big pharma companies, thus confirming the Italian leadership in the field of gene therapy.

From the 2010 analysis, 22 biotech companies have obtained at least one orphan drug designation: 12 pure biotech and 10 pharmaceutical companies, which manage an overall portfolio of 33 products, of which 2 designated by the U.S. FDA, 11 by EMA and 20 by both the regulatory bodies (Table 4e.3).

These data show a clearly increasing trend compared to 2009, in terms of number

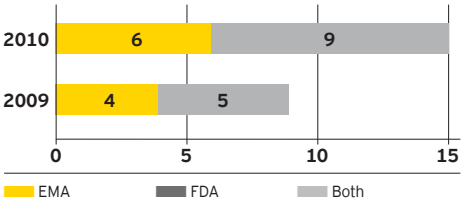
Table 4e.3

Analysis of the orphan drug designations granted (Source: Assobiotec)

		EMA	FDA	Both	Total
Italian-capital companies	Pure biotech companies	6		9	15
	Pharmaceutical companies	4		4	8
Foreign-capital companies		1	2	7	10
Total		11	2	20	33

Figure 4e.9

Italian pure biotech companies: number of the orphan drug designations granted, comparison between 2009 and 2010 (Source: Assobiotec)



of designations (+10%) and number of companies involved (+45%) mainly concerning therapeutic agents for use in oncology (45%), and which are in an advanced phase of clinical development (most of them in Phase II).

The importance of research activities in the Rare Diseases area is further shown by the growing trend in the number of orphan drug designations obtained by pure biotech companies, both by the U.S. and the EU regulatory authorities (Figure 4e.9).

Advanced Therapies

Advanced therapies, which are based on the use of cells and nucleic acids, include cell therapy, gene therapy and tissue engineering (or regenerative medicine), and are on the one hand a great innovation in the concept of drugs and, on the other hand, a new frontier in the treatment of several fatal or invalidating illnesses – some of them falling under the definition of rare diseases – for which today no adequate therapeutic options are available.

There are 22 projects in the AT field currently ongoing in Italy, most of them already in clinical development phase, and 19 of which are carried out by pure biotech companies (Table 4e.4).

MolMed, a medical biotech company focused on the research, development and validation of innovative therapies for the treatment of cancer, which was listed on the Italian Stock Exchange in 2008, certainly deserves to be mentioned worldwide among the pioneers in the field of cell therapy.

Actually, MolMed was the first Italian pure biotech company to achieve Phase III with a cell-therapy product allowing for the transplant of hematopoietic stem cells, by partially compatible donors, in high-risk leukemia. If the results of this clinical trial are positive, TK will be the first Italian biologic product – besides being an orphan drug in the AT field – to be marketed. During 2010, MolMed has also started a second Phase III trial on a recombinant protein able to act in a targeted and selected way on tumor vessels. It is currently being developed in six different indications, of which the most advanced is the treatment of mesothelioma.

Again in 2010, another cell-therapy product has reached Phase III: it is a new protocol of regenerative medicine by means of culture of corneal epithelium stem cells, developed by the academic spin-off Holostem, founded in 2008 by joining the scientific expertise of two scientists of the Centre for Regenerative Medicine of the University of Modena and Reggio Emilia and the industrial capacity of Chiesi Farmaceutici S.p.A., a well established research-based Italian pharmaceutical company.

All the above shows that, after consolidating therapeutic approaches addressed to huge patient populations, modern medicine is increasingly oriented towards the development of several patient-specific models, or to models addressed to special patient sub-groups. This is an important change of perspective for the development of which not only progress in the advanced therapy field, but also in the diagnostics research for selective biomarkers, will be crucial.

Table 4e.4

Analysis of advanced therapy products by type and development phase, OECD biotech companies (Source: Assobiotec)

	Cell therapy	Gene therapy	Regenerative medicine	Total
Discovery			2	2
Preclinical	7		4	11
Phase I	1	1	1	3
Phase II	4			4
Phase III	2			2
Total	14	1	7	22

Green Biotech

In the green biotech field, Italy can boast unique and competitive conditions due to the wide variety of microclimates and level of biodiversity. This results in a multiplicity of research strands ranging from the genetic improvement of specific plant varieties, to the control of origin and quality of food and to the extraction of bioactive substances with limited natural availability. Not to mention that multinational companies are already focusing on the development of a huge variety of market niches as potential alternatives to large cultivations.

Green biotech refers to the use of modern biotech methods in the production of plants and vegetable cultures with applications in the food, chemical and material sector; molecular pharming (production of drugs using plants); testing to reveal the presence of ingredients and contaminants in food.

This year, there are 94 companies operating in the green biotech field; therefore a strong increase in numbers, as compared to the 55 companies recorded in the 2010 report, occurred. In particular, 3 out of 39 newly-censused companies operating within the green biotech field have developed over the last two years, 20 companies were already active in this field, but were identified thanks to a more in-depth analysis of the biotech market, and 18 companies had already been included in the sample of the 2010 Report, but expanded their activity to the green biotech field only last year. Meanwhile, 2 companies shown in the 2010 Report as operating in the green biotech field have re-positioned

Figure 5.1

Green biotech companies: analysis by type (Source: Ernst & Young)

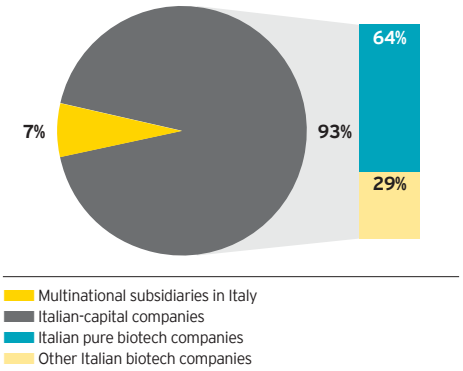
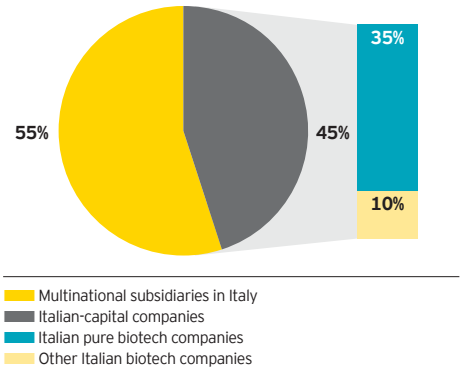


Figure 5.2

Green biotech companies: analysis of the 2009 turnover by type (Source: Ernst & Young)



in the red biotech field during the year, thus terminating their activities in the green sector. Therefore, numerically, the green biotech group ranks second after the red biotech cluster, and includes 52 dedicated green biotech companies plus 42 multi-core companies also operating in other biotech application fields. As we already highlighted in the general chapter on the biotech system in Italy, the number of multi-core companies is rapidly increasing, accounting for 45% of total green companies as compared to 24% in the 2010 Report.

Most of the companies are Italian pure biotech (64%) (Figure 5.1), However, it must be noted that multinationals, though limited in number (7%), do provide more than half (55%) of the green biotech turnover (Figure 5.2). Moreover, when we take into consideration the turnover yielded by dedicated green companies alone, the impact is still important and accounts for approximately 49%. Of the 7 multinational companies included in the sample, 4 have developed green biotech activities originating from the pharmaceutical or red biotech fields: this indicates that companies are very much interested in therapeutic products of animal and vegetable origin as well as nutraceutics.

In terms of size, the green segment is characterized by the predominance of micro and small companies which account for almost 80% of the sample (these data are substantially aligned with those reported in the 2010 Report) as compared to 91% for white biotech, and to 71% for red biotech (Figure 5.3).

With regard to the origin, most of the green companies stem from start-ups (32%), 28% from academic spin-offs, 9% from industrial spin-offs or spin-outs, while 8% are multinationals with subsidiaries in Italy (Figure 5.4). Similarly to what happens in the white biotech segment, the percentage of academic spin-offs is particularly high: even if we consider the detail of the dedicated pure green companies alone, 32% of the companies stem from academic spin-offs. Not surprisingly, 2 out of 3 companies that have developed over the last two years originate from academic spin-offs.

Another crucial element in the development of new green companies is the presence of science parks and incubators. Indeed, the 3 new companies set up during the last two years are all located near one of these facilities. The same analysis by location, when applied to the whole green field, shows that the number of companies located near science parks and incubators has increased from 42% to 48% (Figure 5.5).

Figure 5.3

Green biotech companies: analysis by size
(Source: Ernst & Young)

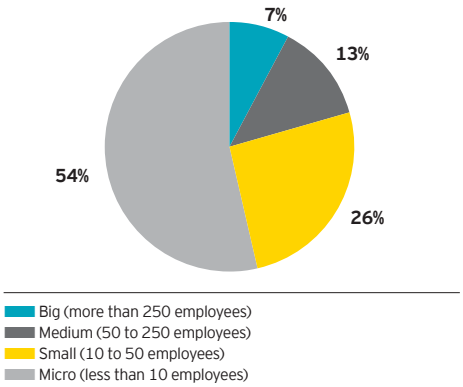


Figure 5.4

Green biotech companies: analysis by origin
(Source: Ernst & Young)

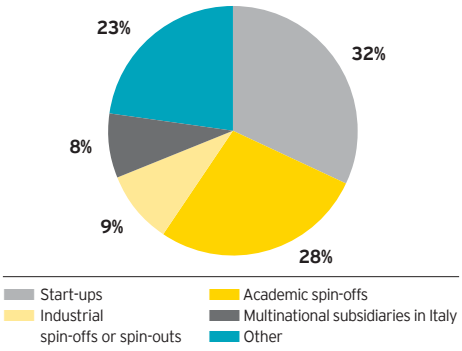
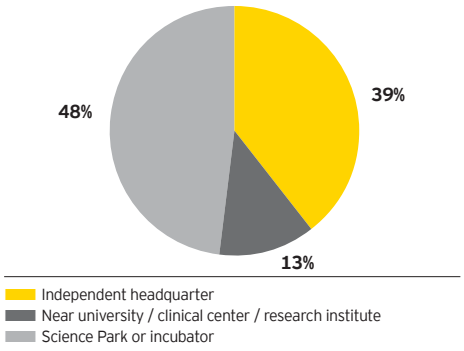


Figure 5.5

Green biotech companies: analysis by location
(Source: Ernst & Young)



The Pivotal Role of PTP in Agro-food Biotechnology

During the last ten years, biotechnology applied to the vegetable sector ("green biotech") has greatly developed in a number of application strands, both on a national and international level. In Italy, green biotechnology has been successfully applied to the agro-food sector, in support of the excellent food production chain of the most typical "Made in Italy" products, also to prevent potential adulterations deriving from the use and introduction of ingredients of foreign origin.

It should be borne in mind that the aggregate commercial balance of "Made in Italy" food and agriculture in 2009 was estimated to be € 6.7 billion, a significant percentage of the overall "Made in Italy" production (36% of the total).

Today, several companies of the agro-food sector already use innovative techniques both for quality control and R&D activities. For example, molecular diagnostics based on DNA fingerprint techniques, i.e., the use of a genetic fingerprint through which it is possible to associate a DNA molecule to a specific person, is used alongside traditional methods of analysis, thus enhancing their effect in the certification of the origin and typicality of several products. Moreover, the use of molecular biology methods allows for the development of foods with the specific aim of improving health and reducing risk of diseases (functional food), with potentially positive consequences for the consumer's wellbeing.

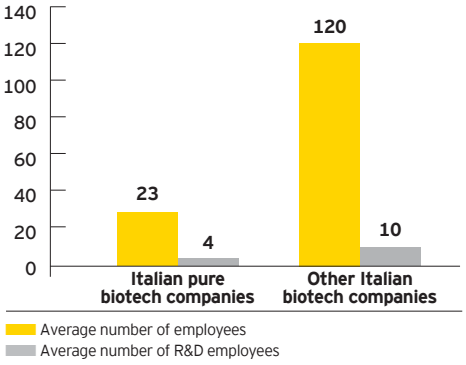
Another very up-to-date application field for green biotechnology is the production of bio-energies. Specific programs of biotech innovation have allowed selecting plants (e.g., maize, rape) that improve the efficiency of bio-fermentation plants for the production of renewable energies.

The Parco Tecnologico Padano (PTP) in Lodi has been operating within this context since 2005; this is a hub of excellence for food biotechnology where all the parties involved (university, research centers, control institutions and companies) have joined forces to foster a sector that strongly calls for innovation in response to the increasing global competition. In particular, the Parco is engaged in developing new biotech approaches to support companies within the agro-food, cosmetic and pharmaceutical sectors so as to encourage production and contribute to maximizing quality control systems. The molecular methods applied to specific production chains including dairy, cereals and tomato for industrial use, ensure the traceability of raw materials and the absence of biological contaminants, i.e., noxious bacteria and fungi.

Specific analytical methods, aiming at certifying Italian typical products, were developed and validated by the Genomics Platform – the main PTP business unit dedicated to the development of innovative solutions – on behalf of the main food companies. An example of this is the project denominated "DNA Provolone

Figure 5.6

Dedicated green biotech companies: average number of total employees and R&D employees (Source: Ernst & Young)



It is estimated that the companies operating within the green biotech field employ almost 10,000 people overall, of whom 820 working on R&D activities. The pure biotech companies dedicated to the green field, as in the white biotech field, account for an important percentage of the sample, with 19% of total employees and 41% of R&D employees. However, in the case of green biotech there is a marked difference in the average number of employees of dedicated companies: the other biotech companies employ on average 120 people, with the subsidiaries of the multinational pharmaceutical companies reaching on average 526 people, while pure biotech companies have about 23 employees (Figure 5.6).
If we consider the green biotech field turnover, the estimate for 2009 is € 144 million. Similarly to white biotech companies, the growth in turnover, as compared to the 2010 Report, is influenced by the high number of companies that are already consolidated in the biotech field and that have expanded in the green field over the last year. Again with regard to 2009, it is estimated that the companies operating in the green biotech field have invested approximately € 139

DOP" (Protected Designation of Origin), carried out in close cooperation with the Consorzio Tutela del Provolone Valpadana (Consortium for the Protection of Provolone Valpadana); this project has finalized a molecular biology-based method for the identification and certification of the origin of Provolone dolce DOP, independently from the information reported on the tag label, thus revealing any food alterations which could damage this and other 'Made in Italy' production chains.

The Park has also contributed decisively to the DNA characterization of cultivated plants and animal breeds of zootechnical importance. The decoding of the genome of economically interesting vegetable species, including grapevines, apple trees, peach trees and durum wheat, has allowed to identify the genetic bases of their productivity and resistance to diseases. Thanks to this genetic information, it is possible today to develop strategies aimed at improving 'Made in Italy' agriculture and food productions by contributing to their competitiveness in the relevant sectors.

Meanwhile, PTP researchers have focused specifically on R&D activities to support the national rice production chain. With 224,000 cultivated hectares – mainly located in Lombardy, Piedmont and Emilia-Romagna – Italy is the first rice producer in Europe, with 1.4 million tons, accounting for 53% of the total European production.

The Park's Rice Genomics Department, within the frame of the European project EURIGEN (financially supported by the Agriculture Directorate-General of the European Commission), has developed a unique method for molecular traceability that allows not only to identify and protect the entire production chain of "Italian rice", but also the origin of raw materials in highly-processed products (i.e., pre-packaged risotto), with particular reference to excellent rice varieties including Carnaroli, Vialone Nano and Arborio.

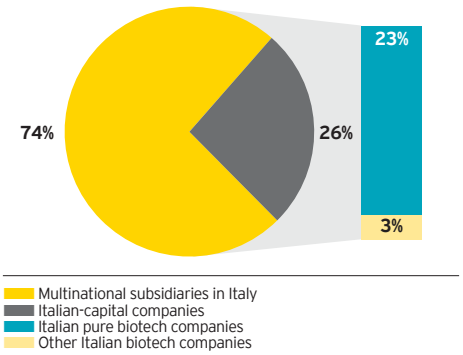
Another vital role played by the Park is related to the transfer of technological know-how generated within its research center CeRSA (Center for Research and Study in the agro-food field) to SMEs, large companies as well as to other public and private research bodies. This role of link between research and production allows identifying solutions for enhancing the activities of the R&D and Quality Assurance departments of several Italian companies operating in the agriculture, food and zootechnical fields.

Scientists at PTP have also focused on the development of innovative approaches aimed at the preservation of biodiversity of several species of zootechnical importance (e.g., cattle, swine, and buffalo). The objectives of this research area, mainly financed by the European Union, are the protection and exploit of native breeds, in order to make them increasingly competitive in terms of health and production within the framework of a global market.

million overall in R&D activities – of which 24% in outsourced R&D. Most of the investments (73%) were made by multinational companies with subsidiaries in Italy, and in particular by the four multinationals that have also expanded their biotech activities into the green sector (Figure 5.7). Indeed, the value of investments in R&D includes those allocated to green biotech together with those allocated to other application fields. Green dedicated pure biotech companies, with a turnover of € 32 million – versus € 23 million of the 2010 Report - have invested about € 11 million in R&D, i.e., 34% of the turnover.

Figure 5.7

Green biotech companies: analysis of R&D investments by type (Source: Ernst & Young)



The Edmund Mach Foundation and the Istituto Agrario di San Michele all'Adige

The Istituto Agrario di San Michele all'Adige (IASMA), founded according to the German model whereby teaching and research join together, was the second agrarian school – the first one being Klosterneunburg (Wien) – within the former Austro-Hungarian Empire; today, it is the first and only model in Italy where research, training, consultancy and service activities in the field of agriculture, environment and agro-food are carried out at the same time.
The Edmund Mach Foundation, which in 2008 inherited the precious historical heritage of the Institute, has kept the name of the ancient institution alive and continues to carry out its activities. The Institute was founded on 12 January 1874, when the regional Tyrolean Diet at Innsbruck voted to open an agrarian school combined with an experiment station at San Michele, on the lands owned by the former Augustinian monastery, for the revival of agriculture in Tyrol.
Its activity was started in the fall of that year, according to the approach of its first Director Edmund Mach, who came from the experiment station at Klosterneuburg.
Over the years, IASMA has reached several important goals on an international level both in the research and training fields, but its vocation – since the beginning – was to carry out studies in the grapevine-enological field. The institute is governed by a President and a Board of Directors and comprises the following centers: education and training, research and innovation, consultancy (technology transfer), administrative services and farm.

The Research and Innovation Center
The Research and Innovation Center (CR&I) promotes studies in the fields of agriculture, food and environment, with the main purpose of producing knowledge and contributing to widespread social and economic growth, as well as improving the quality of life. Using the most advanced scientific technologies and approaches, CR&I operates primarily within the field of genomics of grapevine and fruit trees, transformation and valorization of food systems and the study of the functionality of natural systems. The activities of the center are organized in four departments: Genomics and crop biology, Food quality and nutrition, Sustainable agro-ecosystems and bioresources, Biodiversity and molecular ecology. The departments use a Transversal Platform in Computational Biology supporting the application of the most advanced techniques within the fields of bioinformatics, biochemistry and computational genomics, nutrigenomics and systems biology. In particular, using the information generated by the genome sequencing of cultivated plants (including grapevine, apple tree and small fruits), the CR&I Department of Genomics and biology of fruit trees provides concrete support to the genetic improvement of species and to the creation of new varieties of commercial interest by means of studies ranging from functional genomics to applied molecular genetics. Particularly important is the study of the interactions between plants and pathogens, in order to minimize the dependence on the use of chemical compounds in the fight against pests in agriculture.

Genetic improvement
Within the study activities aimed at the valorization of agriculture resources, the Research and Innovation Center has been focusing in particular on research concerning the genetic improvement of fruit trees. Being aware that some food, including grapes, apples, strawberries and small fruits has a nutraceutic and healthy potential, the Center has supported scientific research programs, enrolment and investment in the application of the most advanced techniques in the field of genomics, bioinformatics, computational models, biochemistry and systems biology. The results obtained on an international level with the genome sequencing of grapevine in 2007, or the completion of DNA sequencing of apple trees and strawberries announced in Nature Genetics in 2010, are milestones in the activities aimed at improving fruit trees from a qualitative point of view. Thanks to these results, the selection of the best plants in terms of specific and most interesting features - including appearance, organoleptic qualities, shelf-life, nutraceutic components, resistance to specific diseases as well as adaptability to specific environmental and cultural conditions - will be more rapid and precise. This wealth of knowledge and expertise is provided by the Center to efficiently meet the requirements of quality, healthiness and sustainability of agro-food products.

Structural and functional genomics, the technological platforms
The expertise developed in the activities of sequencing and study of the genomes of grapevines, apple trees and strawberries is today the basis for further in-depth studies on the evolution of vegetable genomes (angiosperms), as well as studies of epigenetics and control of gene expression. The numerous genes identified are currently reported manually in annotations by the center and its international links and, on some of them, further information on the functions provided for by Gene Ontology are collected. Studies on linkage disequilibrium are ongoing in order to verify any possible applications of association mapping or whole genome scanning approaches.
The Institute has dealt with the genetic transformation of grapevines for 20 years and has recently acquired expertise in the transformation of apple trees and strawberries. These expertise is currently used for a functional validation of some genes which are potentially involved

in the genetic resistance of grapevines and apple trees, in qualitative traits (color and fragrance) in grapevines, agronomic and qualitative traits (posture and fruit development) in apple trees. Some traits which are candidate in the post-transcriptional regulation (miRNA) are particularly interesting for biotechnological applications. Last but not least, the Institute is engaged in projects for the sequencing of other important fruit plants, including pear trees, raspberries and olive trees.

The international PhD program

One of the major recent initiatives promoted by CR&I is the International PhD program in Fruit Plants Genomics and Molecular Physiology (GMPF) which offers high-level study and research programs within the scope of national and international scientific collaboration among PhD students, and more in general, among participating institutions. GMPF is the first highly-qualified program in Italy for the training of scientists and researchers capable of developing, in Europe, more sustainable and competitive fruit farming. This is a state-of-the art organization with which other 14 institutions all over the world cooperate: from the University of Trento to the Washington State University (USA), from the Plant and Food Research Institute of Palmerston North (New Zealand) to the University of Bologna, from the Plant Research International of Wageningen (the Netherlands) to the University of Stellenbosch (South Africa), to the Hebrew University of Jerusalem (Israel). At the end of their study and research path, GMPF students will boast a curriculum of excellence in the field of genomics, informatics, functional genomics, proteomics and metabolomics, genetics, genetic improvement and molecular physiology of fruit tree species.
These are the fields where CR&I provides added value thanks to a decennial experience with worldwide recognition that has been developed over time with an eye on the expectations of consumers and production.

From Plant Cell Cultures some Precious Biologically-active Substances with Benefits for the Humans and the Environment

The plant world, with its constant supply of precious biologically active substances, has always been an unlimited source of medicinal agents for humans. Today, a number of active principles and products of vegetable origin are used not only in the pharmaceutical sector, but also in the nutritional field.

However, a major issue is currently represented by the standards of quality, safety, purity and availability of vegetable extracts, since they are considered a strong restriction to their wider application, especially in the nutritional fields.
Indeed, notwithstanding the efforts of most companies, due to the nature of the traditional production process itself, substances of vegetable origin cannot be declared immune from contamination and alterations of any kind. The presence of polluting agents and microorganisms in the environment, the inevitable exposure to environmental variables capable of influencing the quantity of the plant's active principle of interest, or its presence in rare and protected plants or in plants located in areas difficult to access, are some of the variables that may compromise quality and safety standards of botanicals and therefore, paradoxically, their use in the human health field.

Some very interesting opportunities arise from the use of plant cell culture technology: this method has been known for a long time, even if until now its application has been restricted to the academic environment, due to the high investments necessary for the industrial development of the process. This technique enables production of the same bioactive substances present in the plants and is often the only alternative source available, without any quantitative restrictions, for the production of those active principles that are difficult to find in nature or difficult to produce by chemical synthesis. These features have also been highlighted by FAO (Food and Agriculture Organization) who, in a document issued in 1994, already recommended plant cell culture as an alternative biotechnology process to be used in the production of substances and metabolites.
IRB (Istituto di Ricerche Biotecnologiche), an Italian company with headquarters in Altavilla Vicentina (VI), has developed this method on an industrial scale and has obtained the first and unique vegetable extracts authorized by the European Union as nutritional ingredients.
According to the provision of Article 5 of the Novel Food Regulation (258/97/CE), the Commission for Dietetics and Nutrition of the Ministry of Health has recognized the substantial equivalence of the extracts from plant cell cultures obtained by means of biotechnology compared with the traditional extracts, by confirming the validity of the results of phytochemical analyses based on a metabolomic approach of comparison, presented by IRB.

TEOSIDE® is an exclusive extract, covered by international patent, derived from cell cultures of *Ajuga reptans* and titrated in teupolioside: it has shown an antioxidant activity five times higher than that of resveratrol, as well as highly-significant anti-inflammatory properties, proving to be effective in some pathologic conditions, such as irritable bowel disease. Another extract, ECHIGENA PluS® originating from cell cultures of *Echinacea angustifolia*, titrated at 4% in echinacoside, is characterized by a defined and standardized composition profile, and can ensure a reproducible batch-to-batch efficacy. Both products are obtained by means of the exclusive HTN (High Tech Nature) technology, the IRB technological platform that does not modify genomes and is able to produce plant active principles from cell cultures.

Through this green biotechnology, it is possible to come closer to the profile of the ideal plant active principle, by ensuring a very high level of:

- Standardization, meaning reproducibility of composition and biological effect
- Safety, meaning absence of environmental contaminants (including chemical residues, heavy metals and aflatoxins)
- Availability, being unrestricted and unconditioned by environmental and seasonal factors
- Eco-sustainability

The HTN technology ensures full respect of biodiversity and protection of the flora of rare and protected plant species. Moreover, land occupation and water use necessary for the production of plant extracts with the HTN method are at least three times lower compared to the traditional method. Last but not least, drastic reduction in the use of solvents and CO_2, as well as the lack of use of agro-drugs, is a further aspect to be considered.

White Biotech

Companies involved in industrial biotechnology are already strongly present in several market segments, from bioremediation methods for the decontamination of sites and materials polluted by organic compounds to the production of biomass energy or cellulose from vegetable waste of agricultural origin. The wide and straightforward applicability of these technologies allows to obtain returns on investments in a relatively short time, and this arouses the interest in a sector potentially driving the implementation of industrial development models which are increasingly often designed to meet eco-sustainable parameters.

Industrial biotechnology (white biotech) refers to the use of modern biotech methods for the manufacturing and production of chemicals, materials and fuels, including bioremediation technologies applied to the environment.

Of the 41 companies censused in the survey which are involved in industrial biotechnology, 21 are dedicated white biotech companies and 20 are multi-core biotech companies with activities also in other biotech application fields. Compared to the 2010 Report, the number of multi-core companies quadrupled. Such an important increase is related not only to the 5 companies not included in the previous sample (3 multi-core and 2 dedicated white biotech companies) or to the 2 white biotech companies which have become multi-core during last year, but also to the 10 companies which had activities in other biotech fields and today are also operating within the white biotech field. Thus, this data confirms that those companies already operating in other biotech application fields and in particular in the green biotech field (18 out of a total of 21 multi-core companies) are very much interested in this field too.
Of the 15 new white biotech companies, 10 are pure biotech and 5 are other biotech. Therefore, overall this year the sample includes 66% of pure biotech companies versus 54% of the 2010 report, and more than half are multi-core companies (Figure 6.1). The pure biotech companies are those which better show the growth trends of multi-core companies, growing from 5 in 2010 to 14 this year. Pure biotech companies account for almost all the turnover of white biotech companies: the companies not dedicated to biotech develop their activities within the white biotech field more as a support to their core business, than as an additional source of turnover (Figure 6.2).

Figure 6.1

White biotech companies: analysis by type (Source: Ernst & Young)

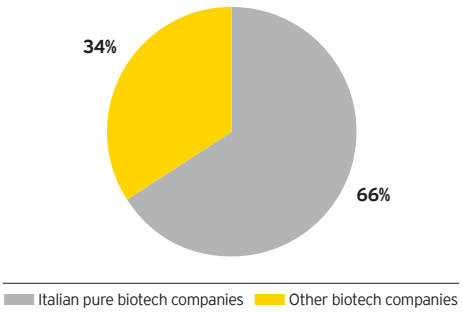
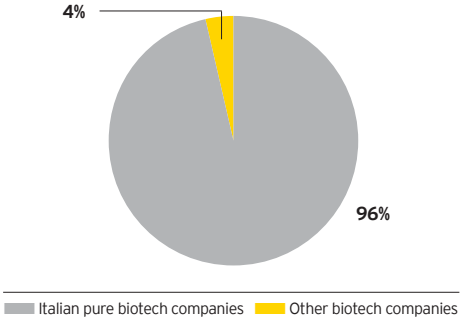


Figure 6.2

White biotech companies: analysis of the 2009 turnover by type (Source: Ernst & Young)



New Biotech Plant for the Production of Polysaccharides

At the heart of the Upper Irpinia region, in a site called Morra de Sanctis, Altergon Italia - an associated company of the Swiss group Altergon – has implemented an extremely modern biotech plant for the production of high-molecular-weight polysaccharides for injection, which have become increasingly important as raw materials for the global pharmaceutical industry. The plant also features a research and development facility and has been created with a contribution by the Second University of Naples and BioTekNet, the Centro Regionale di Competenza in Biotecnologie Industriali (Regional Competence Center for Industrial Biotechnology).

The plant is located within the production site founded by Altergon Italia in 2003, in an area which represents a true center of expertise on an international level in the field of industrialization of production processes by API fermentation (Active Pharmaceutical Ingredients).

The new production process replaces the ones which were based on traditional techniques of extraction from animal matrices. These techniques imply a series of restrictions for the production cycle, including: low extraction yields, issues of raw material supply (of animal origin), risk of contamination by animal viruses, impossibility to intervene on the features of the final product, including the molecular weight which is a particularly important parameter in several applications. More importantly, traditional processes involved significant environmental issues: use of endangered animal species as a source for raw materials (e.g., sharks and cetaceans), high environmental impact of complex product separation and purification procedures, with the wide use solvents which are dangerous for both the environment and human health, but that are today necessary to minimize the risk of contamination of raw materials of animal origin.
Conversely, the biotech process implemented makes use of strains of microorganisms specifically engineered in order to produce, in the appropriate conditions, the molecules of industrial interest and also uses relatively low-cost downstream techniques with a low environmental impact, thus solving several of the above-mentioned production and environmental issues.

The economic advantages of this new process are such that the Swiss owners decided to invest more than 40 million Euros in the production site of Morra de Sanctis in order to supply the entire market worldwide.
Equipped with modern, efficient, highly-automated plants, certified according to the standards of Good Manufacturing Practice required by the international laws, Altergon Italia is looking forward to receiving the authorization for the production of API via GMP biotech fermentation.

With regard to size, the white biotech scenario is much segmented: as much as 61% of the companies employ less than 10 people, and only 9% of them employ more than 50 people (Figure 6.3).
In Italy there are no large white biotech companies (more than 250 employees): although they deal with products and technology for industrial use, the big companies of the biotech field prefer to gather the required expertise through outsourcing.

Most of the companies stem from start-ups (47%), 26% from academic spin-offs and 8% from industrial spin-offs or spin-outs (Figure 6.4). The sample also includes a multinational subsidiary in Italy operating in the white biotech field.
It is of note that compared to the 2010 Report, the concentration of companies originating from academic spin-offs has more than doubled.
As many as 3 out of the 5 companies not included in the previous Report and, more generally, 7 of the 15 new white biotech companies, originate from academic spin-offs: this demonstrates that the academic world is increasingly interested in white biotech.

Moreover, the analysis of company locations leads to the same conclusion: the share of companies with headquarters near universities, clinical centers or research institutes has increased by 6.5% (Figure 6.5). In terms of regions, almost half of the companies are located in Lombardy (22%) and Piedmont (24%).

It is estimated that the companies operating in the white biotech field employ overall 873 people, of whom 290 dedicated to R&D activities. The pure biotech companies dedicated to white biotech are an important part of the sample, accounting for 38% of total employees and 40% of R&D employees; this is important because these companies are operating in a perspective which is not influenced by other application fields (within or not within biotech).

When focusing on dedicated white biotech companies (both pure and non-pure), we see that other biotech companies employ

Figure 6.3

White biotech companies: analysis by size
(Source: Ernst & Young)

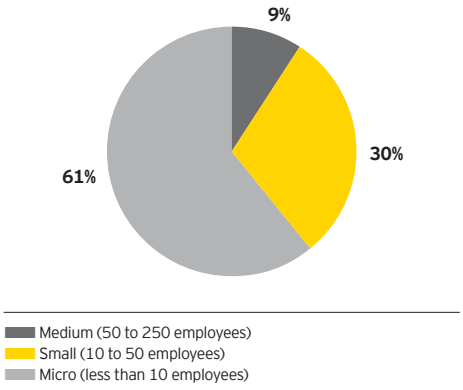


Figure 6.4

White biotech companies: analysis by origin
(Source: Ernst & Young)

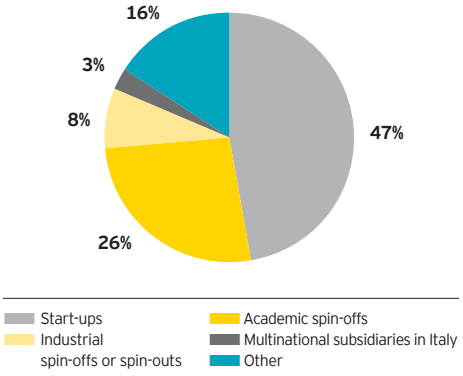
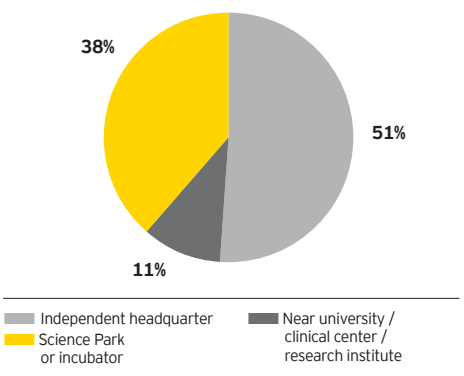


Figure 6.5

White biotech companies: analysis by location
(Source: Ernst & Young)



Environmentally-sustainable Bioplastics

The search for alternative options to the use of traditional plastic materials – every year each single person uses and discards more than 50 kilos of plastic – is an important objective for biotech research; this effort is supported by the increasing attention paid by citizens to environmental sustainability principles and, finally, by an Italian law that has recently implemented the European Directive 94/62 concerning packaging materials and waste.
Despite the progress accomplished in the development of several types of natural polymers capable of technically replacing synthetic products, the production costs of bioplastics for several common uses are still prohibitive. However, the new frontier of research will move more and more from the world of oil companies to that of biotech and agriculture, aiming at having plants capable of producing the biodegradable plastics we need directly.
Therefore, the interest and role of bioplastics from bacteria is crucial, as illustrated in a book edited by some of the major worldwide experts in this field[1]. This is not only interesting from a scientific and technological point of view, or related to our quality of life, but also in an economic and financial perspective since, according to the European Bioplastics Association, the potential biodegradable plastic market is estimated to be 4 million tons in Europe alone, accounting for 10% of the consumption of plastic materials over the entire continent.
It is all based on the idea of exploiting the metabolic attitude of bacteria to use different carbon sources, among which those available in several waste materials: an important opportunity to use waste and surplus industrial and alimentary production, instead of paying for their disposal.
Within this context, the Parco Scientifico e Tecnologico della Sicilia (PSTS) decided to invest together with the University of Catania in putting together expertise, technology and patents concerning the use of *Pseudomonades* having several attitudes, including the production of polyhydroxyalkanoates (PHA), a specific family of polymers of vegetable origin, and the synthesis of molecules partially useful in the agricultural, pharmaceutical and industrial fields, such as biosurfactants, exopolysaccharides, bioactive lipodepsipeptides (cormicin and corpeptin), siderophores and others. In fact, *Pseudomonades* are common Gram-negative bacteria, extremely versatile from a metabolic, physiologic and genetic point of view, since they are able to metabolize more than 100 different compounds as carbon and energy sources.
The bioconversion processes implemented by using *Pseudomonas* strains belonging to the PSTS collection convert triacylglycerol and fat acids present in sub-products of industrial origin and in agriculture wastes for the synthesis of medium-chain-length PHA (PHA-mcl); these are elastomers with properties different from those of the already known polyhydroxybutirate (PHB or PHA-scl), characterized by short six-carbon-atom chains. Following the success of a patent developed at the Company's laboratories concerning a microbial fermentation process of exhausted alimentary oils for the production of PHA-mcl, PSTS researchers have produced specific protocols for the production of other biopolymers, through the conversion of raw glycerol and waste of the industrial production of biodiesel. Thanks to the chemical and physical characteristics of these new polymers, also related to the presence of 16-carbon-atom lateral chains and to their "filmability", they are candidates for several applications, from the coating for composting humid waste, or containers for agricultural use, to the production of micro/nanospheres for the controlled-release of phytodrugs, biostimulants and phytoregulators for plants. All this provides clear benefits for the environment in terms of lower impact of the products obtained and of disposal of production wastes, which would otherwise be an economic burden for producers and consumers.
The Parco Scientifico e Tecnologico della Sicilia (PSTS) is a joint-stock consortium company, mainly owned by Regione Siciliana. The park has developed a complex network of relationships between the universities of Sicily, research centers and companies sharing the mission to increase their region's competitiveness through research, innovation and technological transfer activities as well as the dissemination of the culture of quality and specialist education.

1. Plastic from Bacteria: Natural Functions and Applications. Editor Guo-Qiang Chen Series editor Alexander Steinbuchel. 2010 Springer

Solid-state Fermentation Technology for the Production of Fungal Enzymes for the Treatment of Lignocellulosic Biomass

Fungi are saprophyte organisms with an extraordinary diversity and a huge potential for application in the field of industrial biotech. In fact, the enzymes produced by many fungi are able to digest the polymers of lignocellulosic biomass cell walls, leaving the cellulose fibers unchanged. This is the rationale for the implementation of a technological platform based on the use and development of biodegradation enzyme activities naturally produced by mycelia and microorganisms which use materials from residues originating from agricultural or specialized cultures, for the production of cellulose fibers, aimed at providing a strong contribution to environmental issues such as deforestation, industrial pollution, and disposal of biomass wastes in agriculture.

The project developed by Metapontum Agrobios s.r.l. (a company set up by the Basilicata Region and Agenzia Lucana per lo Sviluppo e l'Innovazione in Agricoltura (A.L.S.I.A.) and which has been engaged for about 15 years in the R&D field and innovation transfer in the agro-food system, especially concerning biotech applications) and carried out in cooperation with the Università della Tuscia of Viterbo and the Università Federico II of Naples, is based on a highly-innovative process for the pilot production of fungal enzymes, by means of a bioreactor allowing for the Solid State Fermentation (SSF) of fungi by simulating their natural growth conditions.

The technique is based on the production of a liquid enzyme mixture under controlled fermentation conditions, such as those ensured by the SSF technology; the mixture is obtained through the colonization of lignocellulosic agricultural waste by the *Lentinus edodes* fungus, an organism that downgrades lignin while leaving cellulose fibers almost unchanged.
The enzyme mix thus obtained can be used in the industrial field in several ways, for treating the biopulping of lignocellulosic biomass, and in particular:

- in paper manufacturing, in order to obtain cellulose fibers from lignocellulosic residues of agriculture origin (wheat, rise and corn straw) and the use of this waste with a consequently positive impact on the environment. The treatment of enzymes greatly reduces both energy costs (30-45%), and the use of polluting agents. In some cases, for example in processing kenaf (*Hibiscus cannabinus*) - a plant widely used as raw material for the production of cellulose mixtures thanks to the characteristics of its trunk - it is possible to completely eliminate all chemical treatments;
- in the textile fiber sector, for the bio-treatment of dedicated cultures, such as hemp;
- in biomass energy production plants, where the pre-treatment of vegetable biomass, by downgrading lignin, allows to increase the yields of the fermentation process of cellulose conversion;
- in the environmental sector, for the decontamination of sites polluted by organic compounds, and the reduction of the organic pollutant burden from agro-industrial effluents.

The above-described process, based on the use of a pilot continuous plant with a SSF bioreactor 8 m^3 in size, includes the following steps:

1. preparation of dry substrate: the straw is fermented and dusts, insects, solid foreign objects are removed;
2. sterilization: the substrate is sterilized using a rapid treatment by applying heat and steam in a vibrant spiral metal tube, with high-voltage and low-amperage power passing through. Therefore, a very innovative technology enabling a reduction of time and energy costs as compared to the traditional self-cleaning process;
3. production of the fungal inoculums in an immersion bioreactor;
4. SSF fermentation: a horizontal reactor is used where the inoculum is added to the sterile substrate, and the solid state fermentation is started with careful monitoring of the environmental parameters which allow the fungal iphae to colonize the biomass;
5. at the end of fermentation, the bioreactor is emptied and the biomass is compressed in order to extract a mix containing the following enzymes: laccase, tyrosinase, peroxyidase, endo-1,4-glucanasi, cellobiohydrolase. Finally, the quality control of enzyme activities is carried out.

on average a higher number of people even if the number of R&D employees is proportionally much lower (Figure 6.6).

With regard to the turnover of the entire white biotech field, it is estimated to be € 103 million in 2009, with a steep increase compared to the 2010 Report; this increase is due to the contribution of the companies which have expanded their activities to the white biotech field during the year. Again in 2009, it is estimated that about € 24 million were invested in R&D, of which about 8% in outsourced R&D. This investment has doubled when compared to the previous year and accounts for 23% of the total turnover.

In particular, pure biotech companies invested € 16 million in R&D, that is 78% of total investments in this field (Figure 6.7); of these, € 9 million were invested by dedicated pure biotech companies (thus accounting for 38% of total investments of the white biotech field), and € 7 million by multi-core companies.

Figure 6.6

Dedicated white biotech companies: average number of total employees and R&D employees (Source: Ernst & Young)

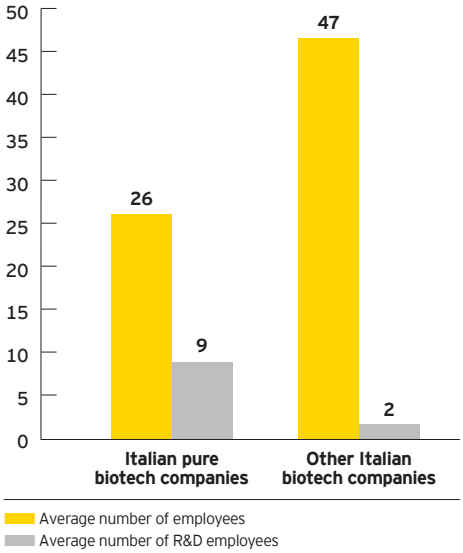
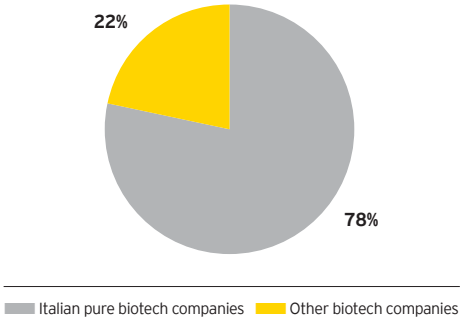


Figure 6.7

White biotech companies: analysis of R&D investments by type (Source: Ernst & Young)



Nanobiotech Companies

Resulting from the application of nanotechnology to biology and biochemistry, nanobiotechnology is one of the most promising fields of scientific research. Although it is often considered at an embryonic stage, the many investigational routes of nanobiotechnology will definitely have, in the medium term, significant applications in the fields of regenerative medicine and diagnostics, as well as in the development of green and white biotech.

Nanobiotechnology is the application of nanotechnology to biology and biochemistry and is one of the most promising fields of scientific research. Medical scientists have hypothesized and studied a number of nanotechnology applications to the diagnosis and treatment of several diseases, for the implementation of controlled release drugs and in the field of biomaterials, with a number of effects on life sciences and human connective tissue engineering, as well as to the custom building of vital organs in the field of regenerative medicine. Although most of these research strands are often considered to be at an embryonic stage, it is reasonable to believe that, in the medium term, nanobiotechnology will play a leading role in the development not only of medicine and diagnostics, but also of the green and white biotech fields.

Before analyzing the nanobiotech cluster, it is necessary to recall the distinction between "core nanobio" and "also nanobio" companies, as further detailed in Chapter10. The first definition refers to companies operating in the field of nanobiotechnology in an exclusive and dedicated way, while the second definition refers to companies having at least one research area in this field.

The analysis that was carried out identified 61 companies operating in the nanobiotechnology field, of which 15 fall completely under the definition of core nanobio companies (Figure 7.1).
This highlights an increase in the number of nanobiotechnology companies as compared to the 2010 Report, which identified 53 nanobiotechnology companies, 15 of which

Figure 7.1

Nanobiotech companies: analysis by type (Source: Ernst & Young)

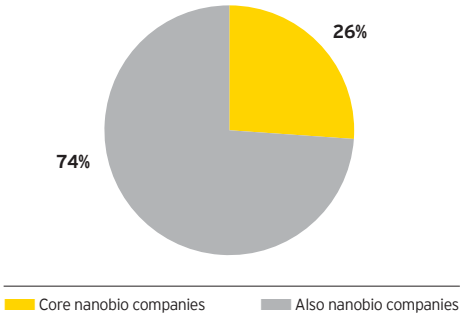


Figure 7.2

Nanobiotech companies: analysis by type, according to EY classification (Source: Ernst & Young)

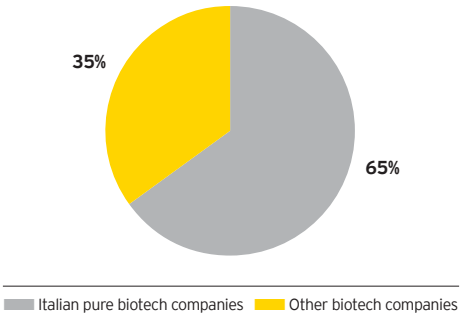


Figure 7.3

Nanobiotech companies: analysis by application field (Source: Ernst & Young)

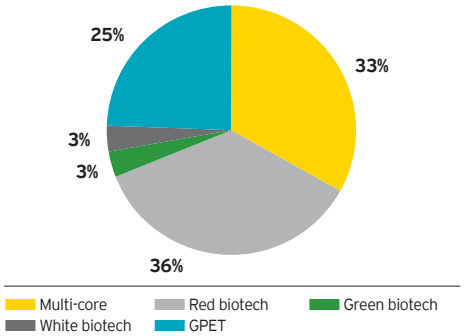
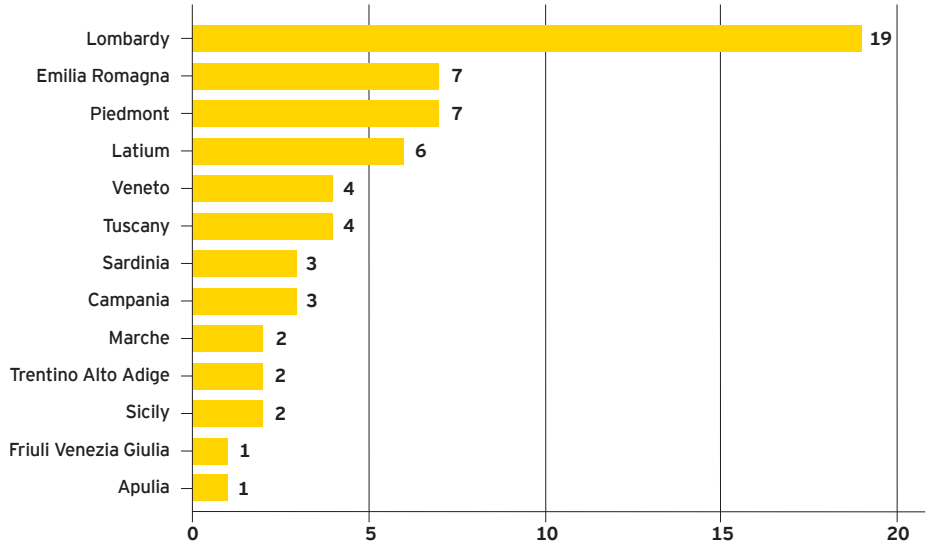


Figure 7.4

Nanobiotech companies: analysis by geographic location (Source: Ernst & Young)



are core nanobio. Since the number of core nanobio companies is stable, the increase in the number of companies is mainly due to the higher number of also nanobio companies. In particular, these 8 new nanobiotecnology companies include one of the 2 new companies that arrived in the biotech field, 3 companies which had not been analyzed in the 2010 Report, and 4 companies already included in the latter that, during the last year of activity, have expanded their business to include research activities in this specific sector.

Interestingly, of the 61 companies identified, almost 65% fall under the Ernst & Young classification of pure biotech companies (Figure 7.2). This shows that pure biotech have a propensity for investing in high-potential fields, even if they are still in a development phase, as well as their long-sightedness in choosing their strategic business.

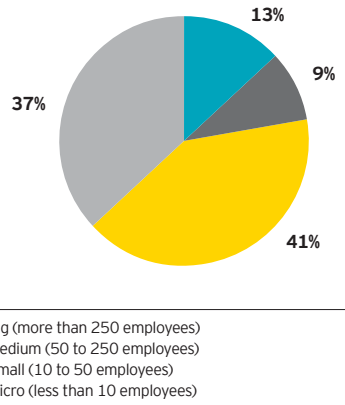
Nanobiotech companies operate in several research fields compared to those addressed by red, green and white biotech companies. In particular, 25% of the companies are active in the field of Genomics, Proteomics and Enabling Technology (GPET), while 36% in the red biotech field. This data confirm the major presence of nanobiotechnology applied to biomedical research (Figure 7.3).

This trend is also proved by the specific analysis of multi-core companies (33%) which, as already shown in Chapter 2, are mainly active in the red biotech field. The analysis by geographic location shows that nanobiotech companies are mostly located in the North of Italy. The region hosting the highest number of companies is Lombardy (31%), followed by Emilia Romagna (12%) and Piedmont (12%) (Figure 7.4).

The analysis of nanobiotech companies by size shows a very interesting feature: 78% of the 61 companies fall under the category of small or micro companies (Figure 7.5). The analysis of core nanobio companies alone shows this feature as even more marked: as many as 74% of

Figure 7.5

Nanobiotech companies: analysis by size
(Source: Ernst & Young)



the companies are micro in size, and the remaining 26% is small.

The economic and financial analysis reveals an increase in the turnover from products and services of pure biotech companies operating in the nanobiotech field.
At the end of 2009, these companies presented total profits equal to € 513 million, accounting for an increase of 5% compared to the turnover shown in the 2010 Report. Moreover, since the number of companies falling under the core nanobio classification has remained unchanged, it is particularly interesting to compare the results, in terms of turnover, of the two years for which data is available.
The 15 companies identified have reported an increase in the turnover produced by biotech products and services of 7%. Total profits went from € 18.4 million in 2008 to € 19.7 million in 2009 (Figure 7.6).

With regard to the number of employees, nanobio companies included, it is difficult to isolate the share concerning exclusively nanobiotechnology, given the intrinsic diversification of this specific sector.
It is more interesting, therefore, to analyze the average number of employees of core nanobio companies that are pure biotech (13 out of 15) and compare it to the number of employees of total pure biotech companies. This comparison, besides confirming the analysis by size, shows that nanobiotech companies have a higher ratio of R&D employees/total employees compared to pure biotech companies in general. In fact, core nanobios employ, on average, one person in R&D every 1.8 employees, versus 2.2 employees in pure biotech companies (Figure 7.7).

Regarding the nanobiotechnology sector our Report also shows an increase in the R&D investments which go from € 98 million in the 2010 Report, to € 109 million in this Report. The most interesting feature highlighted by the analysis of R&D investments is that the amount of investments in outsourced research, in absolute values, has remained stable (€ 19 million), while that of in-house research activities has increased (Figure 7.8).

In conclusion, the analysis of data concerning nanobiotech outlines a positive scenario, since the main variables in this field (turnover and R&D investments) show a marked growing trend.
This trend is confirmed by the experts' forecasts: most of the nanobiotech companies expect a growing, or at least stable, turnover in 2010, and 40% of these companies intend increasing the number of employees.

Figure 7.6

Nanobiotech companies: analysis of the 2009 turnover (Values in million of Euros)
(Source: Ernst & Young)

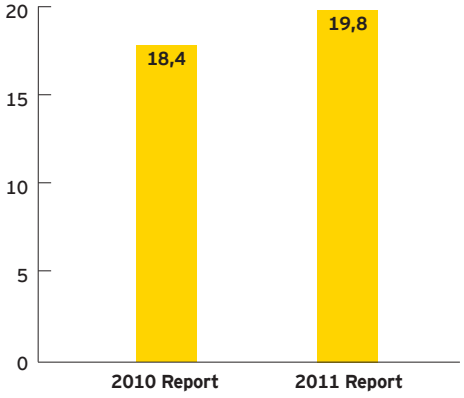


Figure 7.7

Average number of total employees and R&D employees (Source: Ernst & Young)

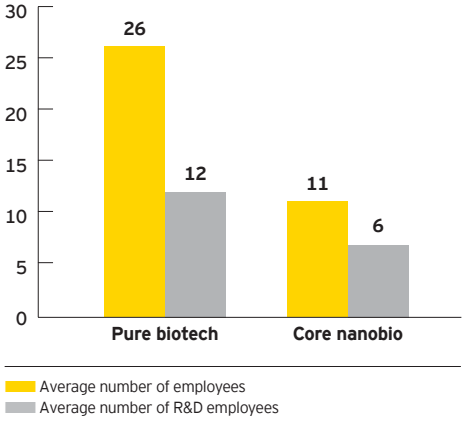
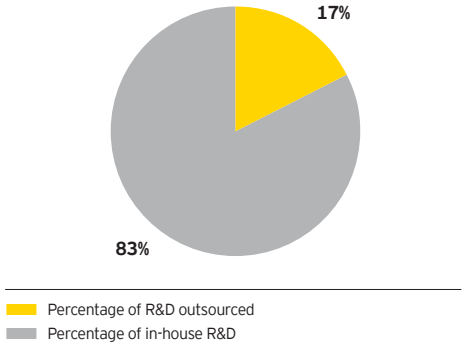
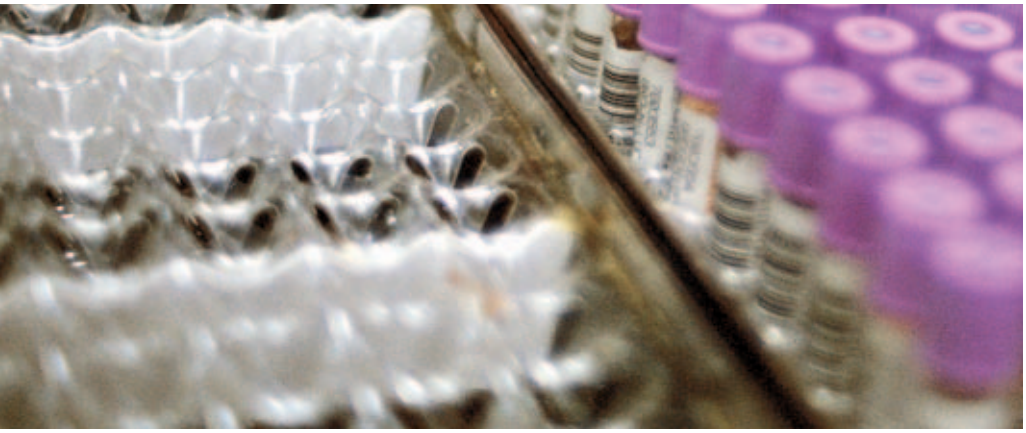


Figure 7.8

Nanobiotech companies: analysis of R&D investments
(Source: Ernst & Young)





Nanomaterials for the Development of New Medical and Diagnostic Devices

The story of Tethis begins in 2004, within the Department of Physics of the University of Milan, where the research team of Paolo Milani, professor of Structure of Matter in that university, worked. It was around the time when Milani and some of his collaborators decided to start up an entrepreneurial activity based on their group's achievements.
The spin-off – also supported by the University – was based on the concept of commercially exploiting the synthesis technology of assembled nanoparticle thin films, which had been patented at the end of '90s by Milani and two of the scientists of his team - Paolo Piseri and Emanuele Barborini – who also were among the founding partners of the company.
After acquiring the industrial rights to this technology, which were owned by CNR-INFM (Istituto Nazionale di Fisica della Materia), Tethis began cooperating in the development of nanomaterial-based gas sensors, within a long-term industrial project.

In 2005, Genextra S.p.A., a holding company operating within the life sciences field, acquired a majority participation in Thetis, with a € 3.5 million investment which allowed starting a number of projects for the development of medical and diagnostic devices based on nanomaterial properties.
This new line was expanded alongside the development of special tools for the synthesis of nanomaterials, a specific field in which Tethis had, meanwhile, fully developed other methods for the gas phase synthesis of nanoparticles and nanodust.

From the interaction of different disciplines and expertise, i.e., biology and nanotechnology, as well as from the deep knowledge of specific technical issues, an ambitious project in the field of in-vitro molecular diagnostics was born.
This project was entirely designed and developed, in all its phases, within the company, starting from the prototype, to the production and commercialization of the product.
A simple and reliable diagnostic device was actually developed in order to turn a consolidated diagnostic test, which is performed manually at high costs today, into an innovative method adapted to modern laboratory needs, which can be performed in any health care structure even in the absence of highly-qualified personnel.
This product, marketed under the brand name microFIND®, is an innovative approach to the diagnosis of important genetic diseases (tumor diseases or genetic syndromes) based on the FISH method (Fluorescence In Situ Hybridization), a cytogenetic technique that allows to detect and localize the presence of specific DNA sequences on chromosomes; the said method had been used in clinical practice for about 30 years, but no investments had been made in terms of innovation and automation since it was introduced in diagnostics.

Ultimately, microFIND® accommodates the value of innovation of a sophisticated technique, i.e., nanotechnology, integrated into a simple-design biomedical device, which meets specific routine diagnostic requirements by offering a solution which adapts to the consolidated working methods of laboratory technicians; this tool has the ambition to implement a revolutionary approach without distorting the current way of performing FISH diagnoses in the clinical routine practice. The final phase of implementation and launch on the market, which took place at the end of 2010, was also supported by the entry into the company's share capital of the investment fund Atlas Ventures, on the occasion of a new financing round for € 3 million overall, in which the original shareholders also participated.

Tethis is currently enlarging its technological and patent portfolio by extending, in particular, the integration between microfluidics and nanomaterial properties to other diagnostic fields. In order to fully exploit all the potential of this approach, the company cooperates – or has cooperated with – a number of institutes and research centers, for two main purposes: firstly, the acquisition of additional know-how for the synthesis of materials or technologies (i.e., University of Milan, ETH Zurich), or new methods for microfluidics (i.e., LATEMAR, Polytechnic University of Turin); secondly, the development of in-depth knowledge of the application needs within diagnostic laboratories (i.e., European Institute of Oncology, IFOM-IEO Campus, Fondazione Centro San Raffaele di Milano, Fondazione IRCCS Policlinico di Milano).

Nanotechnology in Regenerative Medicine: the Importance of the Interaction between Materials and Cells

According to the classical definition, nanotechnology refers to all methods and processes dealing with matter control and modulation on a dimensional scale ranging between 1 and 100 nanometers.

The application of nanotechnology to life sciences is a very topical and interesting field where diverse and complementary disciplines convey (chemistry, physics, materials science, molecular biology, engineering, computer and clinical science), thus offering new opportunities for the treatment and prevention of disease, as well as for the development of theranostics, i.e., the combination of diagnostic and therapeutic tools aiming at personalizing patient care.

A number of achievements in these fields result both from basic and applied research that over the last few years addressed the development of innovative systems of drug-delivery, "smart" materials for regenerative medicine and targeted cell therapy, as well as imaging systems, biosensors and miniaturized prosthetic devices.

The common objective of these studies is the implementation of new tools, techniques and devices which are effective and safe. Therefore, it is very important to understand the phenomena which take place when the "smart" materials, used in the manufacturing of biomedical devices, interact with living biological systems.

In order to regenerate damaged tissues and organs, one of the crucial requirements of regenerative medicine is to enhance the interaction between cells and surfaces, and to make it more effective in terms of tissue engineering. The adhesion of cells to a surface, or scaffold, is a crucial step in the process of cell proliferation and growth, as well as of cell differentiation.
Cells are able to "feel" surfaces and to respond in a different way according to the chemical, physical, topographic and mechanic stimuli they receive. Despite their average size is in the range of dozens of microns, cells are able to perceive structural changes in the materials even on a nanometric scale, which is a size compatible with that of the proteins of an exposed membrane (focal contacts).

Several studies show that surface nanostructuration, on a different size scale (from a few nanometers to dozens of microns), can modulate and influence the cell growth and their spatial organization, both *in vitro* and *in vivo*. With the arrival of stem cells, the interest for this sector has increased even more and several research projects have been focused on the improvement of experimental protocols for stem cell differentiation and on the implementation of biocompatible scaffolds, capable of enhancing tissue engineering, through the design, synthesis and characterization of new materials.

Significant progress has been made in the understanding of the physical, chemical, mechanical and topographic surface parameters that enhance, or hinder, cell adhesion and that can thus modulate their direction of growth also in *ex vivo* implants and devices.
Taking into account that all tissues in the human body are "immersed" in a three-dimensional microenvironment, it is understandable that in regenerative medicine it is crucial to mimic *in vitro* the physiological environment in which cells are hosted. This environment includes not only proteins and support biomolecules, building the so-called extracellular matrix, but also neighboring cells, nutrients and hormonal factors which stimulate those cells.
The complexity of the environment and of cell mechanisms result into the possibility for regenerative medicine to still have wider implementation opportunities in the development of nanostructured supports and matrices sustaining adequately transplanted stem cells, and which allow to supply them with nutrients and growth factors.

The correct spatial cell organization is crucial for tissue functioning: for example, an uncontrolled growth of

regenerated fibers of nervous tissue can have life-threatening consequences for a patient with bone marrow lesions; or, in the corneal stroma, cells "live" in an environment made up of aligned collagen fibers, which is such that this pattern has been demonstrated to be an essential requirement for the transparency of the cornea.

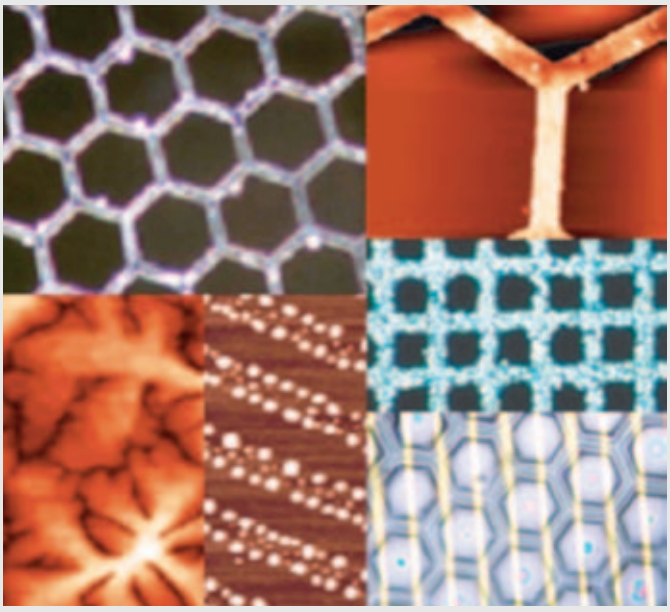
Besides understanding these phenomena and the related development of functionalized eligible materials, the need for biocompatibility and safety of materials should also be taken into account. Currently, all these notions are part of a vast cultural heritage mainly based on research results, although its consequences in medicine and clinical practice could be very important. For these reasons, it is necessary to encourage nanotechnology innovation in the medical field and to work towards having the relevant authorities provide for regulations on its timely access to the market.

In the worldwide scenario, the market of products for cell culture is at present dominated by big pharma companies: in Europe the leader is Invitrogen, followed by Sigma-Aldrich, who markets cell supports, mainly in plastic or glass, which do not reproduce the physiological microenvironment of our body. Some more innovative products come from large U.S. companies including Corning, SurModics and BD Bioscience; these products have surfaces which are chemically or physically treated or which are coated with biomolecules that facilitate or hinder cell adhesion (i.e., poly-lysine, laminin, and collagen), having finely controlled and structured geometry and size. Nowadays, only a few companies have transferred or included this type of know-how into their corporate mission; among these, SurModics Inc. should be mentioned as a leading company in the application of technology for modifying the surface characteristics of biological devices and materials, as well as implant coating and drug delivery. In Italy, Nano4bio S.r.l., a high know-how & technology start-up company, founded in Bologna in 2008 by researchers of the University of Pisa and the National Research Council (CNR), has been one of the first biotech companies in Italy to implement the technology transfer from academia to industry, having understood the importance of applying nanotechnology to cell biology and medicine. The SMART4BIO products, developed by means of a hybrid and innovative technology, can be used in regenerative medicine and biosensoristics. Nano4bio is able to design and implement tailored nanostructured and functionalized (bi- and tri-dimensional) supports with a wide range of biomolecules and synthetic molecules (Figure 1).

The technology used is multi-target, since it offers new options for cell biology, diagnostics, pharmaceutics; it is adaptable, since it allows to control and modify the processes and manufacturing, on the customers' request, on different scales; and it is sustainable, since it is based on a bottom-up process requiring minimum quantities of materials, thus reducing production costs and environmental impact.

Figure 1

Different patterning of biomolecules on substrates with different chemical properties



The Financing Perspective

Access to financing is the most crucial priority for most Italian pure biotech companies, especially in the early stages of their development. In order to grow the system's competitiveness, Italy definitely needs to increase its R&D funding and long-term investments, within a rigorous framework of economic, financial and fiscal interventions, thus allowing innovative companies to rely on adequate available capitals in terms of timing and efficiency.

In a field requiring extensive R&D investments such as biotechnology, companies need to count on adequate financial resources, particularly during the early and extremely uncertain stages of their development.

In 2009, biotech companies have invested € 1,760 million overall in R&D, which accounts for a 2.5% increase as compared to 2008, and confirms the positive investment trend already highlighted in the 2010 report (Figure 8.1).

The analysis of the sample shows that Italian biotech companies actually consider three main financing options: about 56% of the companies resort to debt, 50% to grants (including national and regional funds as well as European and international funds) and 37% to Venture Capital and Private Equity funds (Figure 8.2).

These three financing sources are not mutually exclusive: indeed, a company may raise capital from different sources at the same time.

In comparison to last year, the most significant change is the steep decline in grants, which is mainly due to the decrease in the national funds available. Moreover, the number of companies that resort to VC/PE and debt to support their activities has increased.

Figure 8.1

Analysis of R&D investments. (Values in million of Euros) (Source: Ernst & Young)

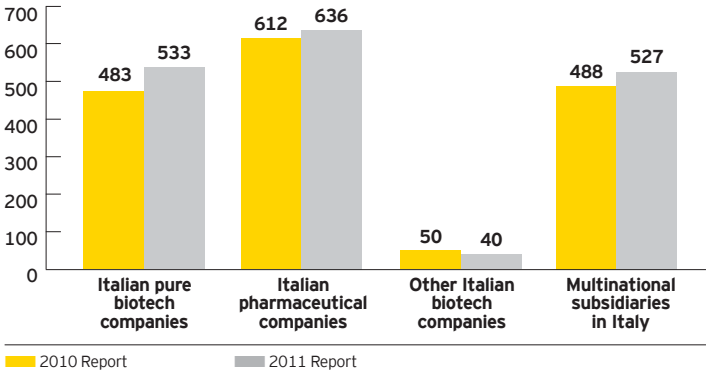


Figure 8.2

Analysis of financing sources (Source: Ernst & Young)

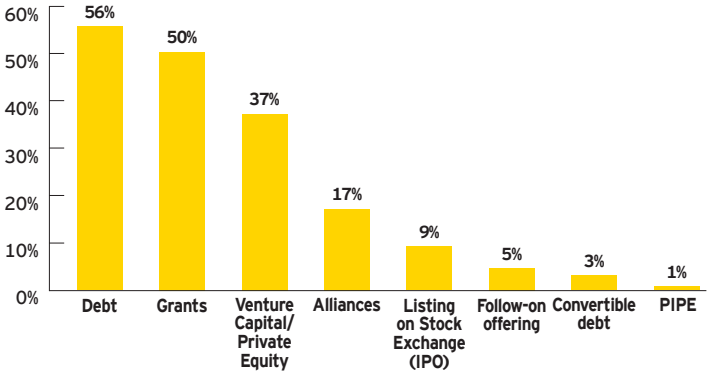


Figure 8.3

Italian pure biotech companies: analysis of financing sources with regard to the past and next two years
(Source: Ernst & Young)

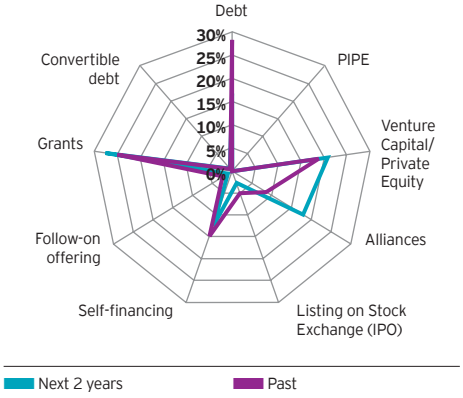


Figure 8.4

Italian biotech companies: analysis by listing market in case of IPO
(Source: Ernst & Young)

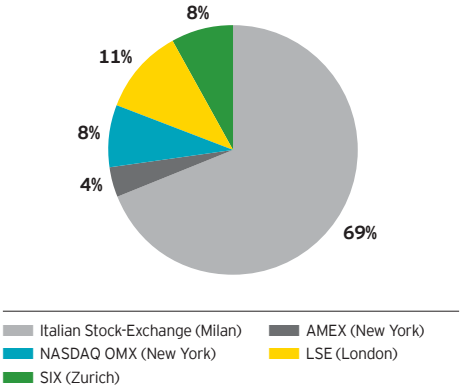
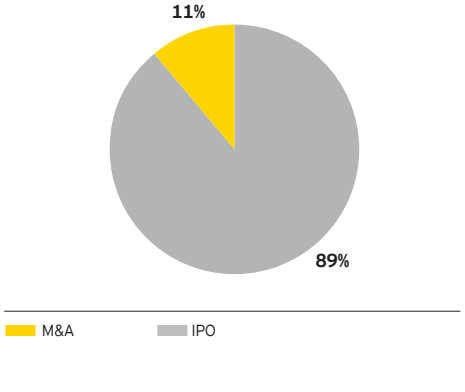


Figure 8.5

Italian biotech companies: analysis by investors' exit strategy
(Source: Ernst & Young)



With regard to the immediate future, besides seeking for VC/PE funding and grants, Italian biotech companies expect to increasingly establish strategic alliances and synergies, with other companies, by actively tracking partnering and M&A deals. (Figure 8.3).

This shows a higher tendency to the exchange of knowledge and expertise, both between the companies of the same cluster and companies involved in other fields, as well as the tendency to concentrate skills in a single entrepreneurial body, in order to increase its competitiveness in terms of critical mass.
Conversely, the companies interviewed expect a decrease in the resort to debt that, up to now, has been the most common financing option among biotech companies.

Moreover, the answers to the questionnaire show that as many as 26 companies consider listing on a stock exchange as a source of financing in the next two years. Ninety percent of these companies would also consider listing on the European stock exchange, even if 69% would prefer going public in the Italian market (Figure 8.4).

Moreover, an attempt has also been made to understand whether stockholders of biotech companies have already taken into account a possible exit strategy and, if this is the case, they would prefer going through an IPO, or tracking an M&A.
The stockholders of 27 companies have already identified an exit strategy and of these, almost 90% stated that they would prefer an M&A deal to an IPO transaction (Figure 8.5).

The vast majority of those stockholders who have already planned for an exit strategy are from pure biotech companies. This may have to do with the fact that, at least in some cases, the mainly scientific background of pure biotech companies' founders, benefits from being complemented with those managerial skills which are fundamental for the management of more complex production, marketing and development activities.

Public funding

National funds

The year 2009 was characterized by a sharp decrease in the national allocation of public funds for scientific research. In fact, in 2009, € 8,377 million were allocated compared to € 8,970 million in 2008. Therefore, a 7% reduction in the overall national funds occurred: this is a countertrend when compared to the 2006-2008 period (Figure 8.6).
Therefore, among the European industrialized countries, Italy is trailing. In fact, in 2009, France, Germany and the United Kingdom contributed with 54% of the overall European Union funds, and Germany's share alone accounted for 24%: more than twice the Italian share (11%).

An analysis of the overall national investments by socio-economic objectives - i.e., in relation to the main objective declared at institutional mission or finance management plans level - shows that more than 45% of the funds allocated to scientific research are addressed to basic university research (the objective being the "promotion of basic knowledge"), and about 10% to human health research (the objective being the "safeguard and promotion of human health") (Figure 8.7).
A more detailed analysis of the mechanisms of fund allocation to human health research, involving a high number of red biotech companies, shows that in Italy the ministries granting most of the funds are:

- the Ministry of Education, University and Research (MIUR)
- the Ministry of Health (MDS)
- the Ministry for Economic Development (MISE)

In 2009, MIUR which allocated about 70% of the overall national funds to research, showed a slight increase of 0.7%, as compared to a steep decrease of 7.2% between 2007 and 2008 (Figure 8.8).
Always in 2009, the share allocated to basic knowledge (63%) and human health (3%) increased by 6% and 40%, respectively.

The Ministry of Health provides funds for the following areas:

- current research, to support research activities aimed at developing the fundamental knowledge in specific fields of biomedicine and public healthcare over time, 85% of which is allocated to IRCCS (Scientific Institutes for Research, Hospitalization & Health Care)
- finalized research, to implement priority biomedical and healthcare objectives, as identified in the National Health Plan

The current research funds kept a stable growth up until 2008, before showing a decline of about 20% during last year.
The finalized research funds show a more irregular trend, with an increase of about 100% from 2008 to 2009 (Figure 8.9).
A trend towards the increase in the share of funds allocated to finalized research can be clearly observed. These different trends are partly due to the strategic planning of research activity, resulting in fund allocation, and to their distribution between finalized and current research.
Every three years, research priorities of the National Health System are set through the *Programma Nazionale di Ricerca* (PNR) (Italian National Research Program) agreed upon by the *Commissione Nazionale della Ricerca Sanitaria* (CNRS) (National Health Research Committee), and the *Ministero del Lavoro della Salute e delle Politiche Sociali* (Ministry of Labor, Health and Social Policies).

The program is adopted in agreement with the *Conferenza Stato-Regioni* (State-Region Conference) within six months from the date on which the National Health Plan becomes effective. The National Research Program is a guideline for the institutional recipients of the health and research funds: the already mentioned IRCCS, the Regions and autonomous Provinces, the

Figure 8.6

Government research grants. (Values in million of Euros) (Source: MIUR on data from the different Ministries)

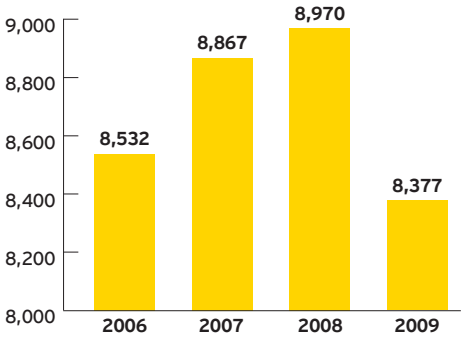


Figure 8.7

Share of government funds by socio-economic objective, 2009 (Source: MIUR)

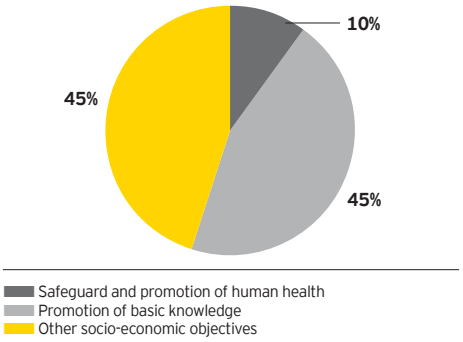
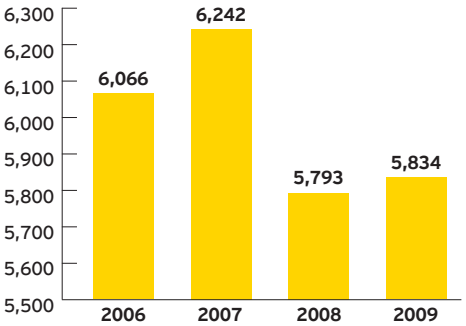


Figure 8.8

MIUR research funding. (Values in million of Euros) (Source: MIUR)



Istituto Superiore di Sanità (ISS) (National Institute of Health), the *Istituto Superiore per la Prevenzione e la Sicurezza sul Lavoro* (ISPESL) (National Institute for Occupational Safety and Prevention), the *Agenzia Nazionale per i Servizi Sanitari Regionali* (Age.Na.S) (National Agency for Regional Health Services), and the *Istituti Zooprofilattici Sperimentali* (IZS) (Experimental Zooprophylactic Institutes). The systems of fund allocation to recipients for current research and finalized research are different.

Lastly, over the last few years, MISE has allocated € 5 million to biotech companies through the *Fondo speciale rotativo per l'Innovazione Tecnologica* (FIT) (Special Rotative Fund for Technological Innovation). These resources can only be accessed by Italian SMEs intending to implement transnational projects of industrial innovation in all biotech application fields in cooperation with European SMEs.

Regional funds

As shown in the 2010 Report, Regions have increasing responsibilities in terms of fund allocation to research. This higher autonomy allows them to develop their own strategic plans for the allocation of funds, through the publication of specific calls for proposals aimed at supporting development in critical or priority areas.

Considering the complex and heterogeneous situation of the different regions, the 2011 Report aims at highlighting the main differences between the various intervention models, with particular reference to certain regions (Lombardy, Piedmont, Tuscany and Sardinia).

International funds and programs

After having performed a structural analysis of FP7 in the 2010 Report, this year we decided to focus on the results obtained by Italian companies in terms of submitted and financed projects.
The analysis of data of the first three and a half years shows that Italian companies' applications to FP7 have a contradictory trend. In fact, despite our Country ranks third among the Member States in terms of number of applications (17,734 proposals eligible for 176 calls for proposal), accounting for 12.68% of EU (25,558 applicants) for a total contribution requested of € 8,465.55 million, Italy has a final percentage of projects actually co-financed by the European Union far below the EU-27 average. In particular, the applicants' success rate accounts for 18.3% of the total, below the EU-27 average of 21.8%.
Since most Italian biotech companies are small or micro in size, it is interesting to focus on SME performance. In this case, too, Italy is below the EU average: in fact, Italian SME applicant success rate, accounting for 15.58%, is below the EU-27 average which is 19.13%; also the SME EC financial contribution is only 13.99%, as compared to the EU-27 average of 17.89%.
The comparison with other Member States, such as France, Germany and the United Kingdom, shows that the Italian data need to improve in order to keep up with some of the countries which boast the best performances in EU research programs.
With regard to the Cooperation sub-program, the FP7-ERANET-2011-RTD call for proposals was launched last year; of the overall € 44.6 million budget, € 8 million were allocated to biotechnology and divided into four two million-Euro projects: two of them are in the red biotech field, while the other two in green biotech.

The three regions with the highest number of financed projects are Lombardy (68), followed by Latium (58) and Tuscany (27) (Figure 8.10).

Figure 8.9

Ministry of Health research funding: analysis by field. (Values in million of Euros)
(Source: Ministry of Health)

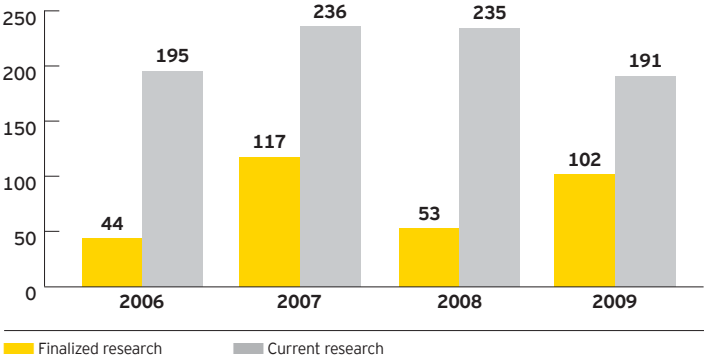
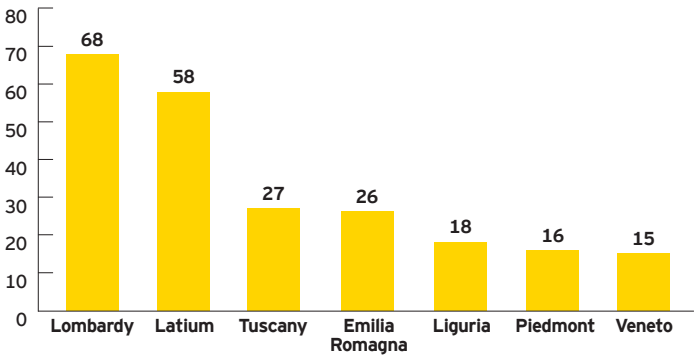


Figure 8.10

Number of the FP7 granted projects, by main Italian regions



Another important source of international funding to research is that from the U.S. National Institutes of Health (NIH). However, unfortunately, funds raises by Italian research bodies have progressively diminished over the years, to reach about € 1 million in 2008-2009 (NIH data).

Private funds

About 37% of the companies included in the sample declare to have benefitted from Venture Capital and Private Equity funds as financing sources: an increased percentage as compared to 30% of the 2010 Report.
This increase mirrors the trend of real VC/PE investments identified by AIFI and described in the below box "Risk Capital Investment: a Fundamental Tool in Supporting Biotech Research in Italy".

VC/PE funding activities may be classified into four main types in relation to the specific development stage of the company they are used to support:

- Seed Stage, when they are used to fund the initial phase of activities, thus allowing the company to reach profitability
- Expansion, when they are used to fund the expansion of the company's production capability, sales growth and entrance into new markets, as well as the early stages of listing on a regulated market, and the acquisition or restructuring of the company
- Buy-out stage, when they are used to fund the purchase of the company by its current management team or by a new management team
- Replacement Finance, when new VC/PE funds are used to purchase shareholding participation from a partner leaving the business or another investment fund.

When considering the VC/PE activities across all fields, in 2009 there was a higher concentration in the Expansion and Buy-out development stage funding: in fact, 27% and 39% of the overall operations performed respectively fall under this definition, and the percentages are decreasing when compared to 2007, when there was a slight increase in the amount of funds allocated to Early Stages (Figure 8.11).

When considering the biotech field alone, the situation is diametrically opposed (see box below). Indeed, this analysis shows that most of the funds coming from VC/PE are Early Stage, and as such supporting companies' early development phases.

Moreover, it should be highlighted that between 2008 and 2009 the amount of funds from VC/PE funds generally allocated to R&D investments was reduced. Indeed, despite an increase of approximately 130% occurring from 2005 to 2007, resources provided by VC/PE funds in 2009 were reduced to € 957 million, less than in 2005 (Figure 8.12).

However, it is important to note that in the expert's opinion the "worst is over" and that investments will soon start again, thanks to the increasing vitality and trust that the biotech market is fueling. On the other hand, the high degree of optimism about the future of this field is clearly shown by the trend of the AMEX Biotechnology Index.

The performance of this index over the 1999-2009 period has been extremely positive and clearly more profitable than the one of the AMEX Pharmaceutical Index and the U.S. S&P 500, as shown by the trend over the last twelve months (March 2010 – February 2011): the AMEX Biotechnology Index is still performing better than the other two indices, even if in 2010 the pharmaceutical index has come much closer in terms of profitability (Figure 8.13).

Figure 8.11

Number of VC/PE transactions by type
(Source: Cotec 2010 Report)

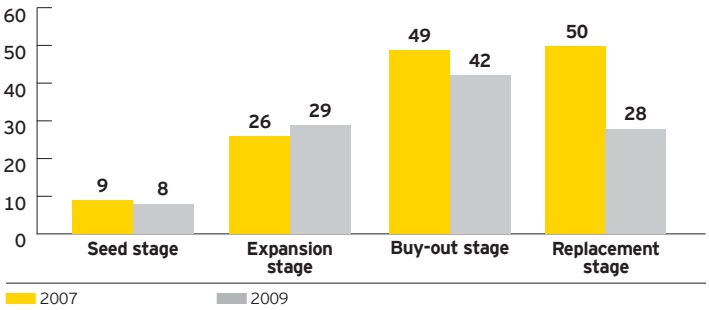


Figure 8.12

Capital raised through VC/PE financing in Italy. (Values in million of Euros)
(Source: Cotec 2010 Report)

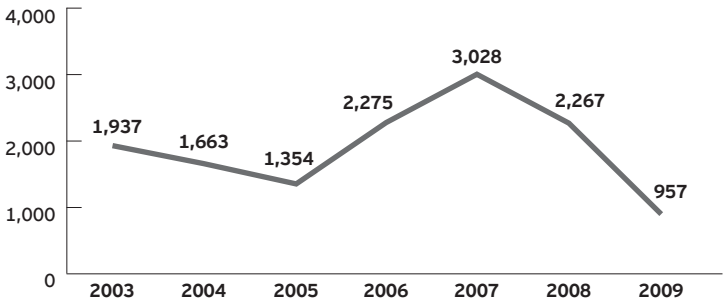
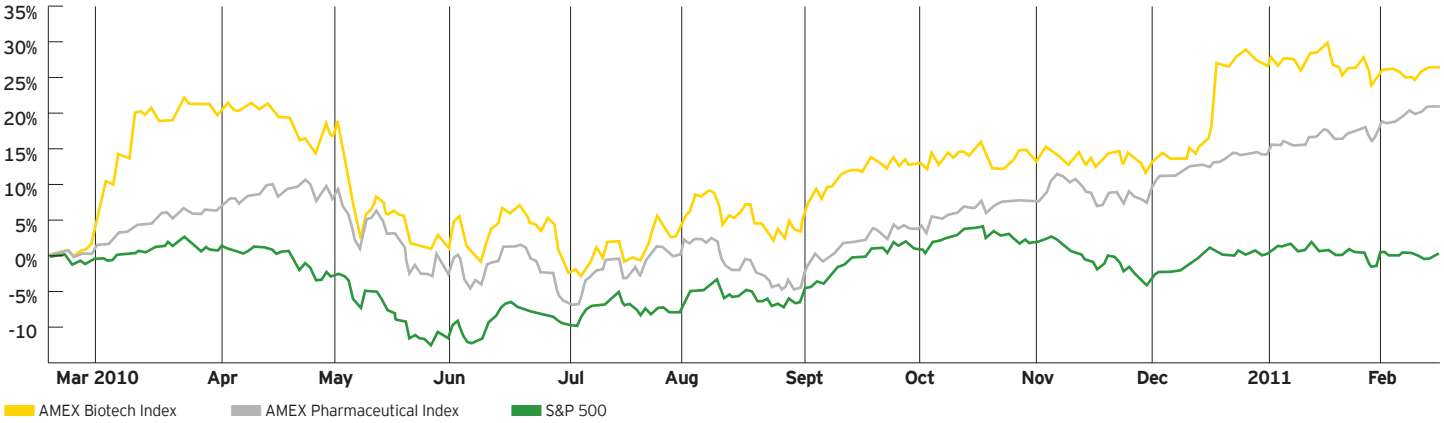


Figure 8.13

Performance of the AMEX Biotech Index vs. AMEX Pharmaceutical Index and S&P 500 (Source: Yahoo Finance, Ernst & Young)



Risk Capital Investment: a Fundamental Tool in Supporting Biotech Research in Italy

Ensuring adequate fundraising is crucial in order to support the R&D activities and plays a key role in allowing growth, innovation and competitiveness of the biotech industry, an entrepreneurial sector characterized by extreme uncertainty, not only in terms of financial requirements, but also in terms of results of the different projects and of the often lengthy time which is needed for their development.

With reference to the Italian market, VC investments allocated to biotech companies have undergone an important growth, in the last few years, which reflects the significant interest of Italian operators for one of the most innovative sectors of the current scenario.

According to Aifi, who collects data on Private Equity and Venture Capital activities in Italy on a six months basis, in the 2005-2009 period the amount invested in companies operating in the biotechnological and medical fields increased from € 53 to € 206 million, accounting for 8% of the overall capital invested in the Country. Conversely, the number of transactions has remained rather stable, with about 30 investments per year accounting for 10% of the total.

Even in an extremely difficult period such as the first half of 2010, with investments falling to the lowest values in the last few years, the biotech field has shown positive signs. In fact, during the first semester, 17 operations were recorded, accounting for 13% of the total number of investments made in Italy, against 12 in the first semester 2009, when they accounted for 8%.

Regarding the characteristics of these investments, the main feature is the prevalence of early stage funding that, from 2008 to the first semester 2010, accounted for 68% of the overall number of deals. In fact, during this period, 47 investment transactions were made in favor of biotech start-ups, and 11 concerned companies in the seed stage, i.e., the pre-competitive research phase necessary for the development of the entrepreneurial concept. Therefore, in most cases the investments have the objective of supporting the early stage of a company development, or even of turning a concept or a project which is deemed very innovative into an entrepreneurial activity.

In conclusion, Italy certainly has a promising biotech and medical industry, which is still being developed. However, since this industrial sector is still relatively "young", there is a clear for wider recognition and greater involvement of the financial community, so as to fuel a number of true success stories which would draw the attention of investors and allow full exploitation of the biotech segment potential.

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Incentives to the Biotechnology Industry: Comparison of Different Regional Models

The developing capability of the biotech sector, as well as of any other highly innovative field, mostly depends on the policies and incentives implemented by the different countries.
This report analyzes incentive policies implemented on a regional level.
Our objective is to verify whether there are different intervention models in Italy and, if so, what are the differences.
Firstly, it must be noted that the mapping of incentive polices is not a simple task.

The first element of complexity is the variety of sources these actions originate from (public and private funds, European, national and regional programs) and the overlapping that often characterizes them. Public contributions allocated within intervention programs are very often mixed in nature: i.e., national/regional, EU/regional, regional/local.
Therefore, defining the boundaries between the different levels of intervention (local, regional, national, supranational) of the financing bodies is often not easy. Moreover, the objectives these interventions aim at achieving should also be considered: e.g., supporting basic research, financing industrial research projects, encouraging the set up of new companies and developing specific territorial areas. Lastly, the increasingly important role of the private sector and, in particular, banking foundations in financing research activities should be also taken into account.

The interpretation scheme which was introduced in order to capture all the above elements of complexity, summarizes the system of research incentives adopted by the different regions.

The innovation incentives matrix which was specifically created by CrESIT identifies both the financing sources from which these interventions originate (public funds: European Union, Government, Regions, Local bodies; private funds: banking foundations and other non-profit organizations), and the different fields they support, which were classified as follows:

- basic research, including financing of academic research projects and research grants
- applied research, including financing to companies for R&D activities
- clustering, i.e., actions and incentives aiming at encouraging the development of scientific and technological parks, the localization of new companies in specific territorial areas, the development of partnerships between companies and research centers and the creation of innovation hubs and districts
- providing support services to companies, including vouchers for highly value-added services: e.g., vouchers for intellectual property, technology intelligence and market research consultancy services
- providing financing services, through seed/venture capital funding to start-ups and innovative companies.

The present report is actually focusing its analysis on four regions, i.e., Lombardy, Piedmont, Tuscany and Sardinia, which were chosen with regard to their importance (about 59% of the Italian biotech companies are herewith located), as well as to the fact that they present different intervention models and situations, both in terms of development level and biotech presence.

The comparison between these regions is, therefore, particularly interesting also in the perspective of potentially extending the support interventions which are herewith analyzed to other regions.

Lombardy

Lombardy is a region of excellence with regard to life sciences and biotechnology, both in terms of public research institutions and investigational centers as well as for entrepreneurial initiatives. Although the traditional industrial districts play a driving role in the Lombard economy, in the last few years *Regione Lombardia* has chosen to focus on those sectors which are key for the economic development of this region (e.g., ICT, biotechnology, agro-food biotechnology and nanotechnology) by implementing several actions for their expansion.

An integrated analysis of the various initiatives which were undertaken, both on a public and private level, shows that these actions are mainly focused on financing basic research and supporting the development of already existing innovative industrial organizations.

Although not exhaustive, we are herewith presenting a number of examples of the Lombard incentive system with specific reference the previously identified intervention areas.

Among the many initiatives in the area of basic research, it is worth mentioning the DOTE Project promoted by *Regione Lombardia* that allocates 30 million Euros to research programs with a potentially positive impact on the entire Lombard system. Also Cariplo Foundation plays an important role by funding, with tens of million Euros every year, innovative research projects in the biomedical field as well as in less specific areas. For example, through the NOBEL Project, Cariplo Foundation has funded six technological platforms that can be accessed by the scientific community, together with the participation of young scientists in highly interdisciplinary projects.

With regards to applied research, *Regione Lombardia* has implemented a series of interventions aimed at supporting the above mentioned strategic sectors. The region has recently allocated almost 50 million Euros to 50 industrial research and experimental development projects within a number of topical areas, i.e., the so called *Aree Tematiche Prioritarie* (ATP), including biotech and agro-food, which are key for the Lombard productive system. An additional intervention specifically focused on biotech was included in the call for proposals made by MIUR-*Regione Lombardia* in 2006, which allocated 8 million Euros for projects aimed at industrial research and development of new entrepreneurial activities in the region.

A further important area of intervention, gathering funds of different nature, goes under the clustering model. A number of actions have been undertaken in order to encourage cooperation strategies between local research institutions as well as the development of a lively entrepreneurial network. Among these, it is worth mentioning the call for proposals for potential projects aimed at increasing the attractiveness of the Lombard region, the promotion of human resources and scientific cooperation in a number of priority technological areas including:

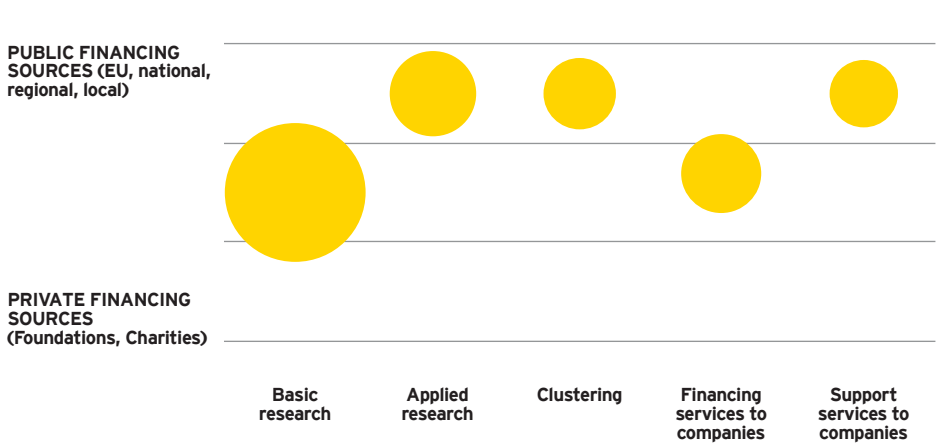
Lombardy

Support to basic conditions for the development of innovation

- *public-private mixed financing model (Regione Lombardia, Banking Foundations)*
- *focus on basic research and support to companies*
- *generic interventions to support innovative sectors and limited actions directed at the biotech field*

Figure 1

Incentives for innovation, Lombardy: CrESIT matrix (Source: CrESIT - 2011)



biotechnology, human health, new materials, ICT, agro-food, energy, environment and advanced manufacturing. The said call was promoted by *Regione Lombardia*, the Lombard universities and the *Scuola Superiore Universitaria* IUSS of Pavia. In 2009, *Regione Lombardia* also issued the DAFNE-DRIADE call for proposals to identify new productive systems, clusters or product value-chains as well as encourage networking activities within this region.

Other local structural interventions funded by a mix of regional and local resources concerned the support to scientific and technological parks, including the *Parco Tecnologico Padano* (a scientific hub which gathers the main players in the agro-biotechnological field, i.e., the School of Veterinary Medicine and Agriculture of the University of Milan, the Experimental Zooprophylactic Institutes, and other public and private research institutions and companies) and the Insubrias BioPark (a science park and incubator, stemming from the former Vicuron research laboratories and aimed at the conversion of the already existing industrial and research organizations). With regards to the Lombard approach to clustering, it is possible to identify the so-called "meta-districts" or "multi-hub districts" model, where the cluster results from the promotion of partnerships between actors playing in different locations (the "hubs"), rather than from the identification of a formal structure where the different players should meet.

Among the actions supporting the creation and development of innovative entrepreneurial realities, the set up of the NEXT Fund by the Lombardy region through its holding company Finlombarda S.p.A., is also worthy of note.
The Fund, created to provide venture capital investments in Lombardy, invests directly in small and medium Lombard companies, which are active in highly innovative technological areas, in their start-up or early stages of development.

Another interesting initiative to support new early stage innovative companies is linked to the "SEED Fund" call for proposals, which already allocated 10 million Euros to micro, small or medium Lombard companies in 2008.
None of these initiatives are specifically dedicated to the biotech sector, but are more generally addressed to innovative companies.
Again in Lombardy, TT Venture, a closed-end fund, was set up by a group of banking foundations with the aim of supporting technology transfer and high technological content initiatives within the biomedical, agro-food, energy-environmental and materials science fields.

Besides the above described initiatives, *Regione Lombardia* together with the local Provinces and Chambers of Commerce, annually provides Lombard companies with vouchers for intellectual property, technology intelligence and market research consultancy services.

Based on this overview, the "Lombard model" seems to be characterized by a mix of private-public financing, where the public action is implemented mainly on a regional administrative level and the private action fundamentally through banking foundations. In terms of intervention areas, a strong focus is addressed to basic research, without neglecting support to companies. Therefore, the regional intervention "strategy" (if this can be the definition of an action implemented by several subjects) would be, on the one hand, to support basic conditions for the development of innovation (by means of strong investments in basic research) and, on the other hand, to support the capability of transferring innovation to company activities (by means of supporting innovative companies and start-ups).
This model is consistent with a context which is characterized by high levels of excellence in R&D (universities, research centers, hospital facilities) and by a strong industrial fabric in terms of number of innovative and traditional industries. In any case, it is not possible to identify a regional strategy specifically aimed at the biotech field, since all actions, with very few exceptions, are addressed to supporting the innovation districts generally.

Piedmont

Piedmont is the second region in Italy in terms of number of biotech companies, and has progressively implemented several actions aimed at supporting highly innovative sectors, including those of biotechnology and energy and environmental technologies.
These sectors are defined in the regional strategic planning document as "neo-industrial transition" districts capable of entering the global market in an increasingly structured way as well as of driving the whole regional economy.
Over the years, Piedmont has benefitted from EU structural funds, including ERDF (European Regional Development Fund) and ESF (European Social Fund) which have allowed *Regione Piemonte* to adopt a series of measures to foster local competitiveness and conversion of the economic structure.
An example for consideration is the case of the Canavese area, which had been linked to the Gruppo Olivetti for many years; when the latter was crisis-stricken in the 90's, the area underwent a transformation process of the productive fabric resulting in the setting up of the Bioindustry

Park Canavese. The Park, which is among the top intervention priorities of *Regione Piemonte* industrial policy, was implemented by using funds allocated by the European Regional Development Fund – in co-financing regime of Government and Region – the objective being to promote and develop biotech research and incubation opportunities for companies operating in the life sciences field.
In this particular case, the interventions have allowed making the best of the existing know-how, as well as supporting the setting up of technologically highly specialized productive activities.
In the period 2006-2008, additional regional funds were allocated to initiatives of company incubation within the park (e.g., the Discovery Project) as well as to actions aimed at attracting companies from other regions (e.g., Bracco Imaging or AAA).

During the last few years, *Regione Piemonte* has implemented various targeted interventions to stimulate innovation by means of international co-operation forms (networking/clustering). In particular, by using European and regional funds, some biotech-specific projects were funded (including BIOCT, ABCEurope, Bioprotech and ALPS BIOCLUSTER) directed at reinforcing cooperation both on the border and transnational level. At this regard, it is important to highlight that the Park is a member of the steering committee of CEBR (Council of European BioRegions). With specific reference to life sciences, the "Innovation Hubs" initiative, which was promoted by *Regione Piemonte* within the POR-FESR 2007-2013, has fueled clustering interventions in this field by funding the bioPmed Hub. The purpose of this hub is that of coordinating the different players in the innovation process in the biotechnology and biomedical field in Piedmont: this is achieved through fostering partnerships between companies, research centers, universities, foundations and associations towards which research funds and facilitations for the use of highly value-added services can be directed. With this system, during last year alone, more than 25 innovative entrepreneurial projects were financed in the bio- and med-tech area. The action described above is characterized by an interesting and qualifying aspect: the participating companies co-finance not only the research projects submitted, but also the hub management model, thus making "Innovation Hubs" a laboratory of public-private cooperation implemented within the sector.

What is more, the effort of attracting research activities to centers having a sufficient critical mass to operate according to international standards and to relate synergistically with the local industrial fabric, should be interpreted in the perspective of reinforcing and qualifying research in the biotech field. Two examples are the Molecular Biotechnology Center and the Center of Excellence in Preclinical Imaging (CEIP) of the University of Turin that have been co-financed with European structural funds.

Moreover, worthy of attention are some significant financial interventions addressed to specific sectors of industrial research which aim at fostering and encouraging (by means of co-financing from governmental and regional funds) the cooperation between universities, research bodies and companies through shared projects requiring a high degree of knowledge (ICT, biosciences, nanosciences).

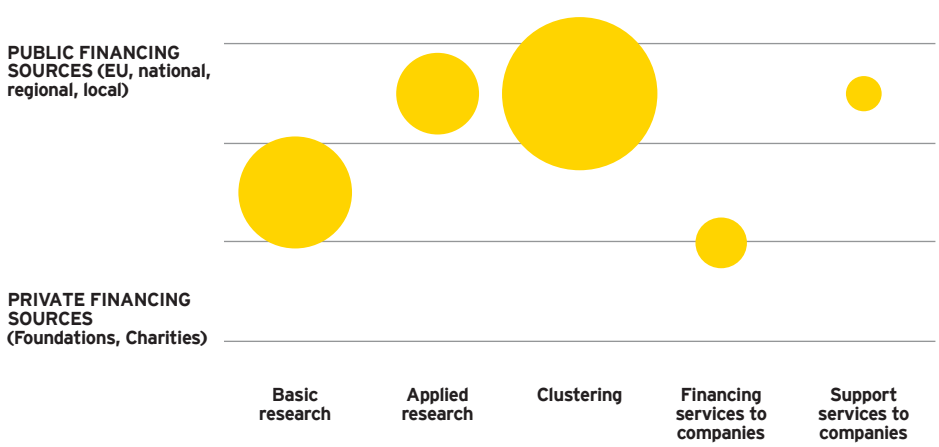
Piedmont

Renewal of the industrial fabric and know-how

- *public-private mixed financing model (European Union, together with Banking Foundations)*
- *focus on clustering actions in an international perspective approach*

Figure 2

Incentives for innovation, Piedmont: CrESIT matrix (Source: CrESIT - 2011)



For example, in the "Technological Platform", "Nanomat" and "Converging Technologies" projects, the biotech field was the priority target. Consistently, actions supporting professional training processes were also implemented, including the "Training hub for Biotechnology", as well as masters organized by universities, companies and innovation hubs.

An example of this is the *Centro Estero per l'Internazionalizzazione del Piemonte* (CEIP) (Foreign Center for Piedmont Internationalization) which supports, by means of specific programs, the promotion of the life sciences field abroad. Since 2005-2006, by using CIPE funds, research projects in innovation areas have been funded (among which those related to life sciences) involving universities, research centers and companies.

Besides financing research projects, regional authorities also provide companies with tools to support the acquisition of high value-added services (e.g., vouchers for intellectual property, technology intelligence and market research consultancy services), to access international markets and for mobility of personnel among research institutions, large enterprises and SMEs.

Moreover, the role of banking foundations, including the CRT Foundation and the *Compagnia di San Paolo*, should be pointed out: the former, through the "Lagrange Project", allocates research grants of various types; the latter, through the "Neuroscience Program", funds scientific research projects in the framework of different disciplines, but all focused on CNS. Furthermore, in 2007 *Compagnia di San Paolo* in partnership with *Università degli Studi* and *Politecnico di Torino*, set up the Human Genetics Foundation (HuGeF), a private non-profit foundation aiming at developing research of excellence and advanced training in the field of human genetics, genomics and proteomics, in a multidisciplinary perspective.

Among the private sources of financing, the role of Eporgen Venture, a private seed capital company financing innovative projects in the area of life sciences, should be noted.
Eporgen contributed to the setting up of several biotech start-up companies incubated within the Bioindustry Park. Moreover, Eporgen Venture also holds a participation in Piemontech, the holding company set up by *Fondazione Torino Wireless* in order to support regional innovation and development. Piemontech invests risk capital in emerging companies in the fields of ICT, biotechnology, biomedical technology, advanced mechanics, energy and innovation services and has implemented several seed capital investments on a regional level.

In order to foster the knowledge and innovation excellence of the Piedmont's territory, Fondazione Sviluppo e Crescita CRT has set up Jstone, a seed and venture capital company operating in several highly innovative fields including nanotechnology, biotechnology, agro-food and biomedical.

Accordingly, the "Piedmontese model" is characterized by its ability to renew the existing industrial structure which has resulted in the progressive development of sectors with a high degree of knowledge. The relevant actions are mostly concentrated on the development of local production systems, focusing on transnational cooperation. This model is implemented using mixed public-private financing schemes. Among the public sources, unlike the Lombard model, the EU sources play a key role along with banking foundations which also have a similarly important role.

Tuscany

Several national and international pharmaceutical companies are located in Tuscany, along with scientific and technological parks, universities of historical tradition, investigation-oriented research centers and clinical institutes. This context has paved the way to the setting up and development of several biotech companies which make Tuscany the forth region in terms of number of companies.

With the "SUBITO Project" (*rete Sociale Unica per l'innovazione BIomedica TOscana*), *Regione Toscana* has recently undertaken to systemize information concerning the Life Sciences field.
The main objective of this project is to create a database and portal to link all the main local public and private subjects operating in the healthcare, biomedical and pharmaceutical fields.

Regarding applied research, *Regione Toscana* has promoted a number of projects concerning industrial research and investigational development, specifically in the Life Sciences area. These are co-financed by Community and national funds, including those allocated by POR - *Programma Operativo Regionale* and PRAI ITT – *Programma Regionale Azioni Innovative* "Technological Innovation in Tuscany". The objective of PRAI ITT is to locally encourage the dissemination process of technological innovation by setting up cooperative network between companies, research centers, universities, local public institutions, innovation centers, centers providing services to companies, training agencies and financial bodies. Moreover, the Region has recently directed a number of interventions aimed both at improving the efficiency of technology transfer centers and

consolidating knowledge and advanced services institutions, such as the *Rete regionale del sistema di incubazione di impresa* (RETE) and the *Rete regionale del sistema di trasferimento tecnologico* (TecnoRETE).

With regards to the actions aimed at supporting processes of aggregation and the creation of cooperation networks and other forms of cooperation, the "*Progetto N.B.A. Toscana*" should be mentioned, i.e., the regional network on biotechnology and environmental genomics. Among the networking activities the initiative "Invest in Tuscany", conceived in order to attract direct investments to Tuscany from abroad, should also be noted. "Invest in Tuscany" is a project by *Toscana Promozione* (a region-supported public agency set up in 2001) which also involves the administrative bodies of the Provinces in Tuscany.

Recently, *Regione Toscana* has promoted a number of clustering interventions.
In 2010, the Region started setting up four technological districts, among which that of Life Sciences, in support of the regional pharmaceutical, biotechnological and biomedical industry. The said districts are conceived as a new local governance tool for research activities, aiming at fostering the "connecting system" already existing in the region (scientific and technological parks, company incubators, services for the technological transfer).
At the beginning of 2011, the Region also approved the setting up of 12 innovation hubs, including that of Life Sciences. These hubs will function as specialized intermediates in the fields of research and scientific and technological knowledge in order to encourage technology transfer and innovation in the regional production system.
The innovation hubs should be included within the technological districts, also by participating in the setting up phase.

The financial support to academic research from the *Fondazione Monte dei Paschi di Siena* also appears to be of relevance: more than 3 million Euros in 2010 were allocated to research grants and projects submitted by Tuscan universities with special focus on the healthcare field.
The Foundation operates in the biotechnology sector through its special purpose entity BioFund S.p.A., a seed capital company supporting start-up companies operating in the biotechnology and Life Sciences field.

Furthermore, the *Fondazione* provides an important support to Toscana Life Sciences, the scientific and technological hub which is being developed in Siena, with the participation of all regional research institutions. Toscana Life Sciences, through the *Ufficio per la Valorizzazione della Ricerca biomedica e farmaceutica* (UVaR), supports the technology transfer of results to companies, as well as the exploitation of the intellectual property held by universities and public research centers, through activities aimed at the setting up of an innovative and competitive cluster.

Tuscany

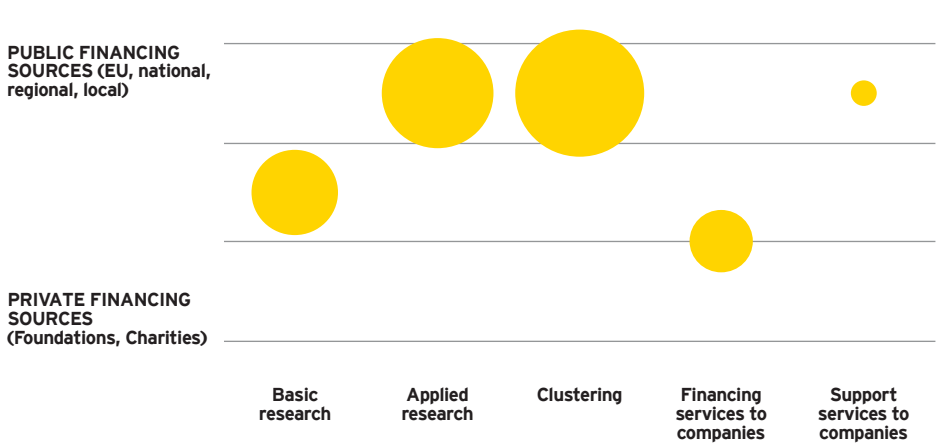
Leverage the pharmaceutical industry structure

- *public-private mixed financing model (Region, European Union, local bodies, together with Banking Foundations)*
- *focus on supporting companies (spillover and clustering)*
- *specific biotechnology-oriented interventions*

Moreover, *Fondazione Monte dei Paschi di Siena* is a member of *Toscana Innovazione*, a fund for highly technological and great innovation value projects, participated also by *Regione Toscana* and other banking foundations operating locally.
With regards to company's supporting services, including the Catalogue of advanced and qualified services for Tuscan SMEs, the Region has set up an aid system addressed to both individual and associated companies.

Figure 3

Incentives for innovation, Tuscany: CrESIT matrix (Source: CrESIT - 2011)



This system provides a valid support for innovative intangible investments and, in particular, those finalized to the acquisition of services sustaining innovation to improve their management, productive, technological and organizational structuring.

The examples provided for each area of intervention allow a definition of the "Tuscan model" as a system capable of implementing actions to support the setting up and development of the biotech field. The focus of interventions on Life Sciences is mainly due to the major role of the pharmaceutical sector within the Tuscan industrial structure. Among the types of intervention adopted, the prevailing actions seem to be those supporting companies (technology transfer, clustering/networking).
This is another model of public-private mixed financing (in particular, regional and EU funds together with banking foundations).

Sardinia

Sardinia has benefitted from extensive EU funds allocated by ERDF (European Regional Development Fund), ESF (European Social Fund) and FAS (Underdeveloped Areas Fund).
The macro objectives of the regional policies are strictly related to the strategic guidelines for the cohesion policy identified by the European Commission: to increase the Sardinian capability of attracting investments and companies and to encourage research, innovation and entrepreneurial expertise.
One of the main investments implemented by *Regione Autonoma della Sardegna* - probably the most important in the biotech field - involves the Framework Program Agreement "*Società dell'informazione ICT per l'eccellenza dei territori*", which was signed by the Ministry of Economy and Finance and the Region.
Within this Agreement, the Region has performed a number of actions focused on the *Distretto Tecnologico Biomedicina* (Pula) and on the *Cluster Biotecnologie Applicate* (Alghero).
By means of these initiatives, the regional policy intends to develop scientific and technological areas of excellence with distinctive and consolidated expertise, with particular reference to the following areas: biomedicine and human health technology; biotechnology and nanobiotechnology; information and communication; energy and environment.

Therefore, the Region has identified two reference areas in which to invest and towards which address a number of specific calls for proposals:

- Polaris, the Science and Technology Park of Sardinia, which currently hosts companies and research units operating in the value chain of ICT, bioinformatics, renewable energies, biotechnology applied to pharmacology and genetics.
- Porto Conte Ricerche, operating in the field of applied biotechnology, hosting entrepreneurial, research and services activities related to the agro-food chain, zootechnics and environmental protection.

Within this Agreement, the Region (through *Sardegna Ricerche*, a publicly held company assisting the regional administration in the management of research, innovation and technological development policies as well as of Polaris) has promoted a number of specific actions in favor of clustering during the last few years: examples of this are the calls for proposals made for attracting high-tech companies from outside the region to the two above-identified reference areas.
Among the biotech-specific interventions, the *Regione Autonoma della Sardegna*, issued a recent call for proposals (December 2010) allocating 3 million Euros for projects of interregional scientific and technological cooperation involving Sardinia and Lombardy. The objective of this call for proposals was to encourage the cooperation and exchange of knowledge in the field of biotechnology and ICT.
In synergy, the PHASE 1 initiative carries out technical and scientific analyses, the market analysis on new potential diagnostic and therapeutic agents and offers high-quality services finalized to the attraction of clinical trials.
Therefore, PHASE 1 is a bridge and facilitator between projects developed by start-ups and the market, with an attraction effect of highly added-value activities.

The "Sardinian model" is focused on the attraction of investments and companies, with much attention being paid to the biotech sector. This model is consistent with the need of building an industrial structure operating in innovative areas. This explains both the reduced focus on research (the investments in which produce very long-term returns) and the strong institutional support to the setting up of systems and facilities capable of hosting companies, both from inside and outside the region. The objective of attracting investments to the two Park headquarters from outside the region has been pursued non only by using incentives to localization (both for new and existing companies), but also by setting up several "state of the art" technological platforms in certain specialized sectors, including bioinformatics, genotyping and massive sequencing. The financing sources of these actions are mainly public: firstly, but also national and regional.
It is hardly possible to comment on the efficacy of these interventions since they are all of recent implementation and their structural nature is such that results will only be evident in the medium-long term.

Conclusions: which regional innovation models?

In attempting to systematize the regional incentives for innovation allocated to the biotech sector, a clear identification of the various lines of intervention is inevitably arduous since actions are often funded by regional, national and supranational funds. Although this overlapping makes it difficult to judge whether the numerous existing interventions are efficacious, it is nonetheless possible to assess the overall effect of these interventions and their possible convergence towards some areas.

The mapping of the system of incentives for innovation herewith proposed has the objective of defining the possible existence of action strategies on a regional level. These include both actions aimed at developing synergies between interventions implemented on the different levels (local, regional, national, supranational), and at favoring some areas of intervention as compared to others.

From this point of view, it is possible to state, on first approximation, that:

- In Lombardy interventions are mainly focused on supporting research (in particular basic research) and innovative entrepreneurial realities. The strategy seems to be that of supporting the development of existing innovative companies, while at the same time creating the conditions for the setting up of new ones.
- In Piedmont efforts concentrate on the renewal of the industrial fabric through the development of highly innovative local systems, including biotechnology and energy and environmental technologies.
- In Tuscany actions seem to converge on supporting its traditional pharmaceutical industry, aiming at implementing new innovation cycles through the setting up of spin-offs and industrial and research partnerships.
- Sardinia appears to be focused on attracting investments from outside, in specific purpose-built areas, by allocating incentives to localization for both new and existing companies.
- In general, the regions do not show a targeted strategy for specifically supporting the biotech field.
  Apart from single initiatives, the actions implemented on a regional level are addressed to supporting innovation in general. Of the four regions we analyzed, only Tuscany and Sardinia are strongly focused on biotech, even though some interesting and important biotech-specific initiatives have been effected also in the other two (i.e., *Polo bioPmed* in Piedmont).

In sum, it can be said that the initiatives enforced by local bodies - which can apply to different areas, as discussed in this report - are crucial in fuelling the development potential of innovation and the growth of the Italian biotech field in particular. Clearly, in order to be efficacious, these actions must be part of a wider strategy within the national system. In this respect, and with regards to the linking of the various locally implemented initiatives, there remains much room for improvement.

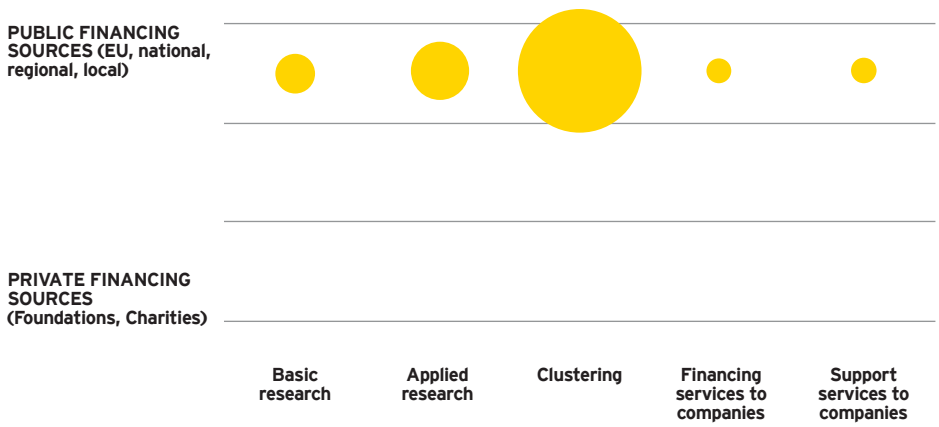
Sardinia

Attracting investments

- *focus on clustering interventions*
- *public financing sources, mainly European Union*

Figure 4

Incentives for innovation, Sardinia: CrESIT matrix (Source: CrESIT - 2011)



International Benchmarking

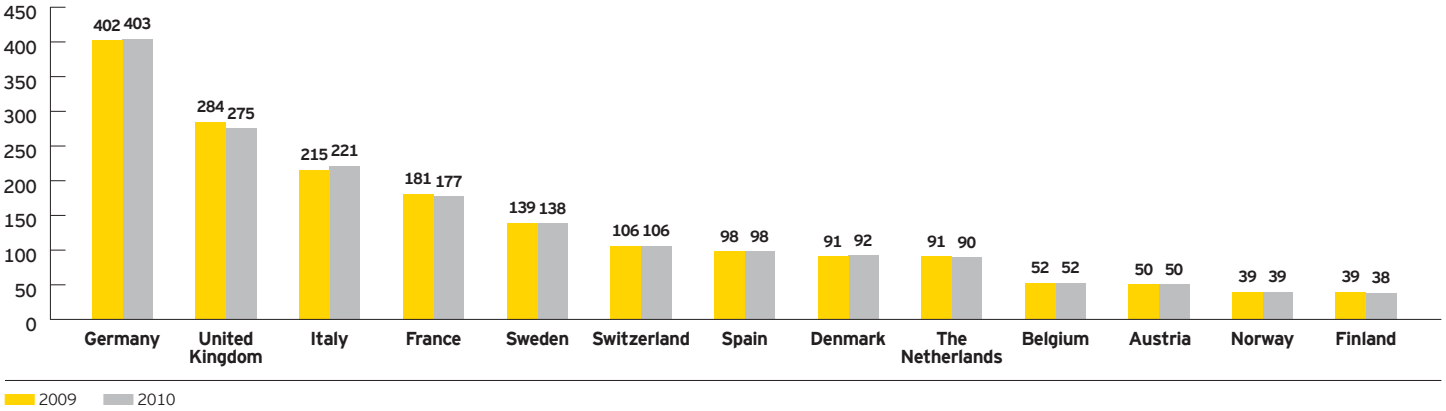
Although the limited availability of financial resources is still one of the most critical issues for the development of the Italian biotech field, Italy is the European country with the highest growth in terms of number of companies, and where companies have succeeded in responding to the international financial crisis in the most effective way. This is a clear indicator that Italian biotech companies are capable of operating with extreme flexibility and efficiency, ensuring a higher return on investments than their European competitors.

After analyzing and describing in this Report the main characteristics of the Italian biotech field, the Italian situation should now be compared to that of the major European countries, in order to ascertain where the strengths lay and which are the areas for improvement so that Italy may become one of the leading countries in the biotech field in Europe. Moreover, since gathering funds is one of the most critical issues for growth, development and success of biotech companies, it was decided to draw the international benchmark on this issue. This benchmark was possible thanks only to the collection of data from the different countries made by the Ernst & Young Global Biotechnology Center, who edits the "Beyond Borders" Report every year in order to 'photograph' the European state of the art in this field. The common factor which allows comparing data reported in the "Italian Biotechnology Report" to "Beyond Borders" data is the Ernst & Young definition of "biotech company".

As discussed in Chapter 2, in Italy there are 221 pure biotech companies; this makes Italy the third European nation in terms of number of dedicated companies, after Germany (403) and the United Kingdom (275).
Very interestingly, Italy is the country reporting the highest growth (+2,8% as compared to the 2010 Report) in terms

Figure 9.1

Number of pure biotech companies in the main European countries (Source: Ernst & Young)



of number of companies in the last year. This situation shows that the Italian companies have succeeded in responding to the financial crisis in the most effective way. The country which has suffered the negative impact of the international economy the most was the United Kingdom, reporting a 3.2% decrease as compared to the year 2009 (Figure 9.1).

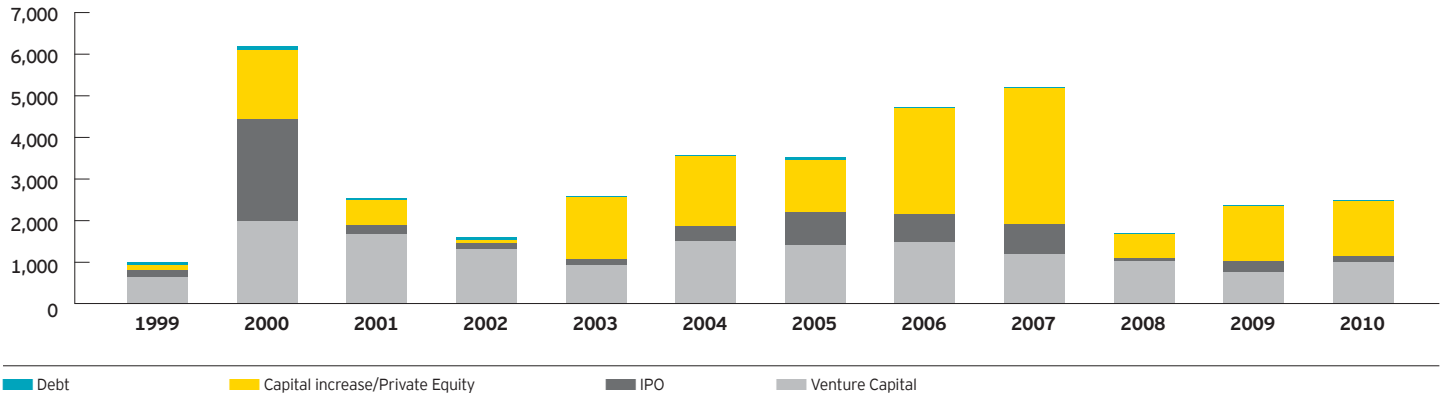
Chapter 8 showed that the main non-institutional sources of financing that are used, or will be used, by biotech companies are Venture Capital funding, strategic alliances and IPO. Before analyzing these financial sources in detail, it is appropriate to examine the trend of funds obtained by biotech companies during the last eleven years on a European level.

Figure 9.2 shows that the 2008 economic crisis caused a dramatic decline in the overall funds allocated to biotech companies.
However, a positive element in this field is the trend of the last two years: indeed, during this period the amount of funds has grown constantly and this allows the assumption that in the near future the situation will return to the pre-crisis scenario.
In 2010, on a European level, € 2,532 million were raised: of these, the highest share came from Private Equity (52%), Venture Capital (40%) and IPO (7%) capital increases, as well as from bank debt (1%).

The trend of funds gathered by Italian companies is more stable compared to that of Europe (Figure 9.3). In both cases,

Figure 9.2

Capital raised by European pure biotech companies per type of financing source. (Values in million of Euros) (Source: Ernst & Young)



2010 saw an increase compared to funds collected in 2009. With regards to Italian companies VC, IPO funds and Private Equity capital increases grew by 27% in 2010, reaching € 72 million.

Considering VC capital, Italy ranks tenth among the countries analyzed in the benchmark, with a total € 12.2 million. This represents a slump compared to 2010: in fact, last year Italy ranked fifth in terms of VC capital, with € 51.8 million. This decrease concerns not only the Italian biotech market, but the Italian venture capital field in general. Indeed, the first semester of 2010 was defined by experts (AIFI) as the "black" semester. However, according to the same experts, this period will be limited in time and there will soon be a recovery due to the trust and interest which the biotech market is fueling again.

On a European level, the VC investment trend differs between the various countries. The country with a higher market cap increase is France, who goes from € 40 s to € 140 million (Figure 9.4). In 2010, the countries that raised the highest amounts of Venture Capital were the United Kingdom (€ 281 million), Germany (€ 273 million) and France (€ 140 million).

The analysis of the average VC funds by single company shows that the country with the highest average is Germany, followed by Switzerland and the United Kingdom. In this specific classification, Italy ranks eighth, two positions higher than in the general classification.
As described in Chapter 8, the experts foresee a growth in strategic alliances involving pure biotech companies over the next two years.

This trend is already confirmed by the 2010 data, when the growth of these alliances accounted for 22% compared to 2009, reaching almost € 10 billion.

Figure 9.3

Capital raised by Italian pure biotech companies, per financing source. (Values in million of Euros) (Source: Ernst & Young)

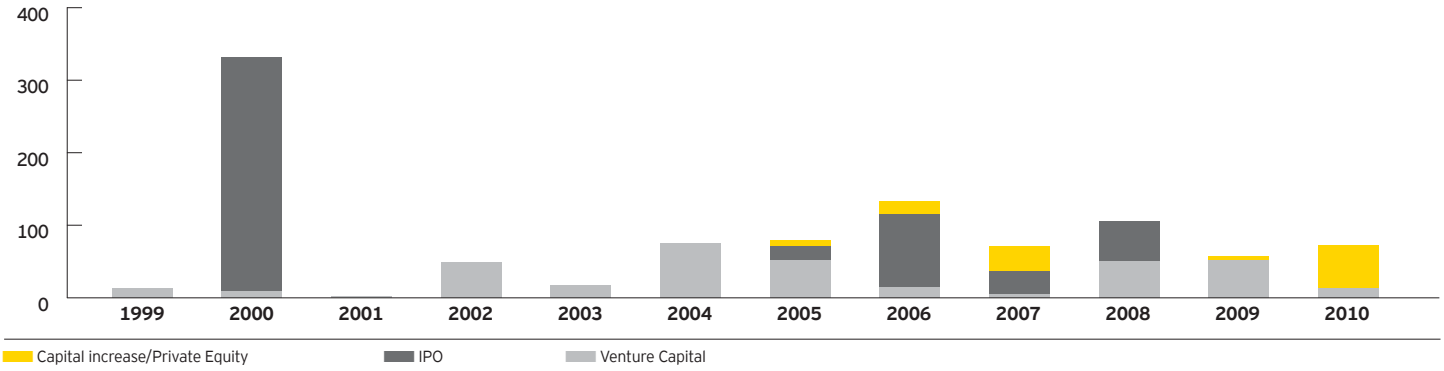
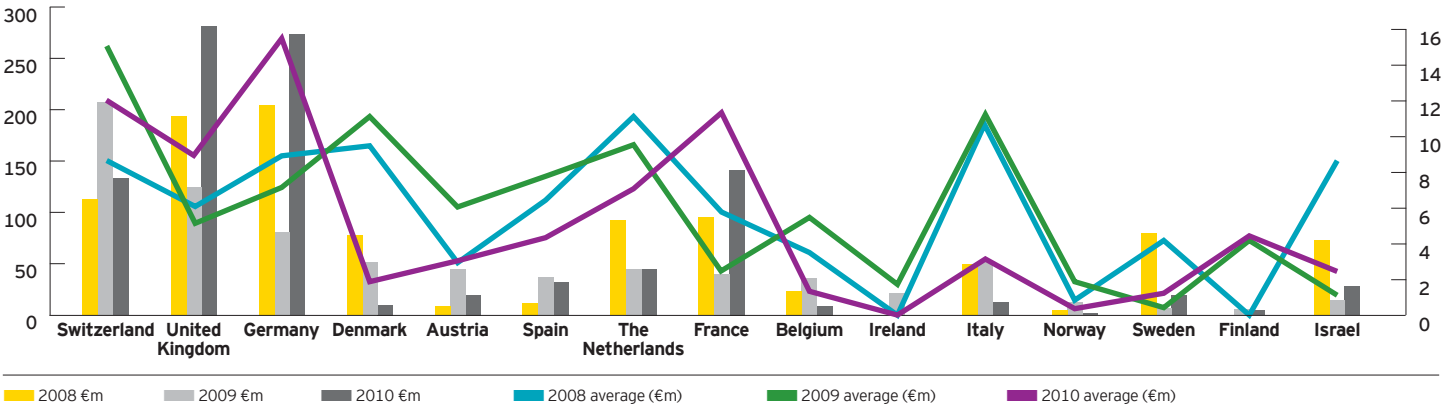


Figure 9.4

Capital raised through VC financing by pure biotech companies in the main European countries. On the left scale (bar chart) are reported VC total transactions, on the right scale (trend line) the average values of the single transactions. (Values in million of Euros) (Source: Ernst & Young)



Of the total financial resources made available by these alliances, 79% originate from the deals between pharmaceutical and biotech companies; the remaining 21% from biotech-biotech alliances (17%), or alliances between companies operating in other businesses and biotech companies (4%).

It is noteworthy that during the last year there has been a considerable increase in the contribution of alliances between pure biotech companies to the total share of alliances: this has more than doubled, going from 8% in 2009 to 17% in 2010 (Figure 9.5).
This figure shows that pure biotech companies are becoming consolidated realities, both from a financial and an organizational point of view.

Table 9.1 lists the major alliance agreements concerning the Italian pure biotech companies, with a brief description of the subject and objective of each deal.

As highlighted in Chapter 2, the experts in the field were asked their opinion on the future of biotech companies.
On a European level, the most common strategies implemented by pure biotech companies in order to expand and to confirm their presence on the market included seeking for alternative sources of capital, new alliances opportunities and possible synergies with other biotech companies.

In fact, more than 60% of the sample has indicated as 'likely' the implementation of these three strategies within the next two years (Figure 9.6). Conversely, the actions that according to the experts will not be implemented are reducing items in the development product pipeline and layoffs.

These responses are very important since they confirm the optimism generated by biotech sector; meantime they are the best proof of how the biotech field will continue to be characterized by a growing trend and by an increasingly rich pipeline in the next few years, both on an Italian and European level.

Lastly, the M&A option also deserves to be mentioned since, as described in Chapter 8, it is considered by the majority of the companies interviewed as the most likely exit strategy.

Figure 9.5

Potential value of alliances in the biotech industry in Europe. (Values in million of Euros) (Source: Ernst & Young)

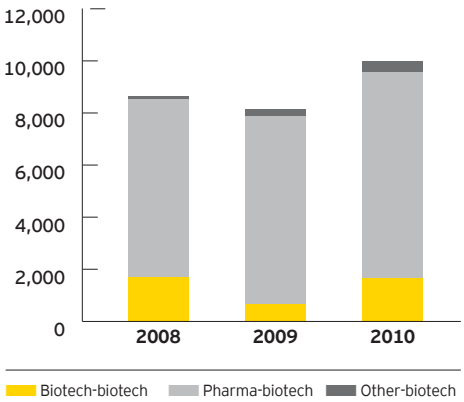


Figure 9.6

European pure biotech companies: analysis of future strategies (Source: Ernst & Young)

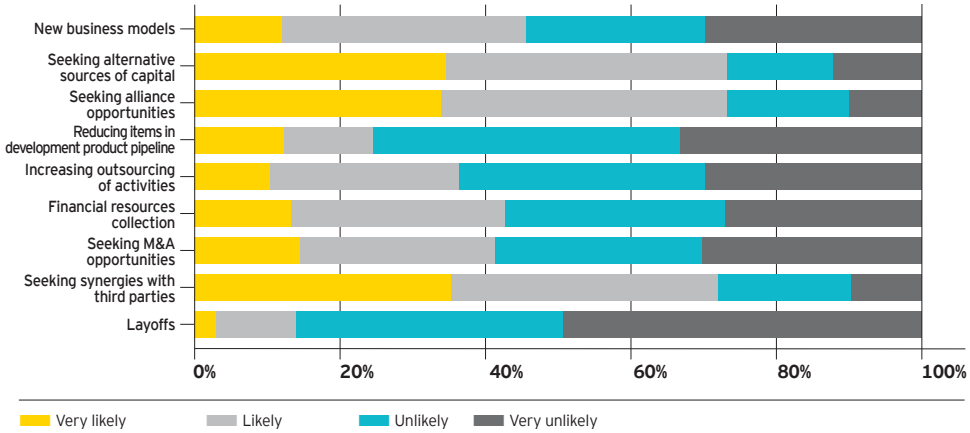


Table 9.1

Selected biotech alliances in Italy (Source: Ernst & Young)

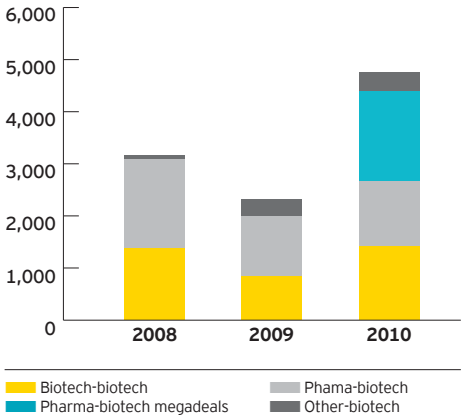
Company 1		Company 2		Subject
Name	Country	Name	Country	
Lonza Group	CH	Axxam	IT	Lonza Group, Ltd., a Swiss manufacturer of pharmaceutical ingredients and active principles signed a licensing agreement with Axxam S.p.A. according to which Lonza will use photoproteins developed by Axxam as biosensors.
Philogen	IT	Bayer	DE	Philogen S.p.A. purchased a production site located in Siena from Bayer AG.
Silicon Biosystems	IT	Cultek	ES	Silicon Biosystems S.p.A. appointed Cultek S.L.U. as its exclusive distributor for the Life Science research market in Spain and Portugal.
Silicon Biosystems	IT	Dync	NL	Silicon Biosystems S.p.A. has appointed Dync BV as its exclusive distributor for the Life Science research market in Benelux and Germany.
Silicon Biosystems	IT	Excilone	FR	Silicon Biosystems S.p.A. has appointed Excilone as its exclusive distributor for the Life Science research market in France.
Silicon Biosystems	IT	RAMCON	SE	Silicon Biosystems S.p.A. has appointed RAMCON A/S as its exclusive distributor for the Life Science research market in Denmark, Sweden, Norway and Finland.
Fast Forward	USA	Axxam	IT	Fast Forward, LLC and the Juvenile Diabetes Research Foundation (JDRF) entered into a collaborative partnership with Axxam S.p.A. to develop new treatments for two atomimmune diseases, multiple sclerosis (MS) and type 1 diabetes (T1D).
Axxam	IT	Xention	UK	Axxam S.p.A. signed a new research agreement with Xention Ltd. for the discovery of new drugs for the treatment of autoimmune diseases.
Axxam	IT	Polyphor	CH	Axxam S.p.A. and Polyphor Ltd. signed a research agreement for the discovery and development of drug candidates for the treatment of pain, inflammatory and metabolic diseases.
Siena Biotech	IT	Experimental Therapeutics Centre of Singapore	SG	Singapore Immunology Network (SIgN) and Experimental Therapeutics Centre (ETC) will cooperate with Siena Biotech S.p.A. in the development, respectively, of a drug and an antibody for the treatment of patients with cancer or bone disease.
Promega	USA	TOP	IT	Promega Corporation and TOP S.r.l have combined their industry leading technologies to develop an extremely sensitive biomarker to be used in preclinical research cancer studies.
Aptuit	USA	Siena Biotech	IT	US pharmaceutical services company Aptuit has entered into a partnership with Siena Biotech, based on which Aptuit will become a provider of choice for Siena Biotech's pipeline of compounds, focused on three key therapeutic areas, including Alzheimer's disease, Huntington's disease and oncology.
Glenmark Pharmaceuticals	CH	Lay Line Genomics	IT	Glenmark Pharmaceuticals SA (GPSA), a wholly owned subsidiary of Glenmark Pharmaceuticals India (GPL) has been granted by Lay Line Genomics, Italy (LLG) an exclusive, worldwide license to LLG's entire intellectual property portfolio in the TrkA field. The licensed assets include BXL1H5 which is a novel monoclonal antibody for the treatment of pain.

M&A activities have suffered very much from the 2008 financial crisis, but during the last three years there has been a recovery both in terms of number of deals and their value.
During last year there has been a steep increase in the value of transactions: from € 2,313 million in 2009 to € 4,786 million, with an increase of over 100% (Figure 9.7).

Moreover, after two years during which no M&A megadeal was signed, i.e., a deal for an equivalent value of more than one billion Euros, an important transaction was carried out in 2010: the U.S. health-care products giant Johnson & Johnson (J&J) acquired the Dutch biotech company Crucell for the equivalent of € 1,750 million.
Besides the financial importance of the acquisition, this is of notable significance for the pharmaceutical companies operating in the biotech field; these companies do consider biotechnology as a natural evolution of their traditional pharmaceutical business, in the perspective of widening their market in specific therapeutic areas (e.g., vaccines, as in the case of J&J).

Figure 9.7

Potential value of M&A transactions in the biotech industry. (Values in million of Euros)
(Source: Ernst & Young)



Methodology

In the 2011 edition of the Italian Biotechnology Report, the definition provided for "biotech companies" is the same as in the 2010 Report, consistently with the Ernst & Young methodology. According to this definition, biotech companies are "companies that use modern biological techniques to develop products or services for human and animal health, agricultural productivity, food processing, renewable resources, industrial manufacturing or environmental management". The companies which perform these activities as their core business are classified in this report as "pure biotech" companies.

The choice of entrusting Ernst & Young with the preparation of this report once again this year was crucial for widening the perspective of our analysis: the comparison of the data from the new questionnaire and those of 2010 allowed to determine the current trends of the biotech market.
Therefore, it is necessary to clarify which data the two reports refer to: the 2010 Report referred to data concerning 2009, but in terms of turnover it included data from the 2008 financial year; consequently the 2011 Report refers to the year 2010 in terms of general information and to 2009 for turnover data.

The main sources of information were the questionnaire sent by Assobiotec to the companies operating in this field, the available balance sheets, corporate internet sites and, with regard to benchmarking, the analysis of the international Ernst & Young database on biotech companies.
In particular the questionnaire allowed gathering the following information:

- company's details
- biotech activities specifically performed (red, green, white, GPET, nanobiotechnology)
- company's origin (start-up, spin-off, etc.)
- company location (independent headquarters, science park, incubator, etc.)
- external partnerships
- international business dimension
- main financing sources (VC/PE, IPO, grants, etc.)
- potential exit strategies identified
- market of interest for a possible listing
- intellectual property assets
- economic and financial situation
- future trends and developments, with regard to the market and the company.

The increased focus on the section related to the international financial benchmark clearly gives great added-value to this Report, as compared to the previous one. This year, in order to include a higher number of items for comparison between biotech companies operating on the European level, some changes were made to the questionnaire sent to Italian companies. The scope of the questionnaire was widened in order to make it as in line as possible with that of Ernst & Young's European Life Science Center.

The targeted companies initially used as a sample for this analysis were 550 (Figure 10.1). After a first selection, due to the unavailability of specific information requirements, including reports on the activities performed, the final sample was reduced to 375 companies, which are listed at the end of this Report. For those companies that have not replied to the questionnaire, the data (wherever possible) were collected through the analysis of the 2009 balance sheets and the information available on the corporate internet sites.

Compared to the previous year, the number of censused companies was increased by 14%: from 319 to 375.
Of the 56 new companies, 6 were set up during last year. The remaining 50 companies were already operating in this field, but they were identified this year thanks to a deeper analysis of the biotech market through balance sheets and internet sites.

Specific solutions were adopted to adjust for the differences in the analyzed sample, which made it possible to compare the new data with those of the 2010 Report. A special care was taken to distinguish the impact of the 6 new companies on turnover, investment and employee data from that of the 56 companies which were not included in the sample of the 2010 Report. In order to do this, the 2010 Report data was analyzed again to include these 50 companies, making it possible to

observe the dynamics of this field without facing any analytical distortions due to an incomplete sample.

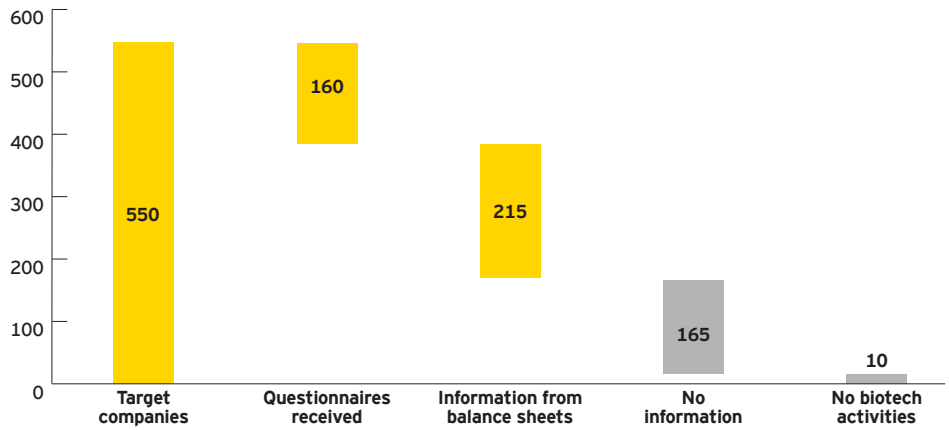
Consistently with the OECD methodology (Organization for Economic Co-operation and Development), as well as the companies defined by Ernst & Young as "pure biotech" companies, other companies whose core business goes beyond biotech activities were also analyzed, including Italian pharmaceutical companies and the Italian subsidiaries of foreign multinational companies.
In fact, according to the OECD methodology, "a biotech company can be defined as such, if it uses at least one biotechnological technique in order to produce goods and services or to perform R&D activities in the biotech field. Some of these companies can be quite large with only a small part of their economical activities dedicated to biotech".

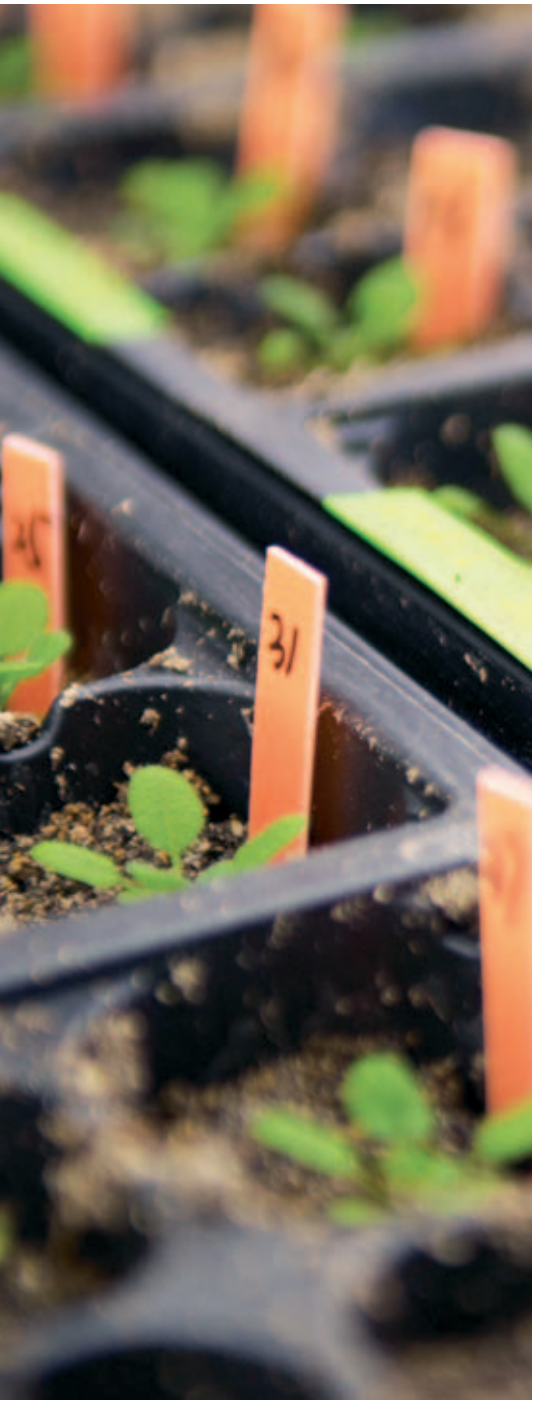
By combining the Ernst & Young and the OECD definitions, the companies operating in the biotech field were divided into two main categories:
- Pure biotech
- Other biotech

In the following analyses, consistently with the previous Report, the companies were segmented into the following categories, according to their field of application:
- Red biotech companies
- Green biotech companies
- White biotech companies

Figure 10.1

Results from data collection: target companies and analyzed companies





- Genomics, Proteomics and Enabling Technologies (GPET)
- Multi-core companies: companies operating in two or more of the above fields.

Moreover, the red biotech field, which deals with human healthcare, was further divided into two categories, based on capital origin:
- Italian-capital companies
- Foreign-capital companies

The Italian-capital companies were further divided into 3 types:
- Italian pure biotech companies
- Italian pharmaceutical companies: pharmaceutical companies with capital in Italy
- Other Italian biotech companies: consortium companies, Contract Research Organizations (CRO) and other companies with marginal activities in the biotech field.

Furthermore, in keeping with the Ernst & Young methodology applied to "Beyond borders: global biotechnology report 2010", the red biotech companies' activities were segmented according to following categories:
- Therapeutics: development of drugs and other therapeutic approaches, such as gene- or cell-based therapies, including:
  - biologicals: medicinal products based on nucleic acid technology and cell therapy
  - small molecules: pharmaceutical products which are developed, tested or discovered by means of screening methods based on biotechnology;
- Tissue engineering: biological substitutes for reconstruction or replacement of tissue and organs, obtained by using stem cells, new biomaterials and growth factors
- Vaccines for prophylaxis and treatment
- Drug delivery technologies used as a vehicle for drugs to reach a specific site by optimizing their absorption and distribution (advanced materials, liposomes, antibodies, cell therapy, etc.)
- Molecular diagnostics: DNA/RNA-based tests and methods for the diagnosis, prognosis and identification of any predispositions to specific diseases and for the analysis of pathogenic mechanisms
- Drug discovery: synthesis, optimization and characterization of drug candidates, assay development and screening and validation activities on medicinal products.

With respect to the other application fields, the companies included were segmented according to the following definitions:
- Industrial biotechnology (white biotech): use of modern biotechnology methods for the processing and manufacturing of chemicals, materials and fuels, including bioremediation technology for environmental protection
- Agro-food biotechnology (green biotech): use of modern biotechnology methods for the production of transgenic plants with applications in the food, chemical, material, molecular pharming (production of drugs in plants), testing for the presence of ingredients or contaminants in food
- Genomics, Proteomics and Enabling Technologies (GPET): all genomics (investigation of the structure and function of genes) and proteomics (analysis of protein regulation, expression, structure, post-translational modification, interactions and function) activities; bioinformatics, biochips, and other bio-related tools; biopharmaceutical

productions, molecular basic research, and further enabling technologies.

As in the 2010 Report, the nanobiotechnology cluster was analyzed separately, given its transverse interest in terms of development potential. As a result, it was possible to identify those companies which operate in the nanobiotechnology field in a dedicated way ("core nanobio" definition), or that have at least a research area in this field ("also nanobio" definition). The homogeneity with respect to the methodology adopted by the Ernst & Young Global Biotechnology Center guarantees consistency of the data for the international benchmarking analysis, regarding the pure biotech companies.

Moreover, following the appreciation shown for the 2010 Report, it was decided to pay special attention to some case histories that represent either positive or negative entrepreneurial experiences. This was done in the hope that linking some of the critical issues presented in this report to specific company contexts could encourage sharing of best practices, i.e., the adoption of solutions already tested by other companies, with the objective of helping new potential entrepreneurs in choosing the best possible strategy to successfully address the biotechnology challenge.
This is why we have presented the case of Eli Lilly, who made one of the highest investments by a pharmaceutical company in the last ten years, and the case of the Edmund Mach Foundation - Istituto Agrario di San Michele all'Adige which is currently the first and only model in Italy where research, training, experimental and consultancy activities in the field of agro-food and environment are carried out.

Table 10.1

Definition of biotech categories

Category	Definition
Pure biotech	Companies whose core business activities are exclusively related to biotechnology
Other biotech	Companies using at least one biotech technique in order to produce goods and services for research in the biotech field, without this being the company's core business
Red biotech	Companies operating in the field of biotechnology applied to human health
Green biotech	Companies operating in the agro-biotechnology field
White biotech	Companies applying biotech methods in the field of industrial processes and environmental protection
GPET	Companies operating in at least one of the following areas: genomics, proteomics and enabling technologies
Multi-core	Companies operating in at least two of the four biotech application fields

Table 10.2

Abbreviations

FP7	Seventh Framework Program
AIFA	Italian Medicines Agency
AIFI	Italian Association for Private Equity and Venture Capital
CrESIT	Research Centre for Innovation and Life Sciences Management
CRO	Contract Research Organisation
EY	Ernst & Young
EMA	European Medicines Agency
FDA	Food and Drug Administration
GPET	Genomics, Proteomics and Enabling Technologies
ICE	Italian Institute for Foreign Trade
IPO	Initial Public Offering
IRCCS	Scientific Institute for Research, Hospitalization and Health Care
M&A	Merger and Acquisition
MISE	Ministry for Economic Development
MIUR	Ministry of Education, University and Research
NIH	National Institutes of Health
OECD	Organization for Economic Co-operation and Development
PE	Private Equity
STP	Scientific and Technological Park
VC	Venture Capital

Appendix

Companies with biotech R&D activities

- A.T. Grade
- Advanced Analytical Technologies
- Ab Analitica
- Abaco Biotech
- Abbott
- Abiogen Pharma
- Accelera
- Actelion Pharmaceuticals Italia
- Actimex
- Actygea
- Adienne
- Adriacell
- Advanced Biotech Italia
- Aequotech
- Aethia
- Agrifield Biotech
- Agrifutur
- Agritest
- Agroindustry Advanced Techonologies
- Agrolabo
- Alchemia Italia
- Alexion Pharma Italy
- Alfa Biotech
- Alfa Wassermann
- Algares
- Allergan
- Allergy Therapeutics Italia
- Alltox
- Alphagenics Diaco Biotechnologies
- Also Biotech
- Altergon Italia
- Ambiotec
- Ambrosia Lab
- Amgen Dompé
- Analisi & Controlli
- Anallergo
- Ananas Nanotech
- Angelini
- Apavadis Biotechnologies
- Aptuit
- ApuliaBiotech
- Archimede R&D
- Areta International
- Arintha Biotech
- Arterra Bioscience
- Astellas Pharma
- Astra Diagnostici
- AstraZeneca
- Avantgarde
- Axxam
- B. & C. Biotech
- Basell Poliolefine Italia
- Baxter World Trade Italy
- Bayer Cropscience
- Bayer
- Bba Biotech
- Bcs Biotech
- Bgt Italia Biogenomic Technology
- Bict
- Bint
- Bio Flag
- Bio Hi-Tech
- Bio3 Research
- Bioaesis
- Bioagro
- Bioanalisi Trentina
- Biocell Center
- Bioci
- Biodec
- Biodigitalvalley
- Biodiversity
- Bioduct
- Bioecopest
- Biofarmitalia
- Biofin Laboratories
- Biogenera
- Bio-Ker
- Biolife Italiana
- Bioman
- Biomarin Europe
- Biomat
- Biomatica
- Biomedical Research
- Biomedical Tissues
- Bionat
- Bionoor Research
- Bionucleon
- Biopaint
- Bioprogress Biotech
- Bio-Rad Laboratories
- Biorep
- Biosearch Ambiente
- Biosensor
- Biosilab
- Biosistema
- Biospa
- Biosphere
- Biostrands
- Biosuma
- Biosynt
- Biotecgen
- Biotecgenetics
- Biotech 4
- Bioteck
- Biotest Italia
- Biotrack
- Biouniversa
- Biounivet
- Bluegreen Biotech
- Blueprint Biotech
- Bmr Genomics
- Boehringer Ingelheim Italia
- Bouty Healthcare
- Bracco Imaging
- Bristol Myers Squibb
- Bsa Ambiente
- C4t
- Cbm
- Ccs Aosta
- Ceinge Biotecnologie Avanzate
- Celgene
- Centro Biotecnologie Avanzate
- Cephalon
- Charles River
- Chemtex Italia
- Chiesi Farmaceutici
- Chorisis
- Clonit
- Cogep
- Comlube
- Congenia
- Consorzio Nbs Biotech
- Consorzio per le Ricerche e lo Sviluppo delle Biotecnologie Biotecne
- Cosmo Pharmaceuticals
- Costantino E C.
- Cpc Biotech
- Creabilis Therapeutics
- Crs4
- Crucell Italy
- Ctg Pharma
- Cutech
- Cyanagen
- Cyanine Technologies
- Cyathus Exquirere Italia
- Dac
- Dalton Biotecnologie
- Degene
- Delos Bioinformatica
- Delos Ricerche
- Derming
- DiaSorin
- Diatech
- Diatheva
- Diesse Diagnostica Senese
- Dinamycode
- Dompé Biogen
- Dompé
- Dompé Pharma
- Ecobioservices and Research
- Ecoil
- Ecotechsystems
- Edx Diagnostics
- Eli Lilly Italia
- Eos
- Ephoran Multi Imaging Solutions
- Erydel
- Espikem
- Eurand
- Euroclone
- Eurosen
- Eurospital
- Exenia Group
- Experteam
- Explera
- Explora
- Externautics
- Farcos
- Fase 1
- Fastest
- Fatro
- Fedra Lab
- Fidia Advanced Biopolymers
- Finceramica Faenza
- Foldless
- Fotosintetica & Microbiologica
- G&Life
- Galileo Oncologics
- Geistlich Biomaterials Italia
- Genalta
- Genedia
- GeneMoRe Italy
- Genespin
- Geneticlab
- Genovax
- Gentium
- Genzyme
- Geymonat Biotech
- Gilead Sciences Italia
- Gio.Eco
- GlaxoSmithKline
- Glyconova
- Gnosis
- Green Lab
- Grifols Italia
- Hmgbiotech
- Ho.P.E.
- Holostem Terapie Avanzate
- Hpf Nutraceutics
- Idrabel Italia
- Iga Technology Services
- Igea
- Inbios
- Incura
- Indena
- Innovate Biotechnology
- Intercept Italia
- International Plant Analysis and Diagnostics
- Intoresearch
- Iom Ricerca
- Ipsen
- Isagro
- Isogem
- Istituto di Ricerche Biomediche Antoine Marxer Rbm
- Istituto di Ricerche Biotecnologiche
- Istituto di Ricerche di Biologia Molecolare P. Angeletti
- Istituto Ganassini
- Italfarmaco
- Ista Veneto Sementi
- Janssen-Cilag
- Kedrion
- Kemotech
- Kos Genetic
- Kron Morelli
- Ktedogen
- L.E.A. Biotech
- Labogen
- Lea Nanotech
- Leaf Bioscience
- Life Line Lab
- Lipinutragen
- Lofarma
- Magistravini
- Mastelli
- Mavi Sud
- Medestea Research & Production
- Mediapharma
- Mediteknology
- Menarini Biotech
- Merck Serono
- Meristema
- Metagenics
- Metapontum Agrobios
- Micro Biological Survey
- Micron Research Service
- Millipore
- Miltenyi Biotec
- Molecular Biotechnology
- Molecular Stamping
- MolMed
- Molteni Therapeutics
- Mybatec
- N.T.I.
- Nano4bio
- Nanomaterials
- Nanovector
- Narvalus
- Natimab Therapeutics

- Naxospharma
- Nbs Biotech Scarl
- Need Pharma
- Nerviano Medical Sciences
- Neuroscienze Pharmaness
- Neuro-Zone
- Newron Pharmaceuticals
- Nexthera
- Ngb Genetics
- Nicox Research Institute
- Nikem Research
- Nobil Bio Ricerche
- Noray Bioinformatics
- Notopharm
- Novagit
- Novamont
- Novartis
- Novartis Vaccines and Diagnostics
- Novo Nordisk Farmaceutici
- Nurex
- Nutraceutica
- Nutrigene
- Nutrisearch
- Nycomed Italia
- Officina Biotecnologica
- Okairos
- P.A.N. Piante Acqua Natura
- Pfizer Italia
- Pharmeste
- Philogen
- Phytoengineering Italia
- Phytoremedial
- Pincell
- Plantechno
- Plasmore
- Poli Industria Chimica
- Polimekon
- Prigen
- Primm
- Probiotical
- Procelltech
- Progefarm
- Proteogen Bio
- Proteotech
- Protera
- Re.D.D.
- Recordati Industria Chimica e Farmaceutica
- Relivia
- Research and Innovation
- Roche
- Rotalactis
- Rottapharm Biotec
- S B Technology
- Sacace Biotecnologies
- Safan Bioninformatics
- Salentec
- Sanofi-Aventis
- Sekmed
- Servier Italia
- Setlance
- Shardna
- Shire Human Genetic Therapies
- Shire
- Siena Biotech
- Sienabiografix
- Sienagen
- Sifi
- Sigea
- Sigma Tau
- Silicon Biosystem
- Sirius-Biotech
- Skin Squared
- Smile Biotech
- Spider Biotech
- Sprin
- Stemgen
- Sulfidris
- Synbiotec
- Syntech
- Takeda Italia Farmaceutici
- Target Heart Biotec
- Tecan Italia
- TechFab
- Technobiochip
- Technogenetics
- Tecna Lab
- Tecnogen
- Tectronik
- Tethis
- Tib Molbiol
- Tissuelab
- Toma Advanced Biomedical Assays
- Top
- Tor
- Toscana Biomarkers
- Transactiva
- Transpharma Med
- Tydockpharma
- Ucb Pharma
- Ufpeptides
- Vetogene
- Virostatics
- Vivabiocell
- Wetware Concept
- Wezen Biopharmaceuticals
- Xeptagen
- Xmedica

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