

Working paper for the preparation of the

**GUIDELINES FOR THE DEVELOPMENT
OF BIOTECHNOLOGY IN ITALY**

7th June 2005

NATIONAL COMMITTEE FOR BIOSAFETY AND BIOTECHNOLOGY

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Preamble

The present document aims at providing an outline to develop a strategy for the development of biotechnology that can be shared by the main public and private involved actors. After supplying a synthetic description of the biotech sector at the European and national levels, the document gives some ideas on the critical topics linked to the development of such sector by suggesting for each of them the most advisable actions to be jointly taken and developed with synergy among the main involved actors.

The document has been worked out by the National Committee for Biosafety and Biotechnology (*Comitato Nazionale per la Biosicurezza e le Biotecnologie – CNBB*) in close collaboration both with the Management Committee, the “Biotechnology, bio-nanotechnology and bioinformatics” Task Force of the Ministry for the Productive Activities and with the Regions’ Group on Biotechnology.

With a view to set the guidelines for the development of the sector supported by the national and regional policy makers, by the industrial, financial system as well as by the research and training-based system, the document will be finalised through ideas and suggestions coming out from the discussion, the investigation and the sharing of the related contents by the main Italian stakeholders acting in the biotech sector.

I. INTRODUCTION

▪ The European context

At this point, biotechnology has achieved a leading position among the EU strategic priorities by means of the publication of the European Action Plan on Life Sciences and Biotechnology in the year 2002. This acknowledgement of the strategic role played by biotechnology, clearly expressed in the text that has been approved by all the Member States, has led not only to an improved transnational integration and interconnection at the research level, but also to trigger a renewed competition for the development of biotechnology involving each Member State and leading to a comparison among them as concerns the offer to potential investors. Despite the increasingly EU economic integration, each national reality can not stay out of such competition. Therefore, the Member States, which have been addressed by the same European strategy to improve their own National Plans for the development of biotechnology, are to equip themselves properly within the competitive system by offering their own territorial, administrative, legislative or fiscal distinctiveness to attract investments and technological know-how.

To verify periodically the actions that are to be taken by the various actors, the European Commission draws up an early report in order to ensure the harmonic development of the several EU initiatives.

- **The national framework**

Despite a level of bio-industry's development that is behind schedule compared to other Countries of equivalent economic importance, nowadays Italy has not only a certain and due possibility of recovery but holds also, paradoxically, a privileged situation, considering its high capability to create biotech entrepreneurship in terms of actual scientific, human and cultural resources still to be widely exploited.

The main *atout* of the Italian system rests upon a primary scientific significance in life sciences of potential absolute value, both in qualitative and quantitative terms, still pending a full valorisation in terms of research capacity transfer into an industrial and entrepreneurial dimension. The source of knowledge and talent is such as to have the capability of offering more than one advantage – both in terms of risk capital, of settling of its own productive realities, of creation of joint-ventures and collaborations with the rising national biotech enterprises – to those who choose Italy to invest in biotechnology in comparison to other European Countries where the growth process of bio-industry is much more advanced.

The biotech activities – particularly at R&D and pilot-scale level – are characterized by a relatively low intensity of capital, at least at the starting phase. Therefore, the Italian industrial structure seems to be *a priori* suitable for the improvement of the biotech entrepreneurship, as its structure is made up of small and medium-sized enterprises (SMEs) and it is often organized into territorial areas with specific and flexible characterization with the capability to fit into the international market, as already widely demonstrated by the levels of excellence achieved in several productive “niches”.

Our Country can clearly play its cards in terms of capabilities of attracting foreign investments, particularly in relation to the existent potential to create new dedicated entrepreneurial realities with such dimension as to reduce the level of risk of the investments necessary to start them off fruitfully. Italian “method of making business” is naturally in line with the current tendency in the biotech industry, where the impressive cases of take-over, mergers and combinations relating to companies operating in the traditional productive sectors touched by the biotech innovation – fine chemistry, pharmacology, agriculture and food production – are accompanied by the widespread establishment of new little entrepreneurial realities with specific characterization. Such small enterprises either were born within a successful business-idea and therefore aim at filling development and market niches that are hardly attractive for big companies, or they carry out R&D activities of potential interest to big companies. Such companies are often spin-offs that were born following the abandonment of highly innovative and high-risk research lines which are not immediately under the core business of the big company from which they stem.

It should be also pointed out that Italy ranks in a particular way within the European life sciences outline because its own territory shows a particularly valuable and diversified patrimony in terms of bio-diversity, which is the raw material of biotechnology. Italy thus offers a major potential in terms of natural, cultural and scientific capabilities of protection, study, working-out and targeted enrichment of a wide range of genetic resources within such a various climatic and environmental conditions which can hardly be found in other industrialized Countries.

- **Guidelines for a key economic sector**

The achieved levels of excellence mainly stem from the national biotechnology-related policy implemented in Italy during the eighties. At that time, when no biotech products were present on the international market, the R&D biotech-related investments fostered both by the Ministry of

Education University and Research – *Ministero dell’Istruzione dell’Università e della Ricerca – MIUR* – (through the National Research Programmes and the Targeted Programmes of the National Research Council - *Consiglio Nazionale delle Ricerche – CNR*) and by the big industrial groups (i.e. Enichem, Montedison) have been of utmost importance either in comparison with other technological areas or compared to other European Countries. Despite the lack of a plan for the development of biotechnology during the following decade, Italy inherits from such a period an original “biotechnological culture” in the academic fabric, in the institutes of the National Research Council, in the National Institute for Atomic Energy (*Ente Nazionale per l’Energia Atomica - ENEA*) as well as in the experimental centres that were under the Ministry of Agriculture, and can count on University training courses for Biotechnologists analytically distributed on the national territory, although there would be a need to better plan their settling as well as to focus on the training offer also with reference to the extent of the market demand. However, it must be pointed out that, while other entrepreneurial innovative activities can count on a limited number of skilled personnel, young people with training in biotechnology have a good scientific knowledge and are in sufficient number to ensure the professional human resources necessary in case of industrial development in such area.

Currently Italy is not only to transpose the indications of the European Action Plan on Biotechnology and Life Sciences, but it has to enhance the available potential through a national plan for the development of biotechnology, to obtain from such a strategic sector those achievements in terms of increased competitiveness at which Italy aims. In this respect, it will be particularly important to concentrate on the national plan both those existent measures, although apparently localized, which are crucial to set the favourable conditions for the development of the biotech enterprises, and a combination of specific interventions aiming either at an industrial innovation policy or at the transfer of the research outcomes into processes and products of high added value for the Country.

Such industrial innovation policy is based on the improvement of new technologies and is to be clearly perceived as a firm engagement by those – persons and institutes – who freely devote themselves to study, to carry out R&D activities as well as to run entrepreneurial and financial risks. Within a European context which is more and more turned to the subsidiarity and the enhancement of the particular vocations of specific territories, the quality of the offer as concerns the infrastructures and “innovative environment” clearly is a basic instrument both to stimulate the increase of the existent resources and “to catch” others, either alternatively or in competition with other areas.

At present, failing a systematic trend, the initiatives supporting the development of biotechnology proceed mostly through specific local or circumscribed tendencies. Thus, the objective difficulty to find a systematic national policy in the sector, as well as the obvious specialization of the productions, have clearly driven towards a “local” and “disunited” promotion of the infrastructures as well as of the technological and market distinctiveness of the different geographic areas of the Country.

Our Country can count Regions where the development of biotechnology has been outlined as one of the strategic priorities, and such “regional trends” have already significantly affected the distribution of the rising Italian bio-industry mainly thanks to initiatives that were born around the existing realities and aimed at both uniting and interconnecting the existing resources as well as at attracting new investments. Such areas, although of limited dimension compared to the biotech clusters of other EU Countries (except for the biotech meta-district with reference point in the Province of Milan), are solid kernels of development of the bio-industry because they are based on

effective needs of infrastructures as well as on the enhancement of the existent resources, often with specific applicative orientations and practical growth prospects.

The success and the actual growth of a significant entrepreneurial fabric stemming from such initiatives, currently at different development stages, depends not only on their abilities to gain the economic operator' confidence, but also on the setting of a national system turned to the transformation of the outcomes of the basic research into either products or processes. The willingness and the efforts of the Regions certainly show the "political commitment" towards an economic biotech-based growth, nonetheless there are some cases showing Regions' biotech policies in agriculture and food production in high contrast with the intention of supporting technology.

This calls for the setting of national guidelines for the development of biotechnology strictly linked to research, technology transfer and creation and development of enterprises, thus following the value-chain creation to increase the competitiveness of our Country.

II. DEVELOPING RESEARCH IN BIOTECHNOLOGY SECTOR

On one part Italy appears to be behind schedule as concerns the industrial exploitation of the biotech research – related knowledge, but on the other part the same does not apply in relation to the scientific expertises available in the Country¹. The remarkable contributions given by the research institutions of our Country to the biotech innovation are only the first and most visible signals revealing a strong and widespread activity in biological sciences having deep roots in the scientific culture of our Country, which has always been much more turned to the applied sciences than to the “pure” ones as testified by a long tradition of excellence both in healthcare and agriculture and food production.

Therefore, in Italy there is both a traditionally fertile cultural fabric and a specific tendency towards the biological research leading to establishing entrepreneurial realities internationally recognised in terms of excellence - despite the lack of an express political support in biotechnology, differently from other Countries where biotechnology has been firmly placed among the national priorities (i.e. UK, Germany, Sweden).

There is a need to identify the priority R&D thematic areas to which the public resources might be turned, to both develop the excellences already existing in our Country and focus on sectors with actual opportunities of growth and market development, such as biotechnology.

- **Increasing R&D resources in the biotechnology sector (*FAR* and *FIT*)**

Even if the central Government has not yet identified the strategic importance of biotechnology for the national innovation, there are some instruments coming from the reform of the Research System – implemented by Legislative Decree 297/99 and finalised in the year 2000 – which, although lacking in specific thematic orientations towards biotechnology, are positively turned to the improvement of new entrepreneurial initiatives in this sector. Actually, the basis created through such instruments, and particularly the “Fund for the Promotion of Research” (*Fondo per l’Agevolazione della Ricerca – FAR*) and the “Fund for Technological Innovation” (*Fondo per l’Innovazione Tecnologica – FIT*), have enabled the growth of a real biotech sector during the last years in Italy, made up of a fabric of specialized quickly-growing enterprises.

An uninterrupted, useful and successful use of such two instruments primarily needs the focusing of the available resources on some thematic priorities identified as strategic, such as biotechnology. This would call for the notification of a national thematic biotech-dedicated announcement linked to the above mentioned *FAR* fund, as for the one notified in information technology. As concerns its contents, such announcement should not to provide too rigorous and detailed categories since biotechnology is very pervading, but it should sign a range of applicative areas including the whole activities and/or technology platforms of major interest to the national bio-industry.

But as concerns the competitive-development-related projects support, considering the necessary remarkable efforts and the limited available resources, there is a need to urgently select the themes to be privileged in connection with their weight for the Country. Within the biotechnological applications, the major urgent interest concerns certainly the innovative drugs. Therefore, a thematic announcement should be issued, focusing the *FIT* support on the testing of innovative biotech drugs.

¹ A confirmation of the quality of the Italian scientific system in the biotech sector is given also by the number of projects to which Italy has participated (420) and that have been approved within the “Life Sciences” area of the EU Seventh Framework Programme, in line with the approved projects which France (452), Germany (538) and UK (448) have joined.

In both cases, the selection of projects is to be based on the quality of the bids and the real competitiveness of the bidders, thus avoiding the indiscriminate distribution of resources. The quality of the selected projects will both ensure major practical effects and allow the creation of success models for increasing the confidence of the bodies competent to distribute higher funds. Considering also the objective difficulty to evaluate projects in biotechnology, this will need the increase of the ability in selecting initiatives through a major involvement of experts coming from the biotech sector in the board of examiners.

- **Fostering public-private collaborations**

Triggering the virtuous circle between public investment and attraction of private investments, and at the same time helping to better guide research carried out in the public institutes towards targeted and “economically productive” outcomes, need stimulus to the biotech enterprises in investing in public research structures through the cutting down of the expenses met by the enterprises in relation to both research contracts and obtainment of licenses from public research centres, through the widening of art. 14 of the Ministerial Decree 593/2000. Such a measure would be not only a remarkable input to technology transfer, but also a measure with a moderate charge as a whole in case it could act together with the cutting down of the public grants to the concerned public bodies.

- **Optimising research in healthcare (Red Biotech)**

The major research incentive to research is clearly to turn an idea into a common good in time; the actual engine of the innovation is thus the market. Therefore, positive actions aiming at facilitating the access of such goods and products to the market would highly boost research and development. Such targeted and immediate action might be accompanied by the other above mentioned measures. The most necessary and effective actions to be taken are the two following ones: firstly, identifying ways of access to the market within a certain deadline in line with, or better than, the other EU Countries, therefore a preferential access to the market for innovative biotech drugs, similarly to the European fast track procedure in case of drugs for rare diseases. Secondly, identifying a premium price for enterprises investing in research, development and production of high innovative products in Italy. Such measures would have considerable effects in terms of attraction of investments and would allow Italy to regain the competitiveness that our Country had in the past in the pharmaceutical sector.

- **Optimising research in agriculture and food production (Green Biotech)**

With the aim of promoting biotech research in Italy, there is another sector within which the enthusiasm of our researchers has been heavily weakened by the situation of the last years. In the agro-food sector, we have been among the first to focus attention both on the protection of the agrobiodiversity and on the quality of products; in line with this, University research and Experimental Institutes research for gene therapy of the hardest pathologies (such as the virosis) threatening high added value species which are typical of the national agricultural tradition, such as several high quality plant productions in some cases threatened with extinction (*carnaroli* rise, S. Marzano tomato, Val D’Aosta apple), are surely in the forefront. Proceeding with the research and development of such a fabric needs the national and regional re-introduction of the possibility of testing new plant varieties in open fields as well as the enhancing of agro-food research.

- **Stimulating research for environmental protection (White Biotech)**

Finally, the two “traditional” biotech sectors, i.e. biotech in healthcare and the agro-food biotech, have to be accompanied by the so called “white biotech” concerning the use of biotechnology for a higher environmental protection (for example, environmental renewal and bio-fuel) as well as the innovation in the industrial productive processes for a more effective sustainability (eco-compatible processes and environmental reduced - impact products).

They are highly socially acceptable technologies, although more distant from competitiveness compared to other applications, and therefore specific research and stimulation initiatives are required, thus reflecting the importance given to such an emerging sector internationally and European-wide (OCDE Countries and first of all Japan).

- **Regulating the use of biobanks**

The rapid advances in medicine-related research and technologies have led to a remarkable increase of interest in the collection of human biological materials. Tissue and cell lines collections, from which nucleic acid and proteins can be obtained, are identified as biobanks and are an important resource for both diagnosis and research – from basic research to the testing of treatments of genetic diseases. The success of research identifying the disease genes, the susceptibility genes and the possible therapeutic applications, including the development of new and specific drugs, makes use of the biological samples relating to persons either suffering from, or carrying, or susceptible to, genetic diseases as well as persons manifesting variable response to drugs. The biological material has become a very valuable resource, thus the improvement and organization of such activity has to be encouraged as well as the use, maintenance and networking among the various biobanks has to be ruled. Such collections are numerous and of various sizes, thus it is almost impossible to quantify them and to get information in relation to their maintenance and management. Therefore, considering the growing increase both of the genetic biobanks and of the interconnected interests, in Italy there is a need to rapidly come to regulate their setting up and their use as well as to map the existing ones.

The biobanks networking has to be strengthened in agreement with the OCDE guidelines, and steps have to be taken with regard to the related authorizations and certifications.

- **Developing European Technology Platforms**

The Ministry of Education University and Research (*Ministero dell’Istruzione Università e Ricerca – MIUR*) is setting European-wide great research projects through the new organizational model of the technology platforms which involve several public and private actors in relation to research topics with high industrial effects. Thus, technology platforms in biotechnology have been activated or are being activated, such as: Biotechnology and Plant Genomics; Sustainable chemistry (industrial biotechnology); Nanomedicine; Bioinformatics. The development of platforms in biotechnology should be fostered and the establishment of new ones is to be encouraged, such as those for innovative drugs and biological resources which are under development by MIUR and MAP.

There would be a need to set up national working “mirror groups” acting as interface with the EU technology platforms to successfully network the national and local R&D activities with the European ones.

III. FOSTERING TECHNOLOGY TRANSFER

Both the European and national situation in relation to technology transfer has been considered for a long time as weak element of the productive branch concerning research up to the production of added value. Technology transfer system from research to industry needs to be strengthened since it is paradoxically weaker in our Country where the specialization and the overall dimension of enterprises would need major efforts to optimise the research outcomes, compared to the other OCDE Countries.

- **Ensuring a fixed intellectual property protection framework**

One of the key points of a national plan for biotechnology has to ensure a regulatory framework for the intellectual property protection of biotechnological inventions at least in line with the one already existent in other EU Member States and, if possible, getting benefit from foreign excellent examples. This actually calls for transposing as soon as possible the European Directive on the legal protection of biotechnological inventions as well as for avoiding to link the ownership of the patent exclusively to the inventor to allow the possible joint ownership of the patent with third parties and, thus, to stimulate technology transfer.

Generally speaking, the inadequate protection and insufficient economic enhancement of the scientific outcomes have clearly led to the current insufficient availability of risk capital to establish dedicated companies, as well as the lack of high qualified personnel willing to take up entrepreneurial activities.

Within the European legislative framework – which is the most rigorous in the world in terms of safety controls and is precautionary in the highest degree – there is a need to counterbalance its burdens with the patent protection, which is the primary instrument currently at disposal to both assess the scientific patrimony of an enterprise and to ensure the protection of the high costs incurred to develop concrete innovative products. It is also important to remind that such Directive reflects the need for clear, transparent and uniform European rules, thus each attempt at transposing it differently from the original text would cause “substantive” damages and could penalize the protection of the national patrimony in comparison with the other EU Countries with the effect of making Italy less attractive for foreign investors.

- **Strengthening the technology transfer system from research to industry**

Technology transfer structures, when existent, seem not to have the sufficient expertise aiming at providing the necessary business development-related support to research. Italian University has not yet weighed up the actual benefits of such activities (whereas they are the driving force of the growth of each research centre in several foreign Universities, first of all in the American ones). Currently, a researcher who has developed a good idea can hardly know how to profit by it because of the lack of an adequate internal support. Technology transfer-related activity needs *in loco* ongoing facilities, and this will need to foster the strengthening/establishment of technology transfer offices all over the territory, acting as access to a network of valuable consultants with reliable industrial background, capable to analyze and assess the entrepreneurial ideas. This calls for strengthening the ongoing initiatives as well as those under development which are intended for both supporting the establishment of academic and research (MAP) spin-offs and strengthening of the University industrial liaison offices (MIUR). Anyway, selecting the technology transfer offices requires focusing on those entrepreneurship-related managed initiatives ensuring not only the

stimulus and assistance to the patent-related activities, but first of all a successful commercial promotion of the research outcomes (patent licensing, setting up of spin-offs, etc.). Moreover, structures support needs to be linked to the actual achieved outcomes, for example by linking them to the number and volume of the signed patent-related license agreements.

Finally, there would be the need to encourage the initiatives aiming at promoting clusters among the various technology transfer actors to cut down the excessive fragmentation of the service offer as well as to steer the users towards higher added value services with major market success opportunity.

- **Promoting the economic exploitation of the public research outcomes**

An efficient and not so onerous way of financing the activities aiming at promoting the public research outcomes and their prompt transfer either to enterprises or within the enterprise itself is the carrying out of a feasibility analysis and the drawing up of a business plan in relation to the most promising projects. Structures of solid expertise (for example investment banks) might be charged to carry out such task, thus acting on projects selected through a national public announcement of competition involving the provision of a certain number (20/30) of scholarships valued 100.000 euros each. This might enable to offer, either to the enterprises or the potential investors, bids “certified” from the point of view of the economic potential of the originated ideas, thus permitting a successful and quick analysis of their attractive potential from the point of view of the product development or their value as base patrimony for creating new entrepreneurial realities (start-up and spin-offs).

- **Encouraging researchers’ mobility**

Fostering technology transfer from the research system to the enterprises requires further strengthening of the measures aiming at facilitating the recruitment of personnel, either young graduates or skilled researchers, also for limited periods of time. Particularly, the possibility given to the public researcher to hold his/her position within University or the Public Research Institute has to be accompanied by the identification of means of promotion and stimulation of the enterprises-related work experiences. In this respect, it is of key importance to facilitate the transfer of researchers from the private sector to the public one (for example by involving them into University training courses) to speed up the transfer of industrial know-how both to the academic world and the public research sector. Moreover, to foster the admittance and introduction of skilled personnel into the various productive sectors, it might be envisaged to provide a successful professional classification of the operators in biotechnology in terms of unitariness and multidisciplinary character and intended to ensure adequate usability and recognizability to the diplomas.

IV. DEVELOPING THE BIOTECH INDUSTRY

- **Boosting intangible investments to develop high-tech enterprises**

The current situation needs to gear to the needs and peculiarities of the highly innovative industry a incentive-related system with considerable financial resources, i.e. the system for the productive and economic development of the depressed areas, bolstered by the EU structural funds. On one part, the 2002 Report of the Ministry of Economy regarding the whole assessment of the incentives-related system points out with concern that the applications coming from the depressed areas for the use of R&D incentives are few, but on the other part it is to be underlined that the main reasons why an innovative entrepreneurship does not currently emerge rests clearly upon the structure of the main entrepreneurial-development-related supporting measures for such areas, still linked to features and needs of old declining industrial sectors. Therefore, such measures need some amendments aiming at including high technology enterprises in the list of the potential addressees of such incentives.

The main national instrument to boost entrepreneurial investments is the Law 488/92, both in terms of the number of facilitated interventions and of the amount of provided resources. A crucial point faced by every highly R&D-activities-related enterprise is the type of grant which is paid out. The grant currently deriving from the Law 488/92 is solely intended either to the building of facilities or their coming into line with the existing regulations (tangible investments), whereas the biotech firms have to meet the main part of the costs in terms of highly skilled personnel and, especially during the start-up phase, do not foresee expenses in terms of fixtures or fittings (at the very beginning, the enterprise can be made up of only one laboratory). Thus, it seems to be in line with the objectives of the law in terms of economic and productive development to widen the grant also to the R&D staff-related expenditures.

The same applies to another instrument with high potential to attract the creation and establishment of biotech enterprises in depressed areas (obviously where there are the basic territorial potentialities, as previously pointed out), i.e. tax credit for the penalized areas. In such case too the measure currently concerns solely “the purchase of auxiliary goods intended either for existent productive structures or for structures established in the above mentioned areas”. Because of what above explained, in case of Law 488/92, attracting highly innovative enterprises requires broadening the incentive to R&D expenditures which amount to 15% or more of the turnover of enterprises with high research and innovation rate and, as already underlined, mainly concern highly skilled-personnel-related expenditures as well as high level training courses.

- **Stimulating the growth of young high-tech enterprises**

In line with the events occurred in other European countries such as France, there would be the need to identify a specific legal status for the Young Innovative Enterprises applicable not only to the biotech enterprises but also intended to create beneficial conditions for the growth and development of high-tech enterprises. The draft measure provides that small and medium-sized enterprises recently set up and investing at least 15% of their yearly total expenditures in R&D activities can benefit, within eight years from the date of establishment, from a reduction in welfare contributions for the R&D activities-related employed personnel, in real property taxes and in corporate income taxes. The reduction will decrease during the eight years.

- **Facilitating the biotechnological entrepreneurship by means of the tax allowance**

Incentive-related measures for the biotech entrepreneurship should be implemented first of all through the use of regulatory instruments either already existent or potentially at disposal, such as the tax allowance, with particular regard to the tax allowances provided for by the EU regulations concerning the orphan drugs for enterprises involved in R&D activities regarding such products. Such model could be used and widened to all enterprises dedicated to R&D-related and biotech-innovation-related projects, for example by means of the tax exemption for the whole period of development of the first product.

- **Facilitating the access to the credit for the biotech enterprises**

The access to the credit by the biotech enterprises, especially those at the initial stage of activity, is particularly difficult. The problems linked to the judgement of a start-up enterprise on its merits are accompanied by the difficulties met by the credit institutions to assess risky complex investments in biotechnology. Mobilizing higher credit capital requires taking measures to reduce the level of the credit-related risk either by giving public security for complex biotech projects or by lowering (for example, by 50%) the applied banking interest rate. Moreover, in this respect some instruments might be scheduled to enable the credit institutions to judge with greater certainty the risk linked to the proposed investment, for example by facilitating the take-over and the use of “technological rating” services for enterprises which intend to have access to the credit.

- **Developing the Venture Capital market with particular reference to the seed and early stage capital**

The need to invest in biotechnology is strategic and obligatory for a Country which intends to go on being one of the most industrialized in the world. However, it is of common knowledge that there are current balance-related problems not enabling to disclose the necessary resources. Thus, it is worth to go the virtuous way, as other Countries have already done, and to support the financing to biotech research and innovation by means of private instruments, to increase the improvement of biotech innovation in Italy and to attract in our Country the establishment of European or cross-border realities.

A particularly suitable instrument seems to be a Fund exclusively restricted to qualified investors (banks, insurance companies, firms, foundations, research institutions, Universities, etc.) having an endowment fund of at least 300 millions euros, lasting for ten years and having a “closed capital” structure investing most of its own capital either in Italian or in foreign enterprises which in turn invest in biotechnological R&D in Italy. For the Fund to be successfully promoted and attractive, it would be of utmost importance that the Government could act as co-financing investor and that a guarantee clause could be provided in order to reduce the risk of underperformance connected to the Fund.

In order to increase the interest of the venture capital operators specialized in technological investments in acting during the start-up stages of the enterprise, which are stages at risk, a considerable share of the fund-related resources might be addressed to seed and early stage interventions.

- **Mobilizing more risk capital on the part of the informal investors (*business angels*)**

Mobilizing more risk capital for high-tech enterprises such as the biotech enterprises requires actions to be taken, also by means of tax relief in relation to the profits of the informal investors “*business angels*”. They know the sector very well and normally, they mainly focus on the *seed financing* stages when the entrepreneurial idea is not yet formalized and the work is still focused on research and product/technology development, thus on a stage at great risk. Particularly, such measure could provide that the *business angels*, investing their own capital in small and medium-sized enterprises recently established and incurring at least 15% of their yearly complex expenditures in R&D activities, could be tax free in connection with the financial return coming from capital gains, provided that they hold the stake for at least three years.

- **Speeding up transposing European Directives**

The whole current regulatory framework concerning biotechnology and its productive applications mainly stems from the European Community and it is very strict and precautionary. Except the subsidiarity principle, while implementing regulations aiming at harmonizing European rules within which the specific territorial needs can freely find a suitable following adaptation, the arbitrary distortion while transposing into national laws the European Directives as well as the distortion of the national regulations at local level should be avoided.

- **Fostering networking and clustering processes**

The development of biotechnology in Italy can take advantage of networking and clustering processes fostering fast innovation processes and synergy, growth and collaboration relationships between enterprises and research institutes. From this point of view, MIUR has promoted, in agreement with the concerned Regions, the set up of technological districts in biotechnology in Lombardia, Friuli – Venezia Giulia, Puglia and Sardegna. The aim is to identify the leading expertise available on the territory and aiming at creating integrated system supporting research and entrepreneurial development in biotechnology, by optimizing the infrastructural, scientific, technological, managerial and entrepreneurial local potentials. There is a need for supporting the strategies aiming at focusing resources on specialized clusters within well-limited research areas to optimize resources, whilst enhancing the expertise already at disposal *in loco* and fostering the local initiatives.

- **Stimulating the attraction of foreign investments and encouraging internationalization**

As regards the attraction of foreign investments, it is of key importance to point out the measures aiming at streamlining the authorization procedures for the establishment of the new productive units and the obligations to be fulfilled to run the enterprise, such as those provided for by the recent Law 80/2005 “Action plan for the economic, social and territorial development”.

In relation to the attraction of foreign investments, there would be the need for promotional activities to give importance and recognizability both to the national and the local model as well as to spread, through dedicated data base too, updated information concerning the main Italian research, development and innovation-related centres. Remarkable examples to be cited are the Padua Exhibition and Bioforum in Milan which periodically ensure a showcase of research and

industrial activities by organising promotional meetings in biotechnology. Moreover, there would be the need to organize and strengthen an adequate institutional venue for the major international biotechnology-related events (exhibitions, conferences, meetings) as well as to be prepared to actively support at national level the organization of networking and partnering events where submitting projects, activities and initiatives to potential investors might be possible.

As regards the internationalization of scientific research, it must be pointed out that the Ministry for Foreign Affairs and the Institute for the Foreign Trade (*Istituto per il Commercio Estero – ICE*), through its offices in Italy and abroad, have identified biotechnology as one of the key sectors to start international collaborations aiming at improving our knowledge. Such commitment is to be supported, first of all from the point of view of the strengthening of the internationalization of the public-private research in biotechnology.

V. HORIZONTAL INTERVENTIONS

▪ **Improving governance**

In Italy, setting and implementing policies in biotechnology involves several Central Administrations. Following the devolution processes of the last years, the Regions now play a vital role in implementing policies for the development of biotechnology. The successful and systematic development of biotechnology avoiding double efforts and encouraging synergies leads to the need of improving governance through a stronger co-ordination among the various actors involved in the sector both at the national and local level. This will need the strengthening of the co-ordination role of the National Committee for Biosafety and Biotechnology. Such Committee will be the institutional office where the representatives of Ministries and Regions can share the experiences made in the sector and set the development-related policies in the sector in a coordinated and synergic way. The Committee will avail itself of a technical advisory Group set up within the National Observatory for Biosafety and Biotechnology.

▪ **Strengthening the National Observatory for Biosafety and Biotechnology**

The National Observatory for Biosafety and Biotechnology has been set up at the Presidency of the Council of the Ministers by Decree of the President of the Council of the Ministers of 14 November 2001 and is effective since the Decree of the President of the Council of the Ministers of 28 November 2003. The Observatory serves several purposes and carries out high added value services beyond the single Institutions offering to the biotech research-industry system the following activities:

- optimizing information coming from the various actors of the sector fitting them in a comprehensive systematic framework;
- fostering the setting up of a widespread knowledge management system enabling the actors to self-orient in research and investment-related activities;
- enhancing the most significant experiences by means of an “integrated reading” and by fitting them into a meaningful context in terms of research / industry and/or networking them as well as identifying the international collaborations;
- pointing out the cases of excellence also to supply indications steering the less successful start-up-related experiences;
- supporting the dissemination, sharing and transfer of the research outcomes also by fostering the direction of the research centres to the market, beginning from the strategic identification of the type of research where resources could be involved;
- monitoring the foreign best practises either as elements of comparison or as junctions of a broader network internationally and European-wide;
- supporting the regional actions in “attracting investments” also by disseminating “catalogues” of offers to foreign investors.

Moreover, the initiatives to be carried out can be manifold from the point of view of the service: periodic drawing up of special reports regarding specific topics (essays) and/or for specific addressees, elaboration of scientific economic and productive data concerning the sector as well as for the implementation of a systematic Communication Plan (see following paragraph).

Also the 2005-2007 National Research Programme gives considerable importance to the National Observatory for Biosafety and Biotechnology set up at the Presidency of the Council of the Ministers. For the Observatory to become a unitary reference point to the operators of the sector as

well as to be able to perform the given remarkable functions, there is the need to provide the structure with adequate resources.

- **Improving the social acceptability of biotechnology**

Biotechnology gives rise to contrasting reactions in the public opinion, from fear to expectation. There are those considering biotechnology as solely driven by economic interests, as well as those believing that the development of such sector could lead to remarkable contributions to the improvement of the quality of both their own life and the life of the entire community. However, both in the former and in the latter cases, there is the lack of an actual awareness of what biotechnology really is. The various opinions linked to conflicting points of view are the effects of pre-existent cultural and ideological positions rather than of a well-grounded knowledge of the topic. The limited knowledge of the subject concerns all the social classes, including the political one.

Achieve a well oriented culture in life sciences requires the development of a communication plan capable of teaching what biotechnology really is as well as of spreading the indication of which tangible advantages biotechnology can bring to people, to the community and for the economy of the country, and which actual risk rates exist as well as what kind of safety and control systems can be taken to lower them or to reduce them to zero.

Develop such plan systematically requires involving the three social actors more directly involved in the process of dissemination of biotechnology-related knowledge: the research system, the media system and the school system. The first one because it is the most reliable and independent source in relation to such topic; the second one because of its capability to propose models and facilitate evaluations; the third one because it has been institutionally appointed to build the source of knowledge for the new generations.

- **Increasing the potentialities of the human resources**

The rapid development of biotechnology is bringing about deep changes both in the research and industry structure. The demand for expertise in such sector has led to the growth of a limited number of postgraduate schools, some of which are of high level, as well as to the development of research doctorates in biotechnology. However, such training mainly turns to Academia and is therefore too distant from the effective need of the biotech industry.

Despite the various courses in the degree courses and the specialist degrees in biotechnology at the main Italian Universities which give a good scientific training, the contribution of our Country to ensure the necessary professional resources in the various biotechnology-related areas is still limited.

There is the need to stimulate the rationalisation and the operative professionalization of the training-related offer, as well as to introduce training studies, also of limited duration, in relation to non “biological” subjects enabling the student to better understand the needs of an innovative sector rapidly changing and its market. Particularly, the subjects to be broached, also by involving actively in the courses teachers coming from enterprises, are the following ones: marketing, creation of enterprise, management of enterprise, project management, innovative finance, intellectual property protection.

ATTACHMENT

Preliminary indications concerning the R&D priorities in biotechnology

1. Biotechnology in healthcare

The healthcare expects from the development of biotechnology a strong stimulus to the diagnostics, the prevention and the therapy based on the development of the basic knowledge, especially those deriving from, for example, the ongoing investigation on the human genome and its expressions mechanisms. The operative stakeholders should act as interface between the academic research and the entrepreneurship, on one hand fostering the improvement of the public research in specific sectors and, on the other hand, encouraging an innovation process of the enterprises in the pharmaceutical sector and/or the establishment of highly innovative enterprises in harmony with the US, European and Israeli models.

A series of highly operative conventions are to be envisaged, some of which are already starting off, steering the academic efforts towards specific fields or niches appearing as national node for the development of concerned applications.

In biotechnology-related research in healthcare, the following priorities strongly linked to objectives for which, within a framework of limited resources, the necessary diagnostic and/or therapeutic answers based on scientific, targeted, effective evidences are urgently required, can be identified:

- a) Development of diagnostic kits based on DNA and DNA microarrays to identify correlations between genes and congenital, hereditary, oncological, degenerative and infectious diseases.
- b) Use of such kits to identify the individuals predisposed to specific infections either to enable the necessary prevention or to draft personalised innovative treatments (see also “*Guidelines for gene testing*” by the National Committee for Biosafety and Biotechnology at the Presidency of the Council of the Ministers).
- c) Production of active principles such as hormones, bio-drugs, bio-regulators, vaccines through genetic engineering procedures to avoid serious risks of infection as well as to make such principles affordable in terms of price and availability.
- d) Study of still not well known biological processes, especially recognition- and communication-among cells mechanisms aiming at designing and developing innovative drugs to treat several loss-of-communication-related diseases (immunodeficiency) as well as overloading-interaction-related diseases (immune diseases, tumoral metastasis, neurodiseases, etc.).
- e) Study and development of diagnostic procedures and therapeutic treatments to monitor the ageing processes at molecular level.
- f) Identification of molecular targets of diseases such as cancer and AIDS to develop highly specific guide compounds.
- g) Use of stem cells for therapeutic treatments.
- h) Development of innovative technologies for membrane proteins crystallization and following characterization of micro-crystals resulting from the atomic resolution through synchrotron light.
- i) Development of materials, vectors and techniques for gene therapy.
- j) Production of immuno-compatible organs for temporary transplants from transgenic animals.
- k) Development of drug delivery and drug targeting systems.
- l) Nanobiotechnology in diagnostics and medicine.
- m) Biomedical biotechnology and new therapeutic approaches.

- n) In vitro toxicology.
- o) New in vivo diagnostic applications.
- p) Certification of the active principles coming from plants used in phytotherapy, cosmetics and pharmacology.

2. Biotechnology in agriculture and food production

The main areas of activity and its objectives in the most promising sectors can be synthetically listed and prioritized as follows:

- a) the plant genome characterisation to identify and isolate useful genes; the development of advanced technologies for gene transfer;
- b) the genetic improvement of plants and animals for specific goals such as:
 - the genetic resistance to diseases (virus, insects, fungus) and environmental stress due to drought, salinity and high or low temperatures, etc.;
 - environmental impact reduction;
 - the improved food nutritional, technological, organoleptic quality;
 - the cutting down of the production costs (plant design, productivity, higher absorption of nutritional elements, etc);
- c) the enhancement of natural plant and animal genetic resources, identification techniques for Protected Designation of Origin (PDO), Protected Geographical Indication (PGI), salvage of plants and animals threatened with extinction, naturalization;
- d) health-care monitoring of food transformation processes;
- e) diagnostics to identify biotech products and diagnostics relating to the state of health of plants, animals and natural systems;
- f) the development of new products such as *novel foods*, *functional foods*, *nutriceuticals*, food integrators. Particularly the nutraceutics, an area of growing interest, enables to insert curative active principles (such as oral vaccines and drugs) in the food;
- g) the development of knowledge related to biological processes of high economic interest such as fruits maturation, ageing, allelopathy, animal reproduction, etc. to develop innovative technologies;
- h) the protection of agro-ecosystems through techniques for the biological control of pathogens, parasites, weeds, etc.
- i) the soil fertilization and the plants nutrition through bacterial inoculation, microarrays, enzymatic products;
- j) the improvement of fermentations through the isolation of specific strains and the molecular characterization of autochthonous strains. The autochthonous strains are of great interest as natural resources as well as of high economic interest as they are the basis for the processes for the Italian production of cheese, wines, salami, etc.;
- k) the development and sequencing of innovative vaccines for pathogens of animal interest, including aquaculture.

3. Biotechnology for industrial processes

Plants and microorganisms are a potential resource of great interest as industrial feedstocks.

Considering the current biotech developments in Europe, USA and Japan and the following “Industrial Biotech Forecasts”, two main objectives can be sorted out: new products development

and improved productive processes development. However, neither the control of such developments nor the training of high skilled personnel can be put aside.

The national industrial-related lines of research which are expected to take priority concern the following:

- a) enzymes and proteins production through genetic and protein engineering, including new hosts development; the optimization of the down stream, the draft and development of fit delivery systems;
- b) the bio-energy production, the bio-mass production, the bio-fuel (fuel and ethanol) production, the bio-gas (natural gas and hydrogen) production. Given such framework, great attention should also be paid to the reduction of the deposition in the atmosphere of carbon dioxide in association with such bio-processes. In such a context, the sewage disposal coming from the agro-industrial plants is included;
- c) the plant fibre ennobling through enzymatic retting;
- d) the conversion, output and productivity improvement of the various fermentation bio-processes using both wild and recombinant organisms;
- e) the fine-chemicals production through fermentation (organic acids, amino acids, solvents, vitamins, etc.) for various industrial sectors, from the food industry to the chemical and pharmaceutical one.

Moreover, plants and microorganisms may be used to produce active principles and enzymes through proper genetic engineering and cultivation, for applications, for example, in the bio-filtering and bio-detergence processes, in the textile sector, for paper and cellulose recycling or production, production for bakery, emulsifier and bio-diesel production, bio-sensors development in healthcare, in salubrity of commodities-related area and in the environmental monitoring-related area (use of bacteria for ecological purposes).

4. Biotechnology for the environment

Environmental biotechnology is a technology based on the use of living organisms, or their parts, for example enzymes, to prevent, monitor and lessen the environmental subversion. They enable in the short/medium term a proper waste and effluents disposal, and in the medium/longer term the obtainment of “clean” products from renewable raw materials connected with no – or few - waste production. Moreover, the high social acceptability of environmental biotechnology has to be pointed out because of the safety features therein connected. Operations do take place in closed environments (bio-reactors) and, in case of operations in open fields (bioremediation of polluted soil and/or water), microorganisms already present in the matrix are used, anyway subject to the assessment of their pathogenic potential.

The bioremediation involves the study, selection and genetic improvement of microorganisms and plants suitable for the biological monitoring of polluted habitats, the cleaning up of no longer used industrial plants as well as of polluting areas and/or fields as a result of faults, the development of a case-to-case operative system. They are topics of overwhelming importance especially for Italy where, since the last decade, the reconversion or the divestment of several industrial areas have taken place. Many researchers have shown interest for such sector. Another interesting area is the agro-waste enhancement or recycling. The transformation of paper waste into pulp is an ambitious but realistic project as well as the application of microbiological processes in the textile industry. Moreover, researches are under development to substitute some stages of the production cycles of the leather tanning industry currently involving the use of highly harmful products, by means of microbiological systems. Genetic engineering actions are highly required also in connection with the increase in the plant photosynthetic efficiency – from woods to grasslands of alga – to remove CO₂ thus helping reduce the increase of the greenhouse effect.

There are valuable studies aiming at improving, in terms of environmental protection, the polluting industrial processes as well as the biological cleaning up processes. Of remarkable interest is the micro- and nano-sensors development based on biological and organic materials such as P450 cytochromes for gas sensing (CO, CO₂, NOX, etc.), polluting fluids and the nano-bio-catalysis: enzymes immobilization via enzymatic monostratum “nano-structuring” for waste processing in plastic materials through depolymerising enzymes. Decomposing the polymer into oligomers and possibly single monomers, thus obtaining virgin material available for re-use, is envisaged.