Industrial biotechnology driving industrial competitiveness and sustainability

Initiatives from the European Union

Alfredo Aguilar

Résumé **Les biotechnologies industrielles, moteur de la compétitivité et du développement durable : les initiatives de l'Union européenne**

Cet article souligne la montée des biotechnologies industrielles en Europe, en particulier ses avancées technologiques, la compétitivité des industries européennes et leur impact sur l'environnement. Les progrès de ces procédés se sont étendus à la chimie fine, à l'industrie du papier, aux textiles, à l'énergie, plaçant les biotechnologies industrielles au cœur même de l'industrie, dans ce que l'on appelle la bioéconomie. Ses technologies clés sont à la source d'un nouveau développement économique, avec la commercialisation de nombreux produits et procédés. Cet article souligne également les initiatives de l'Union européenne pour soutenir leur développement à travers le 7^{e} Programme-cadre (2007-2013) et son successeur, Horizon 2020 (2014-2020).

Mots-clés **Biotechnologie, bioéconomie, biotechnologie européenne, technologie clé, industrie, Horizon 2020, programme cadre européen.**

Abstract This article outlines the drivers of industrial biotechnology in Europe, in particular industrial leadership, competitiveness of European industries and environmental sustainability. The impact of industrial biotechnology has gradually expanded from the classical biochemical processes to others such as fine and bulk chemicals, pulp and paper, textile, automotive and energy, making from industrial biotechnology the core of biotechnology and the leverage for the bioeconomy. Industrial biotechnology has already demonstrated its capacity to be a key enabling technology capable of generating industrial leadership and economic development, reinforcing the bioeconomy and being the main entry gate to the commercialization of biologically derived compounds and processes. This article also outlines the European Union initiatives aimed to promote the development and sustainable applications of industrial biotechnology during Framework Programme 7 (2007-2013) and the prospects for its successor Horizon 2020 (2014-2020).

Keywords **Biotechnology, bioeconomy, European biotechnology, key enabling technology, industrial biotechnology, Horizon 2020, EU Framework programmes.**

Industrial biotechnology, also commonly known as "white biotechnology", constitutes the core of biotechnology and the leverage for the bioeconomy, as it is the application of biotechnology to industrial processes. Between the 50s and the 70s of last century, were developed the science base and the technologies that today constitute the backbone of industrial biotechnology: biocatalysis, microbial fermentations, rational design and scale-up of fermentors, downstream processes, purification and separation techniques. This period was the golden era for the production of antibiotics, vitamins and amino acids by large scale microbial fermentation.

In the years following the end of World War II, the production of penicillin by fermentation of Penicillium chrysogenum rocketed [1]. Behind were left the times where doctors, engineers and microbiologists were impotent of being unable to enhance penicillin production to the levels required to treat patients, mostly soldiers wounded in the front.

Industrial biotechnology has provided a decisive input to the rationalisation of many industrial sectors. Thus the pharmaceutical sector has been able to generate a large collection of antibiotics and other bioactive compounds by microbial fermentation or by combination of fermentation and chemical synthesis. Proteolytic enzymes isolated and purified from different microorganisms are currently used as additives in detergents for washing machines. Industrial biotechnology has also made huge contributions to the food industry by improving yield, quality and diversity of fermentable products and by preserving food by natural preservatives produced by microorganisms. Amino acids, such as glutamic acid, lysine, tryptophan and methionine, used in many applications by the food and feed industries, are produced at large scale by fermentation of hyper producing microbial strains, mostly *Bacillus*, *Corynebacterium* and *Brevibacterium* sp. Microbial production of amino acids and other biological compounds have the advantage over chemical synthesis that it only produces the bioactive enantiomers and not the racemic mixture as in the case of chemical synthesis. The use of enzymes and whole cell biocatalysts has proven particularly valuable in production of both proteinogenic and non-proteinogenic L: -amino acids, D: -amino acids, and enantiomerically pure amino acid derivatives, which are of great interest as building blocks for active ingredients that are applied as pharmaceuticals, cosmetics and agricultural products [2].

The impact of industrial biotechnology has been recently expanded from the traditional pharma and food and feed sectors to others such as fine and bulk chemicals, pulp and paper, textile, automotive and energy. It is worth mentioning that industrial biotechnology has created a new and successful type of industry, that of production of enzymes or biocatalysts, in which Europe is the leader. The global industry enzyme market alone was worth about 2.1 billion euros in 2008 (*figure 1*). Approximately, one third of that figure was accounted by the detergent enzyme sector and another third by food and feed enzymes. The production of detergent enzymes is growing by about 4.5% per year, mainly for dishwashers and liquid detergents. Enzymes for food manufacturing have an estimated annual growth rate of 2-3%.

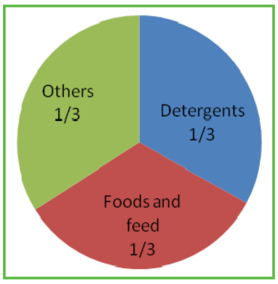
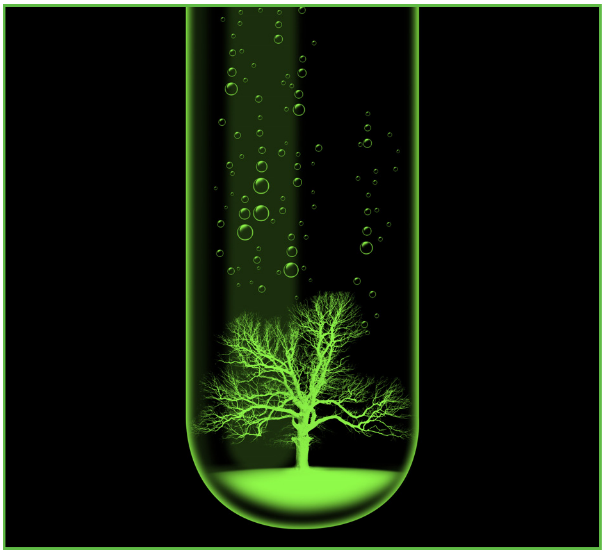


Figure 1 - Enzyme market 2008 (2,1 billion euros).

When compared with the classical chemical processes, biotechnological processes are much more environmentally friendly as they reduce the need for organic solvents, toxic metals and energy because they operate at lower temperature and pressure, require much less energy inputs and consequently emit lower greenhouse gas emissions (GHG), and last but not least, they use renewable biological material. However, it is important to emphasize that biotechnology can be used both on renewable and non-renewable resources [3-4]. European chemical industries are showing an increasing interest in the potential of industrial biotechnology, with nearly 70% of the estimated R&D expenditure of worldwide leading spent by European firms [5]. In 2003, health biotechnology accounted for 87% of the share of total OECD business expenditures on biotechnology R&D while industrial biotechnology accounted for only 2%. However, the estimated potential share of total biotechnology in the OECD area for 2030 is forecasted to be 25% for health biotechnology and 39% for industrial biotechnology [6]. These data clearly show the huge economic potential impact of industrial biotechnology across many economic and social sectors.

In the last couple of decades, industrial biotechnology has overcome many scientific and technological hurdles by a synergistic use of the developments in molecular biology and on bioengineering: cultivation and extraction of bioactive compounds from extremophile microorganisms (*Archaea*); mastering of cultivation of animal and plant cells in fermentors, developing the concept of "cell factories" [7-8]. Many of these scientific and technological breakthroughs are already in the market: new enzymes for industry and household use, biologicals for diagnostic and therapeutical uses, etc. The development of a robust theoretical scientific and technological frame has facilitated the acceleration of new products and processes stemmed from industrial biotechnology.

A new paradigm on industrial biotechnology has led a few years ago with the development of the concept of biorefineries for the large scale production of fuels and chemicals. The biorefinery sector is bound to explode in the coming years, where new, more robust and much higher amount of enzymes will be required. In addition to enzymes, biorefineries will need



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to enhance and sometimes develop completely new biotechnology industrial processes with the aim of making biorefineries fully sustainable and more economic.

Industrial biotechnology has already demonstrated its capacity to be a key enabling technology capable of generating industrial leadership and economic development. A key feature in its development is the operational integration of other branches of biotechnology, such as marine biotechnology, environmental biotechnology, nanobiotechnology, synthetic biology, bioinformatics, etc. Industrial biotechnology is not anymore just one amongst many branches of biotechnology. Industrial biotechnology encompasses the industrial developments and applications of other biotechnology sectors, aimed at reinforcing the bioeconomy and is the main entry gate to the commercialization of biologically derived compounds and processes.

This article outlines the initiatives of the European Union (UE) to promote the development and successful and sustainable applications of industrial biotechnology in new bioproducts and bioprocesses, particularly during Framework Programme 7 (2007-2013) of research [9] and the prospects for its successor, Horizon 2020 (2014-2020) [10]. The emphasis is made on the scientific and technological aspects are expected to contribute to the strengthening of the bioeconomy in Europe.

A more general outline of projects supported by the biotechnology in the EU research programmes in the recent years has been published by Cichocka *et al.* [11]. The readers interested in the most relevant features of the last thirty years of EU biotechnology programmes are invited to read the article from Aguilar *et al.* [12]. The more specific issues dealing with biotechnology research for innovation and sustainability in agriculture in the European Union and on international scientific cooperation have been published elsewhere [13-14].

Drivers of industrial biotechnology

The main policy drivers on industrial biotechnology in the EU are industrial leadership, competitiveness of European industries and environmental sustainability. Industrial biotechnology is a key enabling technology accelerating the transition to a green, low carbon and resource-efficient economy with the potential to impact on a large number of industrial sectors and social activities. Thus, industrial biotechnology processes are crucial for the gradually replacing fossil resources by renewable ones and therefore can contribute to mitigating climate change. The carbon efficiency can be optimised when using bioresidues and biowastes (closing loops) and this also alleviated the pressure on the environment (land use). By using milder conditions than chemical processes (pressure and temperature), industrial biotechnology also contributes to decrease energy consumption and therefore contributing to alleviate the effects of climate change. It is estimated that the use of industrial enzymes in biorefineries have the potential to save between 1-2.5 billion tonnes of carbon dioxide annually by 2030, around 5% of the total worldwide emissions of the gas in 2007 [3].

Industrial biotechnology should gradually replace conventional processes using metal catalysts and organic solvents by greener and resource efficient bioprocesses with high selectivity.

It has been reported that the application of biotechnology in diverse sectors such as chemicals, plastics, food processing, textiles, pulp and paper, mining, metal refining and energy can not only reduce costs but also reduce the environmental footprint for a given level of production. In some cases, capital and operating costs decreased by 10-50%, in others energy and water use decreased 10-80% while the use of petrochemical solvents was reduced by 90% or eliminated completely [15].

By its very nature, industrial biotechnology is grafted across all biotechnology applications, and increasingly on the chemical industry, where it is expanding from the segment of fine and specialities towards bulk chemical production, and into a wide spectrum of industrialised processes and products, *i.e.* biofuels and bioproducts, bio and composite polymers, etc., and last but not the least, in environmental applications [16].

Industrial biotechnology has also some hurdles that need to be properly addressed to guarantee its success. One is the resistance of long established industrial sectors, such some operators in the chemical industry, to invest on the replacement of the existing conventional technologies by new ones coming from Industrial biotechnology, or on the combination of classical chemical technologies with some biotechnology ones. This offers great potential for complex (bio)chemical processes.

Growth, innovation and employment

Biotechnology is knowledge intensive and requires highly-skilled jobs. Innovations are created within a business environment, where SMEs (small and medium-sized enterprises) play an important role, both by providing inputs and innovative solutions to global companies, or by introducing directly new consumer goods to the market. Innovation is also enhanced by cross sector innovation, that is to say bridging different productive sectors (agriculture, forestry, marine environments, biotechnology, chemistry, energy, etc) and integration of those sectors with well established industries, *e.g.* chemical, pulp and paper, etc. This new business environment and cross sector integration is badly needed to make the biobased economy a reality in our societies.

The European strengths

Europe has major strengths on industrial biotechnology: it is the leading producer of enzymes – three quarters of the market worldwide – which are used in the food and detergents sectors, and in the textile, pulp and paper industries. The EU is also a world leading in industrial biotechnological applications for fine chemicals. The European Chemical Industry Council (CEFIC) estimates that by 2015, turnover will have grown to 305 billion euros, a tenfold increase compared to 2005, and that around 20% of all chemical production will involve biotech processes [17].

Industrial biotechnology in Framework Programme 7: main features

Industrial biotechnology research is a priority of the Framework Programme 7 for research, in particular in its Cooperation Specific Programme (2007-2013) under the activity 2.3: “Life sciences, biotechnology and biochemistry for non-food products and processes” (from now on this activity will be referred as Activity 2.3: Biotechnologies). This activity is part of the theme “Food, Agriculture and Fisheries and Biotechnology” and it includes applications in primary production, industry and the environment. Industrial biotechnology is at the core of this activity and channels new know-how generated in novel sources of biomass and bioproducts, marine and environmental biotechnology and the expected breakthroughs of emerging trends in biotechnology into industrial deployment.

By its pivotal role, industrial biotechnology has close interactions and is complimentary to other biotechnology areas, such as plant biotechnology (providing terrestrial feedstock to industry), marine biotechnology (exploiting aquatic environments), environmental biotechnology (environmental services and technologies), and emerging trends in biotechnology (*e.g.* synthetic biology, nano-biotechnology). These are all instrumental for the future advancement in biotechnology and for the rapid, sustainable and efficient development of the bioeconomy.

At the time of writing this article, Framework Programme 7’s Activity 2.3: Biotechnologies has given support to 101 transnational projects for a total budget of about 550 million euros, with nearly 1400 groups specifically channelling biotechnology and know-how into industrial deployment.

Participation of large industry and SMEs is considerable and accounts for about one third of the total in participant numbers (see *figure 2*). This demonstrates the industrial commitment of industry in R&D and that of the European Commission in setting biotechnology, and industrial biotechnology in particular, as one of the main drivers for the bioeconomy. In particular, the large number of companies classified as primarily active in the area of R&D reflects, on the one hand, the need to public support research and innovation activities in the area of biotechnology, while on the other mirrors the potential for innovation and commercialisation of related products and processes.

Overview and assessment of the support to industrial biotechnology in Framework Programme 7

The discovery and development of biocatalysts has attracted substantial attention and resources. The target enzymes went beyond hydrolases (enzymes most commonly used) and include also oxidoreductases, lyases, transferases, etc. Substrates such as starch, carbohydrates, polysaccharides have been specifically supported and applications

Some examples of applications in industrial biotechnology.

Industrial biotechnology		
Target enzymes	Substrates	Applications
Hydrolases	Starch	Food
Hydrolases	Small molecules	Chemical synthesis
Transferases	Polysaccharides	Chemical synthesis
Oxidoreductases	Small molecules	Chemical synthesis
Aldolases	Small molecules	Chemical synthesis

included food, medical uses and very importantly chemical synthesis (see *table* above).

Still, the spectrum and variety of enzyme classes offers a tremendous source for discovery of improved versions of enzymes with known function and for discovering completely novel enzymes. However, the production cost of enzymes and their limited availability in industrial quantities are real bottle-necks for expanding their industrial application. Progress in the understanding of the molecular mechanism of enzyme actions will be crucial to move the science of synthesis towards more complex target molecules. Demonstration activities are important to fill the gap between lab and scaled-up production. In turn, innovation-related activities such as standardisation and labelling, policy driven innovation (*e.g.* REACH), as well as assistance for the better use of public procurement for biobased products, will help bridging the gap from the bench to the market.

The optimisation of microbial metabolism for the production of chemical and pharmaceutical intermediates has been covered by a number of projects and opens new avenues for new functionalities and applications. Selected microorganisms are *e.g. P. pastoris*, *S. cerevisiae*, the unconventional yeast *C. bombicola*, etc. The target compounds include some that are "new-to-nature", such as new biosurfactants and novel poly-unsaturated fatty acids. The industrial demand for robust and flexible microorganisms capable of processing complex feedstocks (waste, C5/C6, inhibitors, etc.) is growing. Fulfilling the goal of producing an increasing number of chemical products in a single step will also require the availability of new or improved industrial hosts. Microbial stress under industrial conditions, pH, temperature, presence of toxic compounds, solvents, etc., is a determining factor to overcome the current technological limitations.

The production of chemical building blocks has been approached through the use of biotechnological tools and through a multidisciplinary approach such as the Biorefinery Joint Call in 2009. In addition, priority has been given to the development of biopolymers, which are a family of compounds with high prospects and that can have also applications in bulk production.

Industrial biotechnology at the crossroad of biotechnologies

The development of industrial biotechnologies also encompasses the strengthening of the knowledge base and development of advanced technologies for terrestrial and marine biomass production for applications in the biobased industrial processes. This research includes plant, animal and microbial "omics" tools to improve the productivity and composition of raw materials to be used as biomass feedstocks or for the optimised conversion to high added-value products.

In this context in recent years there has been a rapid increase in the inventory of marine products and genes of commercial interest derived from bioprospecting efforts. The rapid growth in human appropriation of marine genetic resources with over 18,000 natural products and 4,900 patents associated with genes of marine organisms, the latter growing at 12% per year, illustrates that the use of marine bioresources for industrial biotechnological applications is no longer a vision but a growing source of business opportunities. Marine bioresources are increasingly recognised as an important source of enzymes, biopolymers, biomaterials, biochemicals, pharmaceuticals, neutraceuticals, care products and food additives (*e.g.* colorants).

The concept of the biotechnology based industrial processes also implies environmental sustainability. Industrial biotechnology can provide solutions to acute environmental problems ranging from the identification and detection of biohazard to bioremediation techniques. Previous research in this area has shown the great potential of environmental biotechnology based products and processes to more efficiently remove pollution and more accurately monitor specific contaminants than many conventional methods. However, while good progress has been made in understanding the principles behind these environmental applications, the practical use of this know-how for final industrial products remains to be further developed.

European industry also needs to lay the foundations to stay at the front line of innovation, in the medium and long terms. Thus, the importance of the development of emerging tools such as synthetic biology, bioinformatics, systems biology and exploiting the convergence with other enabling technologies such as nanotechnology (*e.g.* bionanotechnology) and ICT (information and communication technologies, *e.g.* bioelectronics). These and other cutting-edge fields have been at the core of FP7 biotechnologies research and innovation.

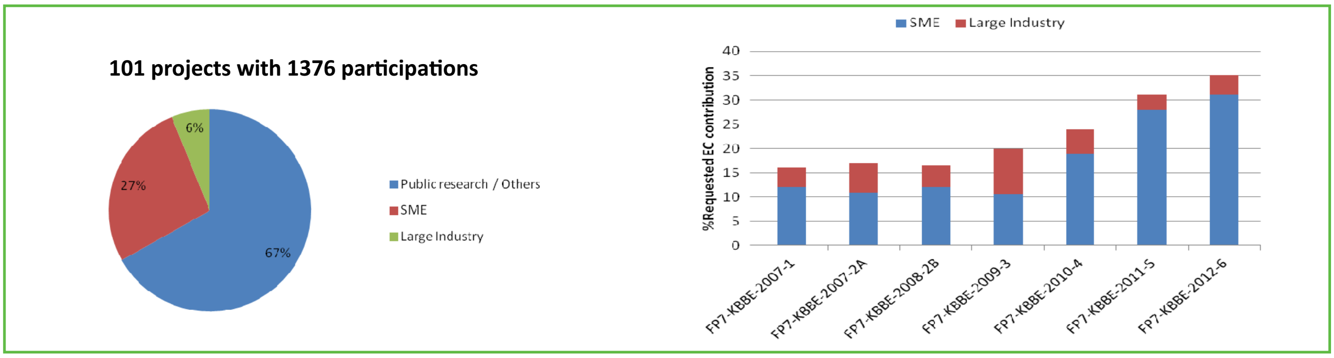

Figure 2 - Private sector participation in % of EC contribution in FP7 projects under KBBE's activity 2.3: Biotechnologies (7 calls).

Social acceptance of biotechnology in the European Union

To be successful, biotechnology, as any new technology, needs to be accepted by society in order to penetrate in the socio-economic tissue. Many products and biotechnology derived processes are already present in our lives (see above). However, any new technology raises questions about its expected benefits and its potential dangers. Biotechnology is not an exception. Whereas medical or environmental applications of biotechnology are generally welcomed, others such as the food applications, in particular the use of genetically modified organisms (GMOs) is still perceived with caution by a large sector of the European population. A summary of the results stemming from the projects funded by the European Commission on biosafety and risk assessment of GMOs for over thirty years can be found in reference [13]. The main conclusion is that GMOs are not *per se* more risky than conventional plant breeding technologies.

Public opinion in democratic societies has important and sometimes crucial influence on policy decisions. Policy makers need on one hand to have solid scientific evidence on which to base their policy decisions and on the other hand they also need precise and timely instruments to assess opinion on subjects of public interest, such as biotechnology [12].

The European Commission is following since 1990 the public opinion and perception of Europeans in relation to biotechnology, through the so-called Eurobarometers. The last one took place in 2010 [18]. The main results indicate that whilst an overall majority of Europeans are in favour of biotechnology, the opinion is less favourable with respect to the applications of GMOs to human food. Only 27% were in favour, 57% were against GMO food and 16% did not have an opinion. These results have been fairly constant since the Eurobarometer surveys started more than twenty years ago.

The European Union is particularly attentive that investment in research and innovation are seen as engines for future growth and development and that the proper regulatory environment should help do so in a responsible and acceptable manner.

Transition from FP7 towards Horizon 2020

Following the launching of Europe 2020's agenda [19] and its flagship initiative "Innovation Union" [20], biotechnology has been in the last two years of FP7 (2012 and 2013) gradually shifting the focus towards a much closer link between research and innovation. Projects are expected to be industry driven and include a substantial share of demonstration activities aimed at achieving proofs-of-concept stage. The participation within the consortia of end-users is of paramount importance to facilitate knowledge transfer actions. The biotech industry, with a large component of SMEs, is therefore envisaged to be at the core of the innovation cycle. A key aspect in the transition towards a more intense deployment of this approach is to increase the awareness of biotechnology's potential in chemical and chemistry-utilising sectors to facilitate the expansion of biotechnology in the bioeconomy.

In the last FP7 calls, a much higher emphasis is made on industry, and in particular on SME participation, requiring that a given percentage of the budget of the project proposals should be earmarked to SMEs. The results of the 2011 and 2012 calls showed that more than one third of the selected partners are SMEs and medium or large companies. In terms of budget appropriations, the percentages are around 30% for SMEs and around 6% for medium or large companies (see *figure 2* p. 71). The idea being to couple research, in which Europe excels in basic and fundamental research, with innovation, where Europe needs to strengthen its dynamism. Our societies are in a need to bring the research results into concrete practical applications, or said in other words, link the ability to discover with the ability to exploit the results, either as products or processes [21].

Based on the positive feedback from the proposers on the industrial participation, the Commission decided for the 2013 biotechnology call for proposals, the last one of Framework Programme 7, to include a large number of topics and consequently of the available budget to demonstration projects on biotechnology. Demonstration projects have the aim to prove the techno-economic feasibility of a research idea. Ideally, demonstration projects should allow managers to take sound informed decisions on, either go towards a full industrial production, or on the contrary stop the project. These demonstration projects are expected to help to cross the "death valley of innovation", that is to say, the gap between fundamental research and industrial exploitation. Biotechnology, and in particular industrial biotechnology must accelerate the change from a fossil-based supply chain to a biobased raw material supply chain [22-23] to respond to the socio-economic expectations.

Industrial biotechnology as a key enabling technology

In Horizon 2020, biotechnology has been identified as one of the key enabling technology (KET) under the pillar for "Competitive Industries". In its communication on the European strategy for KETs, the European Commission outlines their role for enhanced growth and jobs in the EU [24] and develops an integrated strategy for research and innovation financing. The specific objective of biotechnology research and innovation is to develop competitive, sustainable and innovative industrial products and processes and contribute as an innovation driver in a number of European sectors like agriculture, food, chemical and health. A strong scientific, technological and innovation base in biotechnology are badly needed to support European industries in securing leadership in this key enabling technology. This position will be further strengthened by integrating the safety assessment and management aspects of the overall risks in the deployment of biotechnology. The foreseen activities go along three converging axes:

Boosting cutting-edge biotechnologies as future innovation drivers

The objective is to lay the foundations for the European industry to stay at the front line of innovation, also in the medium and long terms. It encompasses the development of emerging tools such as synthetic biology, bioinformatics, systems biology and exploiting the convergence with other enabling technologies such as nanotechnology (*e.g.* bionanotechnology) and ICT (*e.g.* bioelectronics). These and other cutting-edge fields deserve appropriate measures in terms of research and development to facilitate effective transfer and implementation into new applications (drug delivery systems, biosensors, biochips, etc).

Biotechnology-based industrial processes

The objective is twofold: on the one hand, enabling the European industry (*e.g.* chemical, health, mining, energy, pulp and paper, textile, starch, food processing) to develop new products and processes meeting industrial and societal demands, and competitive and enhanced biotechnology-based alternatives to replace established ones; on the other hand, harnessing the potential of biotechnology for detecting, monitoring, preventing and removing pollution. It includes research and innovation activities on enzymatic and metabolic pathways, bio-processes design, advanced fermentation, up- and down-stream processing and gaining insight on the dynamics of microbial communities. It will also encompass the development of prototypes for assessing the techno-economic feasibility of the developed products and processes.

Innovative and competitive platform technologies

The objective is to develop platform technologies (*e.g.* genomics, meta-genomics, proteomics, molecular tools) triggering leadership and competitive advantage on a wide number of economic sectors. It includes aspects, such as underpinning the development of bio-resources with optimised properties and applications beyond conventional alternatives; enabling exploration, understanding and exploitation in a sustainable manner of terrestrial and marine biodiversity for novel applications; and sustaining the development of biotechnology-based healthcare solutions (*e.g.* diagnostics, biologicals, bio-medical devices).

In addition, the importance of biotechnology for the European economy and society has been recognised in the Commission proposal for Horizon 2020 by including biotechnology research and innovation activities in its other two pillars namely "Excellence in Science base", ensuring the solid scientific base for Europe and under the pillar for a "Better Society".

Indeed, research and innovation activities applying biotechnology can be found in the societal challenges identified under the pillar for a "Better Society", for example under the "Health, demographic change and wellbeing challenge" where biotechnology activities will range from basic genomics to the support of personalised medicine. As well under the challenge "Food security, sustainable agriculture, marine and maritime research and the bio-economy" where biotechnology will support the development of sustainable approaches for primary production and new processes and products from biobased industries.

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Until the end of 2012, Head of Biotechnologies Unit, **Alfredo Aguilar** is Chairman "Task Force Bioeconomy", at the European Federation of Biotechnology*.

* Biotechnologies Unit, Directorate for Biotechnologies, Agriculture and Food, Directorate General Research, European Commission, B-1049 Brussels (Belgium).
Email: Alfredo.Aguilar@efb-central.org
www.efb-central.org