Sectoral Innovation Watch

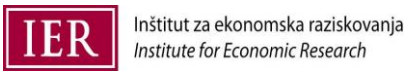
Biotechnology Sector

Final sector report

December 2011

C. Enzing (Technopolis Group)

Consortium Europe INNOVA Sectoral Innovation Watch



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Europe INNOVA Sectoral Innovation Watch

Detailed insights into sectoral innovation performance are essential for the development of effective innovation policy at regional, national and European levels. A fundamental question is to what extent and why innovation performance differs across sectors. The second SIW project phase (2008-2010) aims to provide policy-makers and innovation professionals with a better understanding of current sectoral innovation dynamics across Europe

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Central to the work of the Sectoral Innovation Watch is **analysing trends in, and reporting on, innovation performance in nine sectors** (Task 1). For each of the nine sectors, the focus will be on identifying the innovative agents, innovation performance, necessary skills for innovation, and the relationship between innovation, labour productivity and skills availability.

Sector Innovation Performance: Carlos Montalvo (TNO)	
Automotive: Michael Ploder (Joanneum Research)	Knowledge Intensive Business Services: Christiane Hipp (BTU-Cottbus)
Biotechnology: Christien Enzing (Technopolis)	Space and Aeronautics: Annelieke van der Giessen (TNO)
Construction: Hannes Toivanen (VTT)	Textiles: Bernhard Dachs (AIT)
Electrical and Optical Equipment: Tijs van den Broek (TNO)	Wholesale and Retail Trade: Luis Rubalcaba (Alcala) / Hans Schaffers (Dialogic)
Food and Drinks: Govert Gijsbers (TNO)	

The **foresight of sectoral innovation challenges and opportunities** (Task 2) aims at identifying markets and technologies that may have a disruptive effect in the nine sectors in the future, as well as extracting challenges and implications for European companies and public policy.

Sector Innovation Foresight: Matthias Weber (Austrian Institute of Technology)	
Automotive: Karl Heinz Leitner (AIT)	Knowledge Intensive Business Services: Bernhard Dachs (AIT)
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Task 3 will **identify and analyse current and potential bottlenecks that influence sectoral innovation performance, paying special attention to the role of markets and regulations.** Specifically, the analysis will cover the importance of the different factors in the propensity of firms to innovate.

Role of markets and policy/regulation on sectoral patterns of innovation: Carlos Montalvo (TNO)	
Katrin Pihor (PRAXIS)	Klemen Koman (IER)

Task 4 concerns **five horizontal, cross-cutting, themes related to innovation**. The analyses of these horizontal themes will be fed by the insights from the sectoral innovation studies performed in the previous tasks. The **horizontal reports will also be used for organising five thematic panels** (Task 5). The purpose of these panels is to provide the Commission services with feedback on current and proposed policy initiatives.

Horizontal reports	
National specialisation and innovation performance	Fabio Montobbio (KITes) and Kay Mitusch (KIT-IWW)
Organisational innovation in services	Luis Rubalcaba (Alcala) and Christiane Hipp (BTU-Cottbus)
Emerging lead markets	Bernhard Dachs (AIT) and Hannes Toivanen (VTT)
Potential of eco-innovation	Carlos Montalvo and Fernando Diaz Lopez (TNO)
High-growth companies	Kay Mitusch (KIT-IWW)

Contents

Acknowledgements

The final sector report for the biotechnology sector builds on the result of the various tasks in the Europe INNOVA Sectoral Innovation Watch:

Dachs, B., I. Wanzenböck, M. Weber, J. Hyvönen and H. Toivanen (2011) *Lead Markets*, Final Report Task 4, Horizontal Report 3, for DG Enterprise and Industry, European Commission, March 2011

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Grupp†, H., D. Fornahl, C.A. Tran, J. Stohr, T. Schubert, F. Malerba, Montobbio F., L. Cusmano, E. Bacchiocchi, F. Puzone, (2010) *National Specialisation and Innovation Performance*, Final Report Task 4 Horizontal Report 1, Europe INNOVA Sectoral Innovation Watch, for DG Enterprise and Industry, European Commission, March 2010

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Montalvo, C., F. Diaz Lopez, C. Enzing and K. Koman (2011) Analysis of market and regulatory factors influencing sector innovation patterns – Biotechnology Sector, Final Report Task 3, Europe INNOVA Sectoral Innovation Watch, for DG Enterprise and Industry, European Commission, December 2011

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Executive summary

Biotechnology has evolved from a single set of technologies in the mid 1970s into a full grown technological field that is the driving force in innovation processes in many industrial sectors (pharmaceutical, medical, agriculture, food, chemical, environment, instruments). Nowadays, biotechnology is considered as a very important contributor to future economic growth, job creation, public health, environmental protection and sustainable development. About 1.55% of the EU gross value added can be ascribed to the application of modern biotechnology.

Improving the innovation performance of these EU firms is crucial for them to gain a better competitive position. Within the European Commission there is also a strong need to continue promoting the development of life sciences and biotechnology, in particular by increasing research and promoting competitiveness. For that reason the biotechnology sector has been chosen as one of the nine sectors in the second Sectoral Innovation Watch (SIW-II) study.

The biotechnology sector is very heterogeneous as biotechnology is applied in a wide number of industrial sectors, which innovation systems differ considerably from each other. For that reason this study presents and discusses the innovation characteristics for the three industrial sectors in which biotechnology has its largest impact: pharmaceutical industry, agrifood industry and chemical industry (in combination with the bioremediation industry), i.e.: the red, green and white biotechnology sectors.

Chapter 1 of this report presents – after an elaborate description of the specific characteristics of the innovation process in each of the three biotech subsectors - the innovation performance of the biotechnology sector. The CIS data used for the study are those collected in the period 2002-2004 (CIS4) and deal with the subsection NACE 73.1 ('Research and experimental development on natural science and engineering'). The CIS4 based analysis shows that biotech sector is highly innovative: the large majority of firms are engaged in innovation, and of those firms the large majority introduced products that were actually new to the market and not only new to the firm. All three types of innovation (product innovation, service innovation and innovation of production systems) were found to be of importance. Most of the turnover of the firm results from the sale of existing products, which can be R&D services or performing tests for clients etc. Collaboration, especially with knowledge institutes, seems to be a common practice. International collaboration and collaboration with firms is more common in the Western and Northern European countries than in the other parts of Europe. Patents are commonly used to appropriate returns on investment and the large majority of firms is engaged in training activities. The fact that most new products that are introduced are actually new to the market may indicate that patent protection is quite effectively in biotechnology. A notable difference appeared between country groups and firm sizes where the acquisition of external funding is concerned. Large firms make use of all different sources of funding. Small firms are relatively more dependent on funding by local or regional authorities, and make limited use of EU-level funding opportunities. Especially in Central an Eastern European countries, the level of local funding is low, which could indicate that it is relatively more difficult for small firms to survive in those countries. More generally, it could be that the barriers for obtaining funding from the EU are at this moment too high for

small firms. In addition, performance figures on the three biotech subsectors are presented (private R&D expenditures and employment, public funding, publications, patents, regulatory costs).

The second chapter addresses the carriers of biotech innovations at three different levels: people, organisations and networks/clusters. The 'People' section presents figures on biotech-related employment in Europe. Based on a combination of sources the estimate is made that biotech-related employment in Europe (EU15 + 3 countries) ranges between 1.6 and 2.2 million FTEs. Studies show that there is a shortage of highly qualified personnel especially engineers and technicians in specific application oriented and industry-relevant areas such as bioprocess engineers and qualified personnel with comprehensive knowledge of the industry and professional experience in all aspects of biotech business making such as capital raising, regulatory affairs, marketing, etc. Besides universities public research organisations (such as CNRS, INRA in France, Fraunhofer in Germany, and TNO in The Netherlands) are important research organisations. When comparing the European biotech research centres with those in the US it shows that the first are larger in terms of the total number of research staff and in terms of budgets and employ more researchers on a short-time basis. US centres prefer long-term employment. Although the numbers of doctoral students per centre and per research staff member are similar, European centres have double the productivity of US centres in PhDs awarded for both these measures. Groups of companies and research organisations cluster together in so-called bio clusters or bioregions. Some of these clusters are the result of the spontaneous co-presence of key factors (such as entrepreneurial scientists, or an active Chamber of Commerce); others are triggered by regional or national governments that created the conditions for cluster formation. Europe holds - compared to the USA - relatively more policy driven clusters; also European clusters are younger than most USA clusters.

Chapter 3 focuses on trends and drivers that shape future development in the three biotech sectors. Key drivers of change in biotechnology include rapid advances in science and technology, the convergence of technologies (biotechnologies and ICT for example), and cost reductions in DNA sequencing. In addition to these supply side drivers there are important drivers on the demand side such as economic growth, leading both to investments in biotechnology and a growing demand for advanced products. Public acceptance and regulation are other (Intermediate) key drivers of biotechnology development. Based on a combination of two key drivers which both display high impact and in which there are also significant uncertainties – economic growth and extent of regulation - four scenarios were developed.

Scenario I: 'Loosing Momentum: GMO ban & basic healthcare': There is very limited growth of the biotech sector as a result of low investments and regulatory restrictions.
Scenario II: 'Cost-effective innovation': The extent of regulation is limited, which implies that some new possibilities can be explored. However, this is limited by the lack of investments, so cost-effectiveness is crucial.

Scenario III: 'Acceptable technology, sustainable innovations': Innovation is booming because of the high levels of investments made, but restricted in some application sectors by regulation.

Scenario IV: 'New Horizons': A wide range of new technologies, applications and services has been developed as a result of high investments and limited regulation.

The impact for the three biotech subsectors is elaborated in each scenario. With regard to scenarios there are major differences in the level and types of barriers and requirements. A distinction can be made between regulatory barriers, investment barriers and demand barriers. Obviously, the regulatory barriers are high in the high regulation scenarios. Investment and demand barriers are important in the low economic growth scenarios. In general, industrial biotechnology applications face little objection as they mostly take place in contained environments. Resistance to GMOs in agriculture in Europe is strong but more limited in medical biotech when improved essential medicines are produced. At the same time ethical concerns about the use of human embryonic stem cells may subside as the utilisation of adult stem cells or even ordinary other cells (e.g. skin cells) will improve e.g. through advances in "reprogramming" techniques (the creation of induced pluripotent stem cells) or by even bypassing the "reprogramming" stage through genetic technologies. In addition a number of emerging biotech-based innovations themes are described that may lead to new or improved products and processes in the three biotech subsectors. Finally, potential barriers and requirements for these innovation themes to develop into successful products for (new) markets and more effective production processes are described. They have been grouped in five sets: physical infrastructure, knowledge and skill requirements, organisational change and firm strategies, institutional change and regulatory issues and structural change.

Chapter 4 studies in more detail a number of key drivers, not sufficiently explored in the first Sectoral Innovation Watch (SIW-I) study – market and regulation – and their impact on the innovativeness of firms and a number of factors in the innovation system and their effect on innovation. Based on a survey under European biotech firms and CIS4 data, it provides insight in how the companies themselves perceive the relation between regulation-related and market-related factors on the innovativeness of the firm. The quantitative analysis tested the relationships of dependence in the biotech sector between innovation outcomes, innovation activities, market factors and regulation.

High-oil prices showed to be an important driver of innovation in the biotech sector. This is very much in accordance with what was found in other studies and especially applies for the white biotech sector where second and third generation biomass-based fuels are being developed as alternative to fossil fuels. Also customer preferences and market structure (industry consolidation, market concentration) were found to be drivers of innovation. This also applies for increased demand for products and inputs in Asia and Eastern Europe, supplier power to influence firms' costs structure, incumbents' current market position and pace of innovation in firms' business type. These outcomes confirm the important role of demand side factors that are directly related to the client itself and is in accordance with what one can expect from the type of biotech companies that were involved in the survey: high-tech firms working on a business to business market in close contact with their clients i.e. other companies in the biotechnology innovation chain. Aging of population that was indicated as an important driver, especially for the health-biotech sector in the SIW-I study but also in the foresight study of SIW-II (chapter 3), was not found to be a driver of innovation in the biotech sector. This difference in outcome

could very well be explained by the sample of companies that participated in the survey. Most of them are small biotech companies and these types of companies do not produce for a consumer market (but for the industrial market) which could explain why this specific market trend (aging population) is not relevant for them. Mostly they operate in a business-to business market and sell technologies and services that can be used by many different companies in the red, green of white biotechnology. The outcomes of the analysis for regulation (including many different types of regulations companies should comply with) do not lead to strong conclusions on the effects of specific regulations on innovation in the biotech sector, only 'labour regulations' and 'interoperability-compatibility (between old and new standards)' were highly significantly correlated to innovation in biotech firms. It could be that these outcomes are not specific for the biotechnology sector and that they are more representative for small firms that have to deal with labour regulations and the compliance with these regulations leading to the development of procedures that have a positive effect on the efficiency of their innovation processes. IP regulation was found to be positively associated to the innovation type 'industrial relations' and European regulations to 'product innovation' and 'innovation in supporting activities in the sector'.

Chapter 5 addresses a number of so-called 'horizontal issues' dealing with innovation and innovation performance: technological specialisation, eco-innovation and lead markets. The technological specialisation analysis – based on patent data – showed that in Europe, biotech belongs to the top 5 of the set of selected sectors when it comes to patenting activities. The relative technological advantages in the biotechnology sector are mainly concentrated in Denmark and Belgium. Moreover, the study shows that Europe has a strong disadvantage in pharmaceuticals and biotechnologies and that the US technological profile is more distinctly oriented towards biotech and pharmaceuticals. This pattern – Europe weak, US strong - strongly persists over time. Also other global players are sharpening their biotechnological profiles; India is strongly specialised in pharmaceuticals and organic chemistry and exhibits technological advantages in biotech. Also Japan shows some strength in biotech, but it lags far behind. China shows no clear specialization pattern. Based on co-inventorship data (the team that has been working on the patent and owns the patent), the analysis of collaboration patterns shows that in the biotech sector the network connections are decreasing. Germany is a central player in Europe for the whole network; it holds most of the connections to the EU15 countries and to the New Member States. Beside Germany, the United Kingdom also plays an important role in the first period (1994-1996), but this importance changes in the second period (2000-2002). Furthermore, nearly all collaborations from New Member States to non-EU countries disappear. Most of the strong connections in the first period exist between specialised countries (Belgium, Denmark, United Kingdom and United States). The loss of linkages in the United Kingdom (UK) in the second period may be caused by the country lower specialisation in the 'biotechnology' sector, and the increased specialisation in the USA. The analysis of the eco-opportunities in the biotech sector of a number of eco-priority areas (greenhouse gas abatement, energy efficiency, material efficiency, waste minimisation, new advanced eco-materials, eco-design, recycling and reuse) consisted of three parts: current opportunities, opportunities available but not applied yet, and potential for eco-innovation. The overall conclusion is that eco-innovation opportunities of biotechnology linked to new eco-materials

are manifold but the penetration rate is still low. The 'lead market' analysis concludes that lead times for new innovation designs in biotechnology are long and uncertainty is high in the biotechnology sector. Positive experience with certain products on the lead market will subsequently reduce uncertainty abroad (demonstration effect) and may facilitate the transfer of new products and processes to other markets. Moreover, positive experience with a specific product or process on the home market will reduce potential consumer fears concerning new biotechnology applications and enhance acceptance abroad. A lead market at the forefront of a trend will offer other markets the answers to their open questions and deliver solutions to counter their reluctance. On-going communication and information about technological improvements and advantages arising from application on the lead market will enhance the exportability to other markets. Further export potential may arise from a harmonisation of the currently divergent regulatory framework at the EU-level.

In the sixth and last chapter policy relevant conclusions are drawn: five different issues resulting from the study ask for attention by European policy makers:

- shortage of highly qualified personnel: especially engineers and technicians in specific application oriented and industry-relevant areas such as bioprocess engineers (in the chemical sector) and qualified personnel with comprehensive knowledge of the industry and professional experience in all aspects of biotech business making such as capital raising, regulatory affairs, marketing, etc.;
- Sufficient funds: the lack of funding hampers innovation in this sector. There is a need for more risk capital, seed financing and general research funding at all stages. This financial support is needed for start-ups as well as for existing companies moving to more innovative products;
- sustainability: as Europe still has a strong position in the science base in the field of bio-based production processes and a strong enzyme and chemical industry, strategies should be developed on how to keep and further improve these strengths with Europe;
- Globalisation and offshoring: Europe as a whole lags behind the main international competitors, in terms of investments and capacity to drive new technological trajectories especially in the red biotech sector. The international character of the biotechnological innovation process, combined with a strong market and strong R&D competences in the USA and lower labour costs in Asia, asks for developing new strategic niches for the European red biotech sector;
- Social-economic research to support effective evidence based policy making.

1 Introduction

Biotechnology has evolved from a single set of technologies in the mid 1970s into a full grown technological field that is the driving force in innovation processes in many industrial sectors (pharmaceutical, medical, agriculture, food, chemical, environment, instruments). Nowadays, biotechnology is considered as a very important contributor to future economic growth, job creation, public health, environmental protection and sustainable development. In biotechnology, EU firms face fierce competition, especially from their US and Asian counterparts. Improving the innovation performance of these EU firms is crucial for them to gain a better competitive position. Within the European Commission there is also a strong need to continue promoting the development of life sciences and biotechnology, in particular by increasing research and promoting competitiveness (EC 2007). For that reason the biotechnology sector has been chosen as one of the nine sectors in the second Sectoral Innovation Watch (SIW-II) study.

The biotechnology sector is very heterogeneous as biotechnology is applied in a wide number of industrial sectors, which innovation systems differ considerably from each other. For that reasons this study goes into more depth and presents and discusses the innovation characteristics for the three industrial sectors in which biotechnology has its largest impact: pharmaceutical industry, agrifood industry and chemical industry in combination with the bioremediation industry.

The structure of this report follows the structure that is used by all final sector reports. It is an extensive summary of the most important results that have been achieved under the different tasks of the SIW-II project. Chapter 2 presents the patterns of sectoral innovation in the three biotech subsectors and the innovation performance of the biotech sector. In the second chapter the most important issues with respect to the carriers of innovation – people, organisations and clusters – are being discussed. In chapter 4, the main trends and drivers that have an impact on future developments in the three biotech subsector are presented, based on the outcomes of expert workshops. Chapter 5 presents the results of a quantitative study on the importance of two important drivers of innovation - market and regulation – for innovation activity and outcome. In chapter 6 the results of a number of horizontal studies are being presented: technological specialisation, eco-innovation and lead markets. Chapter 7 presents a policy analysis and conclusions.

2 Patterns and performance of sectoral innovation

2.1 Characterisation of the biotech sector: red, green and white biotech

In order to get a good understanding of the innovation performance of the biotechnology sector, this study focus at the level of the subsectors in which biotechnology is applied: the red, green and white biotechnology as the subsectors differ considerably in innovative performance (see section 2.4) and economic performance (see box 2.1).

Box 2.1 Contribution of red, green and white biotechnology to the European economy

In total, between 1.4 and 1.7% of the EU gross value added (GVA) can be ascribed to the application of modern biotechnology. The contribution of turnover of biotechnology-based applications in the pharmaceutical sector (biopharmaceuticals, diagnostics, and recombinant vaccines) as part of the EU GVA is about 0.04%. The USA turnover of these three pharma product groups was more than two times higher: 28.7 billion EUR compared to 13 billion EUR for EU. The contribution of green biotechnology to the EU GVA, based on data available for 8 EU Member States, was estimated at 0.01%. Data on the economic contribution of white biotech to EU GVA are not available. Biotechnology applied in the development and production of enzymes, which is an important product of the chemical industry and the use of enzymes in products and processes in downstream sectors (food/feed, detergents, textile, pulp/paper and fuels) was estimated to contribute to 0.08% of the EU GVA. Application of enzymes in bioprocessing (biocatalysis) increases labour productivity by 10-20% of the average value for the relevant downstream sectors.

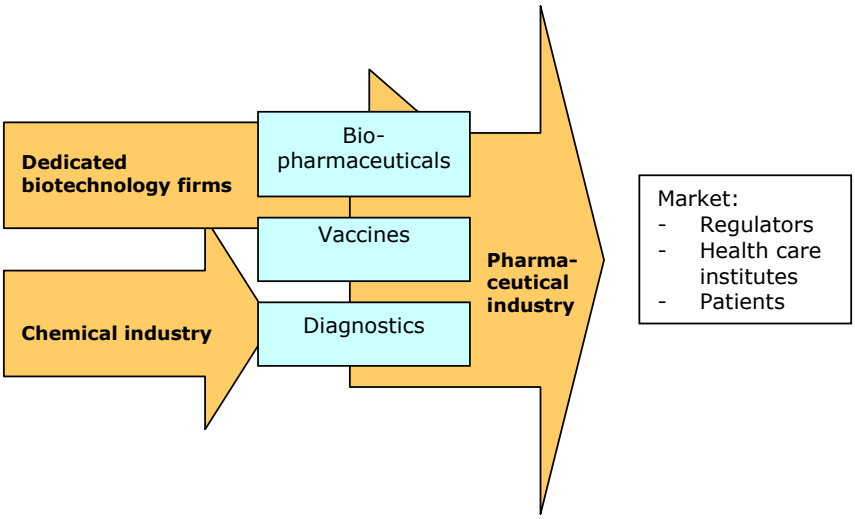
Source: Papatryfon et al., 2007

In the next three sections the main characteristics of the red, green and white biotech subsectors are presented and discussed: the characteristics of the production chain and (changes in) industry structure.

2.1.1 Characterisation of innovation performance in red biotechnology

The red biotechnology subsector – mostly covering the pharmaceutical industry - is a global industry. While the US has traditionally been leading and Europe has been follower, Asia is also becoming increasingly competitive (Ernst & Young, 2007). Small high tech firms are important agents in innovation in red biotechnology. The radical nature of biotechnology developments in pharmaceuticals provided opportunities for small specialised firms to enter this sector. Over time, as large pharmaceutical firms became more knowledgeable about biotechnology themselves dedicated biotechnology firms (DBFs) became explorers of knowledge and new applications (Pyka and Saviotti, 2001). DBFs have therefore acquired an important position in filling the pipelines of pharmaceutical companies, as is shown in figure 2.1. DBFs usually do not develop end products but at some stage during product development, before large scale clinical trials need to be conducted, they sell their product candidates to pharmaceutical firms. Also, the chemical industry provides inputs for the pharmaceutical industry.

Figure 2.1 Red biotech production chain



Networks of relationships in product development in red biotechnology are grouped around large multinationals. DBFs and leading public research institutes have become stable entities in these networks, as they have relationships with these large organisations (Powell et al., 2005). Increased outsourcing has led to the emergence of global manufacturing organisations and clinical research organisations (CROs) (Ernst & Young, 2008b). It is expected that mergers and acquisitions among firms active in red biotechnology will keep taking place in the coming years (PWC, 2007; Tait, 2007).

The value chain in red biotechnology is evolving because of the pressures of globalisation, pricing and decreasing efficiency of R&D (Gassmann et al. 2004; Ernst & Young 2008b). Notable changes for the near future are the increasingly important position of patients and patient organisations, because of the emergence of personalised medicine (Ernst & Young, 2008b). To develop diagnostics to be used in combination with personalised biopharmaceuticals, relationships between companies producing diagnostics and those producing drugs need to be formed. Diagnostic firms are clearly aware of the urgency of setting up this collaboration. This is different for pharmaceutical firms; they do not clearly regard diagnostic firms as partners that are of vital importance in their product development (Van Merkerk and Boon, 2007).

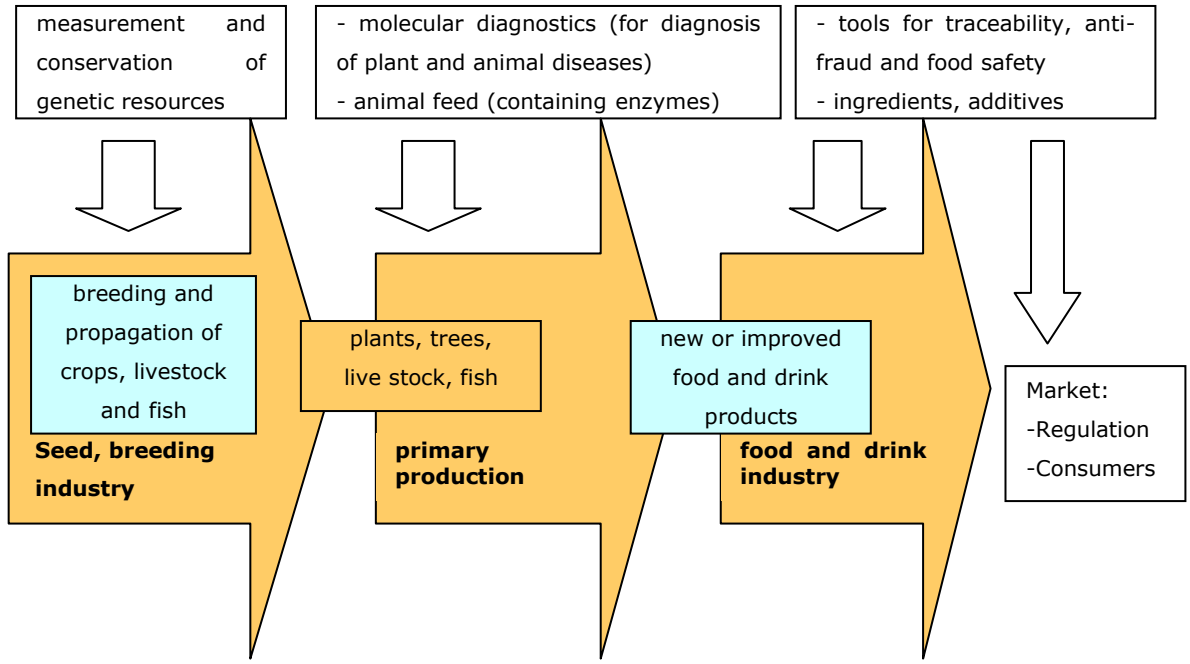
2.1.2 Characterisation of innovation performance in green biotechnology

Green biotechnology is the application of biotechnology in the agrifood sector. Several different biotechnologies are used in the development of a large variety of new or improved products: products that are part of the agrifood production chain (such as seeds, yoghurts) and products that are inputs to this chain (e.g. animal feed containing phytase enzymes, or food additives such as enzymes that are used for fruit juice or wine clarification) or that are used as supportive tool (e.g. diagnostic tools for plant or animal diseases or for food safety). Biotechnology also plays a role as a process technology as it helps speeding up breeding processes of new crop varieties and biotechnology research is used for the improvement of production processes in the food industry. See figure 2.2 for an overview of the

applications of modern biotechnology in the agrifood chain (blue boxes) and the related supplying sectors (white boxes).

The dynamics in the seed industry – which holds important innovative actors in the green biotech innovation system – have been considerable and acquisition of patent rights has been a driving force in this process (Marco and Rausser, 2008). Worldwide consolidation processes have led to a situation where only a few large firms dominate; SMEs that were active in developing plant varieties have been bought up, merged, or disappeared (Brennan et al., 2005; Joly and Lemarie, 1998). Blank (2008) found that the life of an agricultural biotech product or technology is short because new patents held by another firm can block the development of a product, or the creation of new intellectual property which supersedes the original technology. This and the high costs of regulatory requirements for biotech crops especially in the case of food crops are significant barriers for SMEs to enter this market (Chataway et al., 2006) and have been responsible for the consolidation process in this sector (Blank, 2008).

Figure 2.2 Green Biotech Production Chain



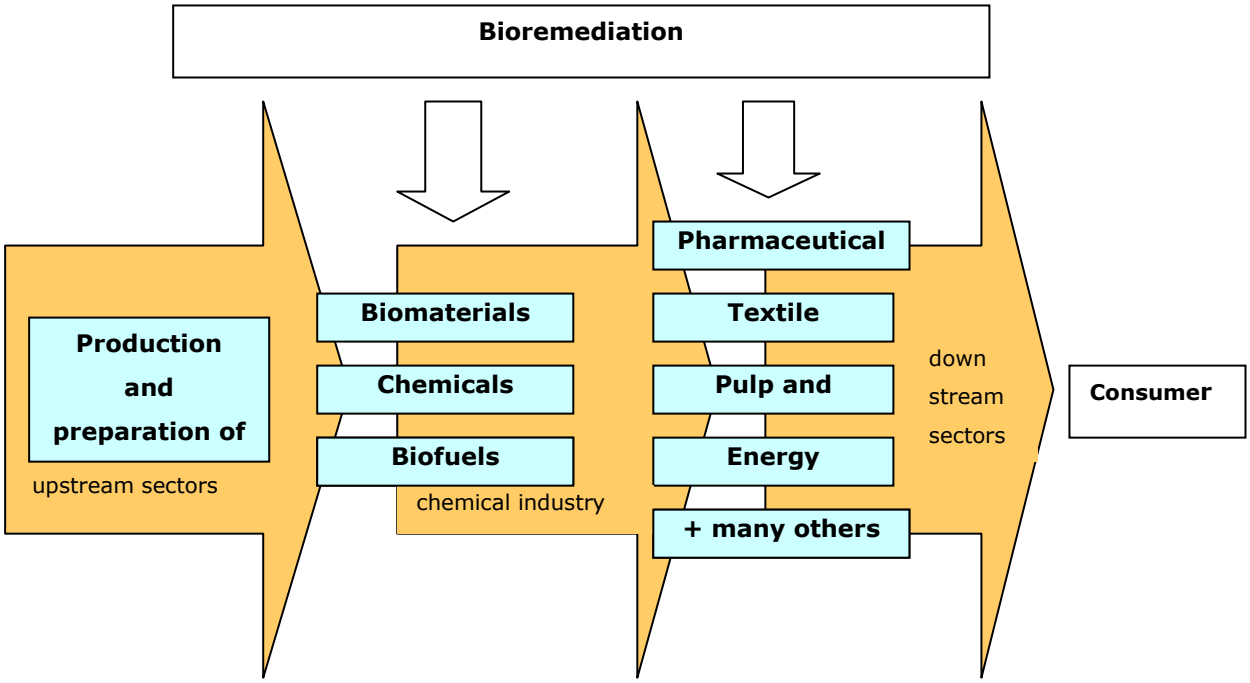
2.1.3 Characterisation of innovation performance in white biotechnology

White biotechnology – also referred to as industrial biotechnology - is the application of modern biotechnology in the development of products and in production processes in the chemical industry and the environmental sector with the ultimate goal of improving the efficiency of industrial processes, using biomass for new applications, and reducing negative environmental impacts. The chemical industry has used biotechnological processes for many years for both bulk chemicals (large production volumes, low product prices, low profit margins) and specialty and fine chemicals (small production volumes, high product prices, high profit margins). Advances in genetic engineering, metabolic

engineering and other molecular biology technologies have expanded the application potential of biotechnology and have overcome many obstacles in fermentative and enzymatic conversion (biocatalysis) processes (OECD, 2001). Although the number of industrial biotransformation processes has increased in the last decades, the overall use of biotechnology in the chemical sector is still rather small. Estimations show that the share of biotechnological processes in the production of chemicals in 2004 was about 5% (world-wide), with an increase to 20% in 2010 (Dechema, 2004).

The most important agents in the biotechnological innovation process in this subsector are chemical companies and dedicated biotech firms specialised in the field; the latter constitute about one third of the 300 companies active in industrial biotech found in Europe (Reiss et al., 2007). These chemical products are inputs for a large variety of business-to-business markets that are positioned downstream in the white biotech production chain (see figure 2.3) and are used in an innumerable large number of consumer products. In those parts of the down stream sectors that use enzymes (one of the products of the chemical industry) as agents in production processes (food, textile, pulp and paper, leather) considerable levels of biotechnology expertise is required in order to make these processes work well (ibid).

Figure 2.3 White Biotech Production Chain



The environmental sector is that part of the instruments/equipment sector that produces instruments that use biological principles for monitoring (biosensors) and cleaning of contaminated environmental media (bioremediation). These bioremediation technologies were first used for wastewater treatment, followed by air and off gas cleaning with biofilters. Nowadays, bioremediation technologies are also used for the treatment of soil (on site and off site) and solid waste. Bioremediation technologies are used in a wide number of sectors, including the chemical sector and downstream sectors (for which it is included in figure 2.3).

The production of biomass-based chemicals has an impact on the structure of this industry as it requires different production chains compared to the existing petro-based chains. New alliances between companies in the chemical industry and the agrofood sector are being made. An example is the production of Bio-PDO in a joint venture of DuPont with Tate and Lyle. Others are the cooperation between Roquette (French starch manufacturer) and Dupont on isosorbide, with the aim to produce more bio-based PET plastics. Recently, DSM (in collaboration with French Roquette) has announced to commercialize the fermentative production of biobased succinic acid. In 2009 a demonstration plant (with capacity of several hundreds of tons) is anticipated, in 2011 large scale production (site unknown) is planned (DSM & Roquette 2008). Also, new trade relations are being established, such as Shell and SABIC buying bio-ethanol for ETBE production. Companies from the agro-food sector such as ADM, Cargill, Tate & Lyle, Abengoa, Cosun, Roquette, Südzucker, Campina, KEMIRA, BER, and Blue Ocean are newcomers in the area of bulk chemical production. These companies are in the process of defining their future strategy towards non-food products; they intensify their activities with regard to the potential production of bulk chemicals.

2.2 Statistical definition of the sector

As biotechnology is not a clearly delineated traditional economic activity, it was not included as a separate sector in by national and international statistics. However, because of the economic importance of biotechnology applications (see also Reiss et al., 2007), efforts have been made to capture this importance and develop a statistical definition. The OECD has taken the initiative to develop a statistical definition of biotechnology and recommends OECD Member States and others to use this definition for statistical data collection. The OECD definition consists of two parts: a single definition and a list based definition. In the single definition, biotechnology is defined as: “The application of science and technology to living organisms, as well as parts, products and models thereof, to alter living or non-living materials for the production of knowledge, goods and services”[1]. As this single definition is very broad the OECD recommends using this single definition always in combination with the list-based definition. This list-based definition provides a list of specific life sciences and biotechnology techniques, which is not exhaustive and is expected to change over time as data collection and biotechnology activities evolve. In addition the OECD is collecting statistical data on biotechnology: the OECD Biotechnology Statistics Report of 2009 (OECD, 2009c) include biotechnology statistics of 26 countries, including 16 European Member States.

In its report on the influence of regulatory and policy issues on innovation (Cleff et al., 2007), the consortium that performed the first Sectoral Innovation Watch (SIW-I) study, used the NACE 73 data and complemented it with data on pharmaceuticals (NACE 24.4) to capture also biotechnology activities on the health application field. A drawback is that NACE 73 also includes R&D activities in the field of social sciences and humanities. Also, application sectors of biotechnology other than pharmaceuticals are omitted. Some of the other application sectors, such as food processing are also

[1] http://www.oecd.org/document/42/0,3343,en_ 2649_34537_1933994_1_1_1_1,00.html

highly important (Bloch, 2006), so the choice to exclusively include pharmaceuticals is not justifiably. In this SIW-II study on biotechnology it was decided to use only data on the NACE 73.1 category ('Research and experimental development on natural science and engineering') for the analysis of innovation performance of the biotechnology sector as this provides a more accurate capturing of biotechnology activities than using NACE 73. However, the results presented in this report should nonetheless be interpreted with caution: they only partly cover the field of biotechnology, and also they include activities that are not (directly) related to biotechnology.

2.3 Common set of performance indicators

In the SIW-II study a common set of performance indicators is used for all nine sectors, including the biotech sector (see table 2.1, first column under a). In addition to the data related to these CIS4-based indicators, data on a number of innovation performance indicators specific for the biotechnology sector distracted coming from available studies have been collected. Both sets of indicators are presented in the first column of table 2.1. In the second column the sources for the additional biotech specific performance indicators that have been used in the SIW-I Biotechnology Sector report (Patel et al. 2008) are presented; the third column mentions the additional data sources used in this SIW-II Report. Besides those presented in table 2.1, no other data sources on the European biotechnology sector are available at the time of this study.

Table 2.1 Set of performance indicators and sources: CIS4-based and additional for biotechnology

Common set of innovation performance indicators: **a) CIS4 (NACE 73.1)** **b), c) etc., additional biotech specific data**	**Sources used in SIW-I Biotech Report**	**Additional sources**
Innovative activity:		
a) four CIS-indicators (see table 2.2)		
Newness of product and turnover:		
a) five CIS-indicators (see table 2.3)		
b) revenues of dedicated biotechnology firms (EU and US)	Critical I 2006	
R&D activities and funding:		
a) ten CIS-indicators (see table 2.4)		
b) R&D expenditures (% of value added) of dedicated biotechnology firms (EU and US)	Critical I 2006	
c) share of dedicated biotech firms innovating in-house (EU and US)	Critical I 2006	
d) number of employees of dedicated biotechnology firms (EU and US)	Critical I 2006	
e) number of biotech firms (EU and US)	OECD 2006	OECD 2009c
f) public funding of biotechnology research (EU)	Enzing et al. 2007	
g) venture capital for dedicated biotech firms	Enzing et al. 2007	
h) regulatory costs		OECD 2009c
Cooperation:		
a) eight CIS-indicators (see table 2.5)		
b) number of strategic alliances in biotechnology	Merit database	
IPR:		
a) five CIS-indicators (see table 2.6)		
b) biotech related patents (EU and US)	OECD 2006	OECD 2009c

In this report we will not again use and present the data that were already presented in the SIW-I report. We use additional sources covering EU (and other world regions) that have become available after 2007 (including OECD, 2009c).

2.4 Performance of the biotechnology sector

2.4.1 Innovation performance: CIS4 data

In this section, CIS4 data (NACE 73.1) on the innovation performance of the biotechnology sector is presented including innovation activities of firms and their returns, external funding, collaborating with other organisations, intellectual property, etc.[2]. Differences between regions in Europe (West&North, Central&East and South) are examined, as well as differences between firms of a different size: small (less than 50 employees), medium-sized (50 to 249 employees) and large companies (250 or more employees). The percentages listed in the tables below indicate the share of firms, in general or of a certain country group or firm size, that have affirmed to make use of a certain practice or procedure. That last column presents the total (for all country groups, for all firm sizes).

Innovative activities

Generally speaking, as was expected, the majority of biotech firms are engaged in innovation. On average, the country group West&North Europe (including EU15 plus Norway) is most innovative: 77% of the firms in these countries are engaged in innovation. Central&East European countries are less innovative with 52% of firms engaged in innovation (see table 2.2).

The country groups differ in regard to the focus of their innovative activities. For the West&North countries, introducing improved goods is most important: about 62% of firms applied this type of innovation. In relative terms, the introduction of new methods of production was least important for firms in this country group (about 46%). The percentage of firms that engaged in service innovation was 57%. The relative importance of the different forms of innovation is somewhat different in the other country groups. The most important innovative activity in Central&Eastern Europe is the introduction of new methods of production (about 37% of firms), while in Southern Europe all three forms of innovation are just about equally important.

Table 2.2 Innovation activities of firms

Innovative activity	EU Country Group			Firm size			All firms
	Central & East	West & North	South	Small	Medium	Large	
General innovation activity (goods, services, process)	52,3%	77,3%	61,4%	61,0%	77,3%	90,9%	66,4%
Introduced onto the market new or significantly improved good	34,1%	61,6%	31,5%	40,9%	54,4%	71,8%	45,8%
Introduced onto the market new or significantly improved service	26,4%	57,4%	35,8%	39,9%	48,4%	70,3%	43,5%
Introduced onto the market a new or significantly improved method of production	37,5%	45,7%	35,2%	35,7%	47,0%	74,5%	40,5%

[2] The CIS4 data has been obtained directly at the premises of the Eurostat Safe Centre in Luxembourg. Due to reasons of anonymity, data availability and data protection policies at Eurostat, the data sets are limited. Overall the CIS4 data is mostly suitable for comparative analysis between firms from different country groups and different size classes.

In general, large firms are the most innovative. About 91% of these firms introduced a new product, service or method of production compared to 61% of the small firms and 77% of the medium-sized firms. For small and medium-sized firms product innovation is most important, whereas large firms are about equally involved in all three forms of innovation. These differences in innovation performance of firms of different sizes could possibly be explained by the fact that small firms often focus on the commercialisation of their existing knowledge, in order to achieve some financial independence.

New products and their importance for generating turnover

New products can either be new to the market or only new to the firm. From the data presented in table 2.3 it can be observed that most new products that were introduced were new to the market. As is shown in the table about 70% of all firms introduced a product that was new to the market, and about 55% introduced a product that was only new to the firm.

For all country groups and firm size categories, products that are only new to the firm are relatively of less importance. This shows the highly innovative nature of biotech firms belonging. Central&Eastern European countries have the highest share of firms that introduced new products to the market (74% compared to 70% for West&North and about 67% for Southern Europe). On the other hand, Southern European countries have the highest share of firms that induced products that were only new to the firm (64% compared to 55% for Central&Eastern Europe and 50% for West&North Europe).

Table 2.3 New products and their turnover of firms

Newness of product and turnover	Country group			Firm size			All firms
	Central & East	West & North	South	Small	Medium	Large	
The enterprise introduced product new to the market	74,0%	70,5%	66,6%	69,1%	70,8%	75,7%	70,1%
The enterprise introduced product new to the firm	55,3%	50,2%	64,4%	50,8%	61,4%	68,3%	55,0%
% of turnover in new or improved products new to the market and introduced during 2002-2004	29,5%	22,3%	22,0%	25,0%	19,5%	25,0%	23,5%
% of turnover in new or improved products new to the firm, during 2002-2004	16,0%	10,8%	22,7%	15,4%	14,2%	18,1%	15,3%
% of turnover in unchanged or marginally modified products during 2002-2004	51,9%	66,3%	41,9%	55,6%	58,4%	57,0%	56,5%

The importance of innovation for a firm as well as the commercial success of innovation can be examined by looking at statistics on turnover derived from innovations. The CIS4 statistics on turnover show that the largest share of turnover is generated from products that are unchanged or only marginally modified. This is the case for firms in all country groups and for all firms of sizes. About 56% of all turnover is generated from these non-innovative products, while 23% derives from the sale of products that were new to the market and 15% from the sale of products that are new to the firm. These figures are similar when subdividing the firms into the three size categories, as can be concluded from table 2.3.

When looking at the specific data for each of the country groups separately it can be observed that especially in the West and North group returns are based on non-innovative products. This is 66% compared to 52% for the Central&Eastern European countries and 42% for the Southern European countries. Firms from Southern European countries generate the largest percentage of turnover from innovative products that are new to the firm (about 23% compared to 16% for Central&Eastern European countries and 11% for West&North). The percentage of turnover deriving from the sale of innovative products that are new to the market is highest among Eastern European countries (29% compared to 22% for West&North and 22% for Southern European countries).

Overall, the percentage of turnover derived from innovations is higher for the biotech firms than for manufacturing firms in general. This means that while the largest share of income is still gained from existing products, innovations are relatively important in this sector compared to the average of all other sectors.

R&D and funding for innovation

In most firms R&D activities are an important source for developing new or improved products and processes. These activities require intramural and extramural expenditures, expenditures for purchase of machinery, training of personnel, marketing, and possibly also expenditures to acquire other external knowledge. On average the R&D intensity (percentage of total turnover that is spend on R&D) of firms is 64%. About 48% of the firms were involved in market introduction of new products, services and/or processes. Training was a source of innovation for more than 70% of the firms (this figure is 49% for all manufacturing sectors). Another important source of innovation was acquisition of machinery: 70%. To cover the R&D expenses, the large majority of firms (90%) used external funding. In general, the most important sources of funding for this R&D are the central governments of the countries in which the firms reside (about 64% of all firms use this source) and FP5 and FP6 of the EC (63% of all firms use this source). Local governments and the EC in general are a bit less important (43% and 41% respectively). In table 2.4, the findings on engagement in R&D and its funding are summarized.

Within Europe, there are clear differences between regions. Although the engagement of companies in intramural R&D across Europe (Central&East, West&North and South) is rather even, the R&D expenditures as percentage of the total turnover of South-European countries is relatively larger (78%) than that of Central&East (38%) and West&North (64%). These outcomes show a rather diverse picture that does not confirm that West&North Europe is more active in high-tech biotech; it could indicate that South-Europe has been able to catch up in this respect with West&Europe. Also remarkably are the differences in the use of public funding. While 79% of the companies in West&North Europe use FP5 and FP6 EC funding compared to 41% in Central&East and 61% in South-Europe, the use of local or regional funding is quite different. Here the South-European region scores the highest (65%), against 44% for West/North and a very small 5% for Central&East. This again could confirm the catching up of Southern-Europe in biotech; in some countries like Spain and Italy specific regions are rather active in biotech.

With respect to the size groups also several differences appear. First of all, large firms make more use of all different sources of funding for R&D. The difference with small firms is especially large where EU funding is concerned: 94% of large firms obtain funding from the EU RTD programs and 82% from other EU funding, while of all small firms only about 53% are involved in the R&D programs and only 33% obtain other EU funding (for medium-sized firms these figures are 72% and 48%, respectively). Compared to medium-sized firms, small firms gain relatively much from funding by local or regional authorities (44% compared to 39% for medium-sized firms). Funding from central governments is more important for these medium-sized firms (66% compared to 61% for small firms).

Table 2.4 Engagement in R&D and R&D funding of firms

R&D activities and funding	Country group			Firm size			All firms
	Central & East	West & North	South	Small	Medium	Large	
Engagement in intramural R&D	93,0%	95,2%	99,0%	94,7%	97,8%	100,0%	95,9%
Total R&D expenditure / Total turnover in 2004	38,4%	64,0%	78,8%	62,0%	63,9%	82,4%	64,0%
Engagement in training	52,4%	73,6%	74,5%	65,5%	77,0%	85,0%	70,1%
Engagement in market introduction of innovation[3]	47,2%	52,7%	41,2%	46,4%	49,6%	60,3%	48,3%
Engagement in acquisition of machinery	68,3%	72,1%	65,8%	64,6%	76,1%	89,8%	69,5%
Any public funding	72,6%	100,0%	89,4%	89,4%	90,1%	100,0%	90,4%
Public funding from local or regional authorities	5,3%	43,8%	65,0%	43,6%	38,8%	52,5%	42,9%
Public funding from central government	49,9%	66,9%	67,6%	61,0%	66,0%	77,1%	63,6%
Public funding from the EU	23,7%	41,6%	50,4%	33,0%	48,0%	82,4%	40,9%
Funding from EU's 5th or 6th RTD	40,7%	79,0%	60,5%	52,7%	71,9%	94,2%	63,1%

Overall, it can be concluded that large firms are most active in R&D and related activities, and are also most engaged in obtaining external funding from the different kinds of public sources. Large firms are more likely to have sufficient and specialised human resources to devote to these activities, as well as to engage in procedures to acquire public funding. Although large firms have relatively more new (to firm, to market) product introductions (table 2.3), their performance in terms of turnover of 'new to the market' products is similar as that of small firms and higher that that of medium-sized firms. Large firms perform better for 'new to the firm' products; this can be explained by their larger absorptive capacity.

Cooperation and collaboration

To realise successful performance, in many sectors engaging in collaboration with other organisations has become essential for firms. International collaboration within Europe is well above the average of all manufacturing sectors. As is confirmed by the CIS4 data, this has also become common practice in

[3] This variable measures the marketing activities for innovations

biotechnology (see table 2.5). Almost all firms (96%) were engaged in collaboration with domestic partners, and 78% indicates to collaborate with organisations from other countries. Collaborations with scientific institutes are more common than collaborations with other firms, which is in line with the science-based character of biotechnology. These conclusions apply for all country groups and all firm size categories.

When considering domestic collaborations, no differences between the country groups can be observed. Firms from North and West Europe are more active in international collaborations than firms from the other two country groups. A reason for this could be the existence of language barriers between Eastern and Southern European firms and organisations in other countries. In the western and northern parts of Europe, the use of English could be more common. Collaborations with other enterprises are also more common in West&North European countries than in the Central&Eastern and Southern European countries (21% and 30%, respectively; compared to 36% of the firms residing in West&North Europe).

The activities in regard to collaboration differ by firm size. While large firms only engage a bit more in domestic collaborations than small and medium-sized firms do, this difference becomes larger where international collaborations are concerned. Compared to small and medium-sized firms, large firms are more involved in collaborations with international partners. International collaborations are often more complex to manage, which may explain why this is more common in large firms. In general, large firms also have more resources to manage cooperation arrangements than small firms.

Table 2.5 Cooperation activities of firms

Cooperation	Country group			Firm size			All firms
	Central & East	West & North	South	Small	Medium	Large	
Cooperation arrangements on innovation activities	72,8%	86,1%	75,8%	80,1%	77,6%	96,7%	80,6%
National cooperation	94,6%	96,1%	95,5%	96,5%	92,9%	98,7%	95,7%
Cooperation with international partners	72,4%	86,3%	65,3%	72,7%	85,4%	97,0%	78,2%
Cooperation with international partners outside own enterprise	70,7%	83,4%	64,1%	70,7%	82,7%	95,2%	76,0%
Cooperation with other enterprises within enterprise	21,0%	35,5%	30,3%	24,7%	39,9%	58,7%	31,7%
Cooperation with national universities / government or research institutes	81,3%	88,3%	81,3%	84,9%	82,6%	95,4%	85,2%
Cooperation with International universities / government or research institutes	32,6%	49,3%	53,6%	41,9%	50,1%	84,9%	47,8%
Cooperation with national firms	75,3%	75,4%	76,6%	74,3%	76,7%	83,8%	75,7%

Intellectual property rights

International competition in biotech has increased the last decade; this applies most for the red and white biotech sectors that operate on a global scale. This competition is also reflected in patenting activities. Patents are the main mechanism to secure intellectual property in this high-tech sector with long development trajectories. However, to secure the returns on investments in innovation, firms can

also use other forms of securing intellectual property rights, such as trademarks, industrial designs and copyrights. In general and also across all three country groups and firm size categories, patents are the primary way to protect intellectual property in biotechnology: overall about 51% of the companies in the selected NACE subsector have protected their intellectual capital with patents (see table 2.6). Patents are more applied in West&North Europe (63%) as in the rest of Europe, and also more by large firms (88%), as compared to SMEs. Especially industrial designs and trademarks are only limitedly used (13% and 17% respectively, compared to 51% for patents and 32% for trademarks).

Table 2.6 The use of different types of intellectual property rights by firms in NACE 73.1

Indicators IPR	Country group			Firm size			All firms
	Central & East	West & North	South	Small	Medium	Large	
General intellectual property rights	47,7%	55,9%	65,7%	53,3%	59,0%	87,3%	57,3%
Applied for a patent	31,7%	63,3%	47,0%	48,1%	48,8%	87,8%	51,3%
Registered an industrial design	9,1%	15,4%	11,9%	12,0%	11,1%	27,0%	12,9%
Registered a trademark	7,9%	41,4%	32,5%	28,6%	33,1%	50,7%	31,5%
Claimed copyright	16,5%	20,8%	11,1%	14,8%	12,1%	49,2%	16,7%

The results on IP protection, summarized in table 2.6, are in line with the general perception that patenting is an effective means to claim IP in biotechnology. IP is the only certificate of value during the long and expensive process that it takes to develop new biotechnology-based products and processes.

Conclusions

Based on the analysis of the CIS4 data, several conclusions can be drawn. First of all, as was expected, biotechnology is a highly innovative and R&D-intensive sector. The large majority of firms are engaged in innovation, and of those firms the large majority introduced products that were actually new to the market and not only new to the firm. All three types of innovation included (product innovation, service innovation and innovation of production systems) were found to be of importance. Secondly, most of the turnover of the firm results from the sale of existing products, which can be R&D services or performing tests for clients etc. Thirdly, collaboration, especially with knowledge institutes, seems to be a common practice. International collaboration and collaboration with firms is more common in the West&North European countries than in the other parts of Europe. Patents are commonly used to appropriate returns on investment and the large majority of firms is engaged in training activities. The fact that most new products that are introduced are actually new to the market may indicate that patent protection is quite effectively in biotechnology.

A notable difference appeared between different country groups and firm sizes where the acquisition of external funding is concerned. Large firms make use of all different sources of funding. Small firms are relatively more dependent on funding by local or regional authorities, and make limited use of EU-level funding opportunities. Especially in Central&Eastern European countries, the level of local

funding is low, which could indicate that it is relatively more difficult for small firms to survive in those countries. More generally, it could be that the barriers for obtaining funding from the EU are at this moment too high for small firms.

2.4.2 Innovation performance of the biotech sector as revealed by other quantitative data

As explained already in the previous section, these CIS4 data need to be interpreted with caution as they do not reflect the whole biotechnology sector. For that reasons the CIS4 data are complemented with data on the innovation performance of biotechnology firms derived from other sources. However, these sources are very scarce; the OECD Biotechnology Statistics reports, which recently has been updated (OECD, 2009c) is the only source that provides comparative data, but still not for all counties and only for a few innovation performance indicators.

In the period 2003 to 2006 the number of biotechnology firms (firms that are active in biotechnology) in Europe showed a small increase of 7%, while for the US that figure was over 50% (see table 2.7 for the absolute figures). Also the core or dedicated biotech R&D firms (which are part of the overall biotech firms group) showed a similar increase (52%).

Table 2.7 Number of biotech firms and dedicated biotech firms (for 2003 and 2006)

	2003		2006	
	Biotech firms	Core biotech firms	Biotech firms	Dedicated biotech R&D firms
EU average [1]	3,154	na	3,377	2,075
US	2,196	Ca 1,800	3,301	2,744

[1] Underestimate, as only European countries for which data was available were included (15 countries)
Source: OECD (2006, 2009c)

Most R&D activities in biotechnology are carried out by large firms (OECD 2009c). This is in accordance with the findings based on the CIS4 data: large firms were found to be more active in intramural R&D and had a higher R&D intensity as compared to SMEs.

The CIS4 data showed that patents remain to be the primary means of IP protection in biotechnology. Additional data showed that in the period between 1994-96 and 2004-06 the number of European patent applications almost doubled (92% raise), while those of the USA raised with about 50%. However, the relative number of patent applications in biotechnology of the total number of patent applications has decreased over the past decade. The share of biotech PCT patents out of total PCT patent applications showed a decrease for EU27, USA, Japan, BRIC, with a decrease from 10.3% average per country in the mid 1990s to 6.5% in the early 2000s. This decrease could mainly be explained due to the more stringent regulation on patenting of genetic material (OECD, 2009c).

2.4.3 Innovation performance of the red, green and white biotech sub-sectors

R&D expenditures and employees

At the end of 2003, the European biotech sector comprised of 2200 dedicated biotech companies (based on data from 18 countries; Critical I, 2006), of which 51% was active in red biotech and 7% in green biotech (Critical I, 2005a). The data on relative size of the white subsector are not complete as they are only available for the bioremediation part: 7% (ibid). At the end of 2004, the absolute number of dedicated biotech companies showed a small decrease compared to the previous year (2163); but there was a small relative increase in red dedicated biotech companies (55%). Dedicated biotech companies are companies whose primary commercial activity depends on biotechnology. This means that big pharma, seed or food companies are not included as for these companies biotech is only one of the technologies they apply.

Table 2.8 shows the relative R&D expenditures and employees (high qualified as most of these companies are mainly active in R&D) of dedicated biotech companies active in red, green or white biotech in France, Germany and the UK and for comparison also in the USA. The data show clearly that both R&D expenditures and employment of dedicated biotech firms in the red biotechnology are by far the highest. On a long distance come the other two sectors; first comes white biotech than green biotech (Critical I 2005b).

Table 2.8 Private R&D expenditures and employment per subsector of dedicated biotech companies in three European countries and the US (% of total; 2003)

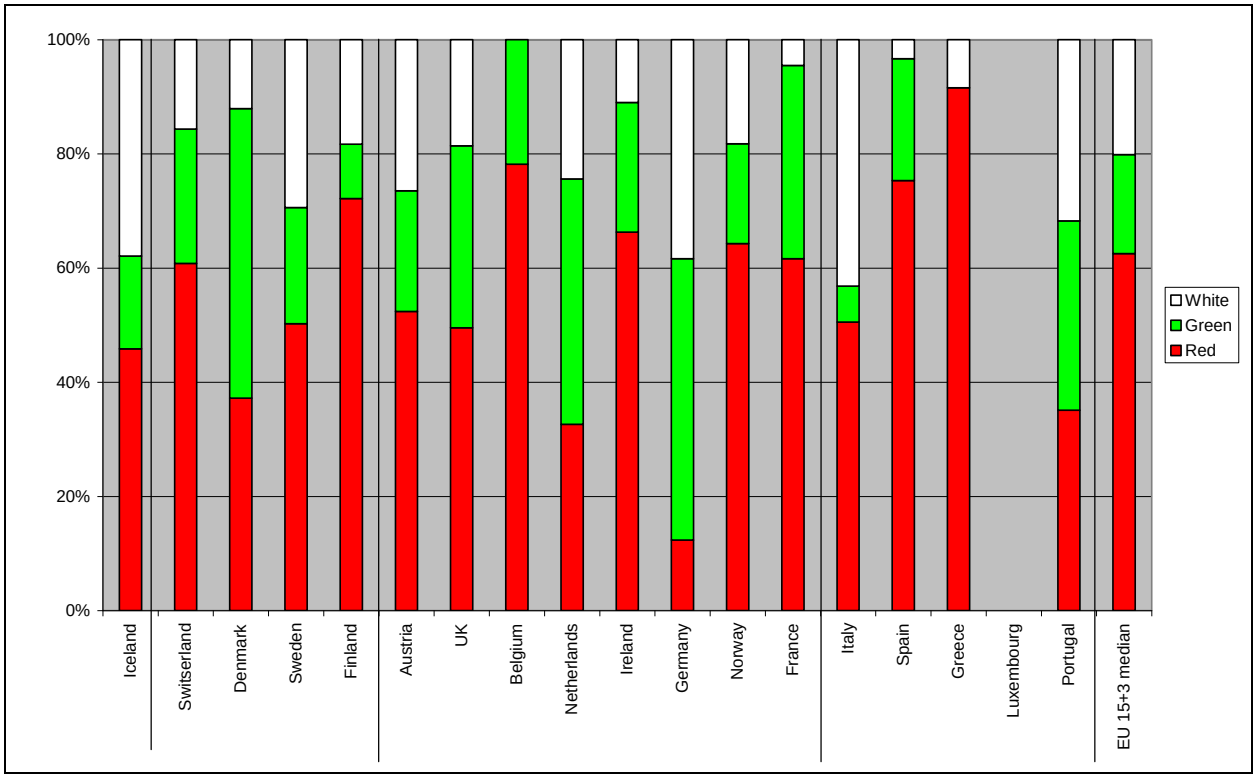
	R&D expenditures				Employees			
	France	Germany	UK	USA	France	Germany	UK	USA
Red biotech	83%	77%	87%	90%	69%	60%	59%	71%
Green biotech	2%	1%	5%	1%	4%	5%	7%	5%
White biotech	0%	1%	0%	0%	4%	6%	4%	1%
Other *	15%	21%	8%	9%	23%	29%	30%	23%

*: Other includes: contract research, (technology) services providers, contract manufacturing
Sources: Critical I (2005b)

Public funding

The differences in relative innovative performance of red, green and white biotech is also reflected in the public funds that the 15 old Member States and three European countries have invested in these areas in the period 2002-2005. Figure 2.4 shows the relative distribution of public funds through specific programs aimed at stimulating R&D in these biotech subsectors (Enzing et al., 2007).

Figure 2.4 Public funding of red, green and white biotechnology in Europe (2002-2005)



* There are no data for Luxembourg: biotechnology was supported through non-policy directed instruments only.
Source: Enzing et al., 2007

Publications

A comparative analysis between Europe and the USA of the relative changes in specialization in biotech research based on relative growth rates of publications showed that in the period between 1994-1996 and 2002-2004 overall Europe (EU15) has higher growth rates than the USA. The strongest growth rates are observed for the smaller (in terms of absolute numbers of publications) fields: food biotechnology (Europe: 98%; USA: 82%), industrial biotechnology (90% versus 47%) and environmental biotechnology (90% versus 57%). Red biotech publications grew in Europe 54% versus 36% for the USA. Surprising is the difference in low growth rate in the field of plant biotechnology (35% versus 10%): this difference cannot be explained by a size effect as both have a similar absolute number of publications (Enzing et al., 2007).

Patents

However, the specialisation indices based on patent applications in the period 1995-2004 (Table 2.9) show that Europe (EU15) is lagging behind in all three subsectors. Surprisingly, the USA has the strongest patent position in green biotech (Knecht, 2006).

Table 2.9 Specialisation indices based on biotech patent applications (1995-2004)

	EU15	USA	Japan	Canada	China	South Korea
Red biotech	0,75	1,50	0,55	1,93	1,03	0,44
Green biotech	0,57	1,60	0,59	2,49	2,21	1,28
White biotech	0,75	1,45	0,66	1,68	1,05	0,57

Source: Knecht, 2006

Regulatory costs

Rather common for all three subsectors are the long-term developments trajectories of their innovative products. The life cycle of a life science product is much longer compared to other high-tech products such as for instance in the electronics industry. For most biotechnology innovations, the R&D and commercialisation process take more than 10 years, going up to 15 years. This applies for instance for new biopolymers, many food products, pharmaceutical entities, enzymes for industrial processes in downstream sectors and for biofuel production.

The research and especially the development trajectories are expensive due to the cost of e.g. field trails for new plant varieties, (pre)clinical trials and the amount of resources to get approval by regulatory authorities. The regulatory requirements to protect consumers, required by regulation are very costly; the ICH, FDA, EMEA, GMO, and novel food regulatory guidelines are getting more and more complex. Table 2.10 provides an overview of the indicative costs for commercialisation of biotechnology products in the three biotech sectors. The regulatory costs are the highest in the green biotech (agro and food), where regulation costs concerning genetically modified plants varieties varies between USD 0.4 and 13.5 million per variety. The open release of genetically modified micro-organisms (for instance for bioremediation applications) is also very costly: about USD 3 million per release (OECD, 2009a). The less costly are MAS crops (Marker Assisted Breeding). As the risk profiles are very high because of the high failure rates of the development process, this affects the return on investment of capital investment providers, who usually choose to be on the safe side.

Table 2.10 Regulatory costs for commercialisation of a biotech product

Biotech subsector	Biotech product	Costs (USD thousands)
Red biotechnology	Therapeutics *In vitro* diagnostics	1,300 150 – 600
Green biotechnology	GM crop MAS crop Animal vaccine Animal therapeutics Animal diagnostics	435 – 13,460 5 – 11 242 – 469 176 – 329 9 – 189
White biotechnology	GM open release GM in closed loop	1,200 – 3,000 unknown

Source: OECD, 2009a

3 Carriers of innovation

3 People

3.1.1 Employment

The development and application of biotechnology has had important employment effects. It has led to the creation of new jobs in academia and in new start-up companies and to the guarantee of existing ones. Due to limited data availability, it is rather difficult to evaluate whether and how much employment was created as a result of modern biotechnology adoption in Europe (Reiss et al., 2007). Data are available on employment in so-called biotechnology R&D firms (firms hat perform biotech R&D) in some countries, as these data are captured by R&D surveys in the specific country (OECD, 2009c). For Europe this applies only for 12 countries (ibid). However, based on a study on biotechnology employment in Germany (Nusser et al., 2007a), combined with data on the biotech sector in European countries (Critical I, 2006; OECD, 2009c), a very rough estimate says learns that total biotech-related employment in 18 European countries (EU15, minus Luxembourg, plus Estonia, Hungary, Norway and Switzerland) would be in the range between 1.6 and 2.2 million FTE's. The German study also showed that the growth in the biotech provider and applicant sectors has a positive effect on the so-called Biotech inputs sector, including upstream sectors such as those delivering machinery and equipment, measurement techniques, chemicals, R&D services, etc. (Nusser et al., 2007a). For the pharmaceutical and (fine) chemical industry this concerns the raw materials industry i.e. specific products from the chemical industry. For the environmental application sector measurement and control engineering and the manufacturers of metal goods are relevant. They calculated that the indirect employment effect in the biotech inputs sector is even larger than the direct employment impacts in the applicants sectors. It was estimated at 369,000-682,000 for the year 2020. However, there are also some negative employment effects, such as through substitution of conventional processes and products, such as in the chemical and pharmaceutical sector where chemical processes are replaced by biotechnological processes and in the fuels sector where biofuels are replacing fossil fuels. Biotech inputs to providers would amount to 94,000-106,000 in 2020 (Nusser et al., 2007a).

3.1.2 Skills in biotechnology

Nusser et al. (2007a) in their study on the German biotech sector found considerable differences between the qualification profiles of the three biotechnology sub-segments (providers, applicators, inputs). The providers' segment has significantly more academics (48%) than the applicators segment (7%). In the food and agriculture application subfields the shares of personnel with a vocational training and those with a qualification as technician are relatively high: 62% and 64% and 10% and 15%. In the other application fields the share of academics is higher. The qualification profile in the inputs segment is comparable with that of the whole economy. They also found that the frequently inadequate expertise in patent and technology transfer offices as well as low personnel mobility between science and industry are serious barriers for knowledge and technology transfer from

academia to industry. Also the lack of specialised knowledge of the relevant national and international laws and their compatibility is mentioned (ibid). Moreover, there is a shortage of highly qualified personnel especially engineers and technicians in specific application oriented and industry-relevant areas such as bioprocess engineers (Senker et al., 2002) and qualified personnel with comprehensive knowledge of the industry and professional experience in all aspects of biotech business (Nusser et al., 2007b).

In the public sector research organisations experiences some shortages of skilled staff in a number of disciplines, such as bio-informatics, systems biology and clinical research; here the public sector has to compete with the private sector (Reiss et al., 2006).

Overall, non-technical competences are becoming increasingly important as technical competences (Watson, 2003). Non-technical competences relate to business development, regulatory affairs, alliance management, marketing and public relations (Hayward and Griffin, 1994; Watson, 2003; Bagchi-Sen, 2007; Brink et al., 2007). Some studies indicate that the importance of the different skills fluctuates along the product development cycle and more specifically that scientific skills are most important at the beginning, while marketing and public relation skills are more important later on (Rhyne 2009). Also as R&D personnel need to collaborate in multidisciplinary teams and often these teams do not seem to function properly (York et al. 2009); managing such teams demands specific managerial skills. Fund raising skills and management skills are important throughout the cycle (ibid).

3.1.3 Labour mobility

In Europe, labour mobility is lower than in the US, due to cultural, language and institutional factors (Hayward and Griffin, 1994). However, institutional barriers have been reduced over the past years. A lack of harmonisation of qualifications leads to a limited labour mobility across EU countries. In biotechnology labour mobility is also influenced by differences in regulation between countries. These differences especially exist in research areas that are more controversial (Levine 2006). To illustrate, the US government attitude toward stem cell research until recently used to be quite negative, making stem cell researchers inclined to locate elsewhere. Prior research in the US shows that geographical proximity is important to explain labour mobility in biotechnology: access to labour is enabled by geographical proximity (Bagchi-Sen, 2007). As such, gaining access to a pool of specialised labour is also a reason for relocating. This indicated the importance of organising activities in clusters and may explain the emergence of clusters in biotechnology.

3.2 Organisations

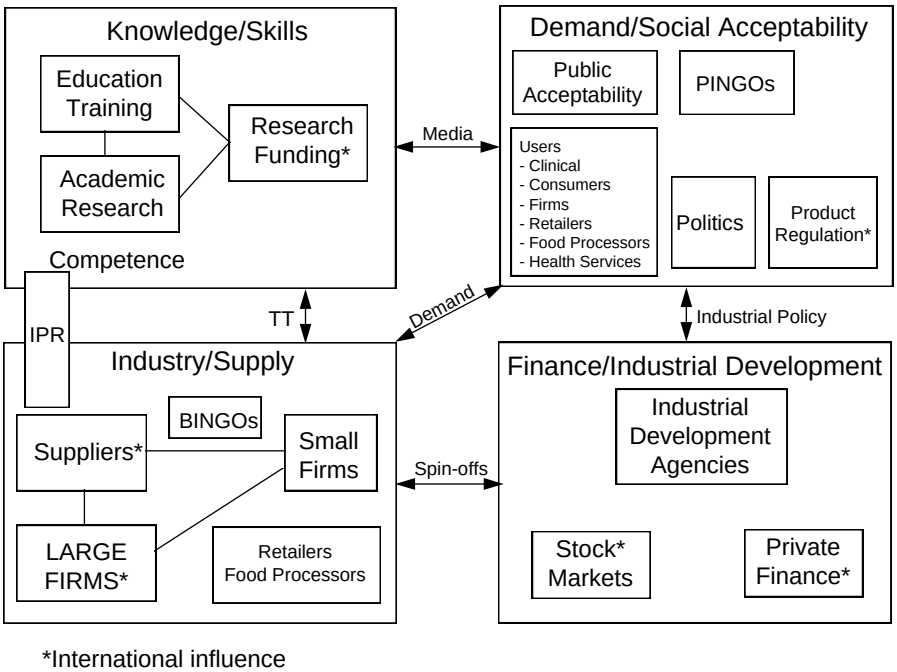
3.2.1 Key actors, their interrelationships and innovation performance

Figure 3.1 provides an overview of the organisations that are involved in, or influence the biotechnology innovation process (Senker et al., 2001). It presents the networks within which these organisations are embedded and their inter-relationships. As shown, the main components of the

framework are networks of knowledge and skills; industry and supply; demand and social acceptability; and finance and industrial development. The figure distinguishes business interest non-government organisations (BINGOs) such as the European biotechnology industry association EuropaBio, and national biotechnology industry associations and public interest non-governmental organisations (PINGOs) such as consumers' organizations or environmental organisations.

Key actors in the biotechnology sector are public research organisations and companies, both because they are active in science and technology, which is the main driver in this science driven sector; companies also as actors that develop and market biotech products. Other key actors are the government as financer of research and as regulator, and venture capitalists as financers. In this section the focus is on the public funded biotech research centres.

Figure 3.1 Networks of key factors influencing innovation



*International influence

TT = technology transfer IPR = Intellectual Property Rights PINGOs = Public interest non-government organisations
BINGOs = Business interest non-government organisations
Source: Senker et al. 2001

3.2.2 Biotechnology research centres

Public research organizations (including universities, academic hospitals and research institutes) and companies are the key actors involved in generation in new biotechnological knowledge and technologies. In 2002 in EU15 plus Switzerland, 194 biotechnology research centres were identified. Biotech research centres are centres that have at least 50% of its research activities focusing on biotechnology, be receiving at least 50% of its funding from public sources, and have a specific mission related to biotechnology. This mission can include providing education and training, building up the knowledge base, creating a national centre of research excellence or fostering commercialization (Peter 2004). In a comparative study between European and US biotechnology research centres it was observed that in the US the formation of a centre is seen as a typical

academic development strategy, while European biotech centres were primarily created through incentives for existing research centres to move into this area, by establishing new ones or by renamed existing ones (ibid).Interesting differences between Europe and the US are first of all that in Europe about three-quarters of the centres were established during the last two decades, the rest were older, most of them have shifted their research focus to biotechnology, such as for instance research centres that focused on traditional agricultural research have shifted their focus to biotech research. Also the European centres are affiliated universities and with other types of organizations: cooperative or 'virtual' centres in the same town or in different geographic areas. Half of the European biotechnology research centres has a commercialisation mission. In the US all centres were established during the last two decades and are only affiliated with universities, although 'virtual' centres also exist in the United States. Almost three-quarters of US centres have a mission to foster commercialization. Also US centres have a higher launch rate for spin-off firms than European centres, while the latter have a higher percentage of industrial research collaborations and a higher average number of collaborations per centre (ibid). European centres are larger in terms of the total number of research staff and in terms of budgets and employ more researchers on a short-time basis, whereas US centres prefer long-term employment (ibid). Although the numbers of doctoral students per centre and per research staff member are similar, European centres have double the productivity of US centres in PhDs awarded for both these measures. Also European centres have more members of editorial and scientific committees (ibid).

In specific fields within biotechnology public research organizations and companies are organized within so-called European Technology Platform (ETPs), aiming at developing a European research agenda for the field and at providing input into the process of agenda setting within Europe. Joint Technology Initiatives (JTIs) are a means to implement the Strategic Research Agendas (SRAs) of a limited number of ETPs. Relevant JTI's and ETP that also address biotechnology are included in table 3.1.

Table 3.1 JTIs and ETPs in the field of biotech/life sciences

Red biotech	Green biotech	White biotech
Innovative Medicines Initiative (JTI)	Farm Animal Breeding and Reproduction Technology Platform (ETP) Food for Life (ETP) Global Animal Health (ETP) Plants for the Future (ETP)	European Biofuels Technology Platform (ETP) Sustainable Chemistry (ETP)

3.3 Clusters and networks

Innovation networks are crucial in the biotechnology industry; open innovation - collaboration between academia and industry, and within industry between high tech firms and the larger incumbents – is a one of the main characteristics and success factors of the biotechnology innovation process in all three subsectors.

A specific phenomenon are the so-called bio clusters, local systems where public research organisations and companies interact for research, innovation and economic growth. Bio clusters (also

referred to as bioregions) are scattered across Europe. Some of these bioregions are the result of the spontaneous co-presence of key factors (such as entrepreneurial scientists, or an active Chamber of Commerce); others are triggered by regional or national governments that created the conditions for cluster formation. In a few cases, both forms of cluster creation coexist, thus determining a hybrid process (Chiaroni and Chiesa, 2006). In Europe, compared to the USA, there are relatively more policy driven clusters (ibid). These European clusters are younger than most USA clusters, perhaps except for those in the UK. It might be interesting to investigate if this aspect of how the cluster was created is a key factor for the (potential) success of biotech clusters. Corrolleur et al. (2003) in a study on the development stages of French biotech clusters found that most biotech firms progress from an entry stage in which they are very dependent on local cluster infrastructures, to a mature phase in which their network becomes more national and international in focus. They grouped biotech firms in four general types: 1) Successful start-ups: geographical proximity is of little importance for these firms although they can profit from local knowledge spill-overs; 2) Stable firms in niches: strong reference to geographical proximity; they seek research and/or market resources in their immediate environment. Relation with users are formed on the basis of geographical proximity; 3) Firms affiliated to a parent company (organisational proximity) and 4) Firms which are taken over. The localisation effects differ strongly across these types of firms, especially for the first two.

Biotech start-ups – successful or not – cluster nearby research universities and research centres because they can profit from the availability of external economies, mainly local knowledge spill-overs that help to reduce the uncertainty from a disruptive technology faced by these companies (van Geenhuizen and Reyes-Gonzalez, 2007). In this science-driven industry (Cooke, 2008), the transmission of tacit knowledge goes mostly through frequent and personal contacts (Fuchs 2003). It requires mutual trust, a sharing of language and culture, as well as intense non-business relations, so transmission of tacit knowledge is facilitated by geographical proximity. The key to this unusual kind of economy is proximity to knowledge institutions. Within this context, "clusterisation" is typically explained by the importance of specialised knowledge to the life sciences. Another requirement for successful clustering is a local high level labour market: star scientists that become entrepreneurs, qualified technical staff, advisors, associates. The success of young high tech industries depends largely on their embeddedness in an environment of supporting institutions (e. g. venture capital companies) and organisations and more specific their relation with downstream industries (Prevezer, 2003). PWC (2011) found that among the key success factors for biotechnology clusters (scientific, industrial, financial, supporting and cultural) financial is the most important. The lack of funds along the whole value chain especially lack of Venture Capital, together with difficulties on accessing to the existing funds is the most challenging problem for biotech clusters.

3.3.1 Regional biotechnology policy

In the period 1994-1998, regional biotechnology policy-making was mainly concentrated in those European member states where the regions have responsibility for supporting university research and economic development (Germany, Belgium and Spain). In addition some regions in Norway and the UK also played a limited role in research and technology development policy, as part of

responsibilities delegated from national governments in these countries (Enzing et al., 1999). Eight years later - in the period 2002-2005 - in all these countries regions were playing a much more active role in regional biotechnology-making. They operated a wide range of new innovation policy instruments and also regions in other countries (Austria, France, Italy and Switzerland) had become involved in biotech policy-making (Enzing et al., 2007).

These first indications of regional activities with respect to innovation policies in biotechnology performance need to be reflected against general trends in terms of regional innovation activities and regional innovation policies. There is increasing support within national innovation policy-making for the spatial dimension of innovation. Also the strategic dimension of regional innovation and research policy-making has gained importance. Since the second half of the 1990ies, the regional level in many European Countries (and beyond) has become the starting-point for policy measures aiming at the better exploitation of innovation and technology potential. Within this context, the cluster approach (Porter, 1998) and the network idea or the "network paradigm" (Cooke and Morgan, 1993) and possibilities for making use of spatial and cultural proximity between firms and supporting institutions are considered as being crucial. Several studies argue that today we are seeing the strong rebirth of regionalism as far as government support for science, technology and knowledge-based industries is concerned (although regional funding is only limitedly available in eastern European countries, as was shown in the CIS4 data analysis). Garrett-Jones (2004) in a study on the evolution of regional policies observes that the locus of power in science and technology policy and policies towards knowledge-based industries is moving (from the national/federal government) towards the regions. He argues that the focus on regions is not new, but the strong emphasis on knowledge infrastructure and knowledge is. Since 2000 regional policies have become less compartmentalised in terms of not only focusing on science & technology parks but also on education and skills, public and industrial awareness campaigns, commercialisation activities and support for infrastructure. Also science and technology policy has become more integrated with economic and social planning of states. Also he found more specialisation (regions focus on their regional strengths), more connected and partnership oriented, and a new relationship with federal/national agencies (ibid). Diez and Esteban (2000) describe how the traditional model of regional policy that mainly deals with building physical infrastructure has been replaced by a new generation of regional policy that has an accent on social capital. They argue that for that reason the main focus of regional policies should be on creating frameworks for interactions. Related to this, it has been shown that these interactions represent an important mechanism by which clusters generate added value for innovation (Casper, 2007).

4 Sectoral innovation futures

This chapter focuses on the future development in the three biotech sub-sectors. Firstly, it addresses the current and future trends in the sectors (section 4.1). Based on a number of future scenarios (section 4.2) and the most important innovation themes (section 4.3), the main requirement for future sectoral innovation are identified (section 4.4) and policy conclusions are drawn (section 4.5).

4.1 Emerging and future drivers of innovation

4.1.1 Current drivers influencing firm performance the biotechnology sector

Red biotechnology: Bio-ICT convergence: biomedical equipment and bio devices

Most relevant for the red biotech sector is the so-called convergence of biotechnology with ICT, nanotechnology and cognitive sciences: NBIC. Biotechnology is having, and will continue to have, a pervasive effect on a large number of industrial sectors. Biotechnology enables nanotechnology and ICT by identifying chemical-physical processes and algorithmic structures in living systems that are traced to their material basis in cellular and genetic organization. It provides mechanisms of cellular recognition and targeted transport and promises to enable information technology by developing, for example, the foundations for DNA-based computing.

In the short term the progress in the field of converging technologies is most relevant for new product innovations in the health sector. The fields where biotechnology has converted with ICT and that have large market potential are biosensors and bio devices (Van Lieshout et al., 2006). Biosensors can be integrated in (non) invasive monitoring/diagnostic techniques which link biosensors to smart ICT environments, also referred to as molecular imaging, bio-imaging orbiophotonics (Enzing et al., 2008b). Through the identification of biomarkers (in these biosensors) for specific conditions, metabolic monitoring for high-risk health and safety factors will facilitate early diagnosis. Combines these developments with those in the field of E-health and biomedical informatics lead to very powerful tools that will have a major impact on public health systems and personal well-being, but also on the relationship between patients and doctors. Based on a bottom-up approach (starting from the revenues of relevant companies), the size of the bio photonics market (including bio imaging, biosensors, bioassays and medical devices for monitoring, diagnosis or therapy) can be estimated at over USD 63 billion; based on a top-down approach (evaluating industry-specific market reports), the size of the bio photonics market was estimated at well over USD 53 billion, with the caveat that not all bio photonics-related industry segments are covered in readily available market reports (Lee, 2007). Main drivers of these developments are companies in the medical devices and diagnostics industry.

Bio devices combine biosensors with bio-actuators. These are small devices that do the bio-work in the body. For example a sensor to provide continuous monitoring of blood sugar levels that is coupled with an electronic pancreas, which would introduce the right amounts of insulin at the right time. New manufacturing techniques, use of new materials and information technology enable the production of

biomedical structures which custom size and shape; for example ceramic replacement of bones for injured hands (Enzing et al., 2008b). Biomedical materials can capture 10% of the USD 305 billion market for traditional organ replacement therapies within the next 10 years (BMM, 2008). Bio devices represent a very large market.

Bio imaging is a new field bringing together molecular biology and *in vivo* imaging in order to localise and detect molecules in living organisms and to visualise gene expression in vivo. Biosensors and biomarkers allows an early and precise diagnosis of tumours, the development of customised treatments and the real-time evaluation of treatment effect. By linking molecular diagnostic platforms to imaging technology platform leads to new types of medical instruments that present real-time medical imaging which are now subject of strategic alliances between biotechnologies companies and companies in medical equipment (CTMM, 2007).

The ability to apply functional coatings to medical implants also is a promising new development. These coatings can consist of for instance *in vitro* cultivated cells or anti-microbial substances. The combination of synthetic materials and the biological coating reduces the treat of infections and inflammation and also enables a faster recovery of the patient, also contributing to an increase of the efficiency of treatments (BMM 2008). Promising applications are coated (drug eluding) stents and coated artificial joints (e.g. knees and hips) and in the long term perhaps even artificial organs. The US is most favourably positioned to benefit from these opportunities. Within Europe, the UK, Germany, The Netherlands and Switzerland have a strong position as they are leading in research and have relatively many firms (both large firms and SMEs) specialised in this field (ibid). Over time, medical technology may become a prominent partner of red biotechnology in product development.

Red biotechnology: The end of Block-buster model – towards new business models

So far, firms active in medical biotechnology, and pharmaceutical firms in general have relied heavily on a limited number of products for profit generation: the so-called block busters. However, due to the ending of patents, product portfolios need to be completely renewed every 12 to 15 years (PWC 2007). The relatively 'easy targets' for treatment with medicines have been addressed, which has resulted in a reduction of the number of products in the pipelines of firms (Tait 2007). Due to these developments, firms active in this field have to look for alternative strategies to recoup their investments (Gassmann et al., 2004). The increased attention for the prevention of diseases constitutes a business opportunity for firms (PWC, 2007). But overall the most promising business opportunities are thought to derive from the use of genomics knowledge in drug development. This could potentially lead to the discovery of many new targets for drug development (Martin and Morrison, 2006) and thereby fuel development pipelines of pharmaceutical firms. It could put an end to the 'blockbuster era' as the markets targeted by these products are inherently smaller. Also, a restructuring of firms is needed to deal with the stratification of patient populations (ibid) and the emergence of multi-busters; i.e. products that can be used for treatment of stratified patient populations suffering from different diseases but with similar disease pathways (Omenn, 2005). This also implies a restructuring of clinical trials.

Red biotechnology: (Corporate) venture capital

The biotech sector is characterised by a high level of investments and is strongly dependent on external financial resources. These can be provided by private venture capitalists ('business angels'), corporate venturing or support programs of regional development agencies or national programs.

The level of investments can be considered as a proxy for performance: the more promising business the more venture capital investments. Venture capital is very important for start-up and early growth stages of biotechnology companies. Since the mid 1990s there is an increasing flow of venture capital into almost all European countries considered. Smaller countries (Austria, Denmark, Sweden, Switzerland) and the United Kingdom attracted the highest venture capital flow between 2002 and 2004. France, Germany, Belgium and Finland have been performing at a medium, and most Mediterranean countries on the lowest. Some countries show a considerable growth in venture capital investment, starting from a low level; these include Denmark, Sweden, France and Germany. In the United Kingdom already in the mid 1990s large amounts of venture capital have been invested into biotechnology. Since then, addition investments more than doubled. Other countries with high investment levels in the mid 1990s, such as Belgium and the Netherlands – have shown moderate growth rates since that time (Enzing et al. 2007).

The venture capital invested in Europe in life sciences (include biotechnology, pharmaceuticals, health services, and medical devices and equipment) increased also in the period 2003 to 2007. In 2007 the investments had more than doubled (OECD 2006; 2009c). Most countries showed an increase. However, compared to Europe, the USA is far ahead with 5 507.0 million PPP$, against 1 812.5 million PPP$ for Europe (OECD 2009c). There are no figures available for each of the three biotech sectors separately, although it is recognized widely that the red biotech sector is the most 'venture capital intensive'.

Due to the economic crises in 2008, venture capital investment has decreased considerably. For instance in the UK, investments and deals in biotech dropped by about 25%. This was one of the arguments for the UK government to start its own venture capital fund: the U.K. Innovation Fund wants attract investment from pension funds and the private sector to create a USD 1.6 billion fund within 10 years.[4] However, others argue that there is enough public and private venture capital available; the problem is that there is a need of good propositions.[5] Recently venture capitalists indicate that venture capital funding in the biotech sector raised again considerably the past year.[6]

[4] http://nds.coi.gov.uk/content/Detail.aspx?ReleaseID=404169&NewsAreaID=2
[5] Personal communication Valorisation Officer of the Life Science Funds, of the Netherlands Genomics Initiative.
[6] http://www.ventureworthy.com/Biotech_venture_capital.asp

Red biotechnology: Corporate venturing

Corporate venturing is increasing, especially in red biotechnology: investment funds set up by big pharma companies are beginning to dominate early-stage financing of biotech firms (Mitchell, 2009a). In general corporate investments in other companies (corporate venturing) follows the overall trend in corporate profitability. However, compared to traditional venture capital, corporate venture capital is generally more long term oriented and strategic; it often comprises of multiple rounds of financing (Website BioE2E.org; Mullin, 2003). As a result investing firms seem to focus on early stage financing of promising innovative projects; these investments can serve the purpose of acting as a 'probe' into a new technological option (Henderson 2007). Compared to independent ventures, corporately sponsored ventures have higher R&D expenditures, are more focused on obtaining patents and are more active in external technology sourcing (Zahra 1996). Henderson (2007) found that corporate venture capital in biotechnology has a higher return on investment than venture capital from other sources. This is especially the case for those investments aimed at upgrading the technological core competences of the investing firm.

Worldwide the red biotech sector was the second highest corporate venture capital investment sector in 2007/2008 with investment of US$959 million, mainly concentrated in the USA such as (http://www.firstwordplus.com/FWD0070909.do). Red biotech companies that have a CVC division include: Gegentech, Amgen, Ely-Lilly, MedImmune, Johnson and Johnson in the USA, Takeda Pharmaceutical Company Limited in Japan and GlaxoSmithKline, Novartis and Merck Serono in Europe.

Red biotechnology: Outsourcing and off shoring

Pharma and biotech companies increasingly follow a global approach, which relies on offshore strategic partnerships, academic collaboration and outsourcing to established networks of scientific expertise (also referred to as 'open innovation'). A key incentive for offshore investments is the availability of scientific and technological excellence in emerging economies. Both outsourcing and off shoring are considered to be increasingly attractive for biotechnology firms (Brower 2004). Pharmaceutical companies have become routinely outsourcing various aspects of R&D and drug manufacturing for many years. A majority of the active pharmaceutical ingredients and excipients are routinely manufactured in South-East Asia (mostly China and India). Other countries that have succeeded to deliberately attract foreign red biotechnology activity include Ireland, Puerto Rico and Singapore (ibid). The increasing costs of conducting R&D coupled with the growing availability of low-cost but high-qualified scientific workers in other parts of the world, has made the practice of outsourcing R&D operations less risky and more economically feasible. After all, many of the scientists who work in company-owned foreign research facilities or foreign-owned contract research organisations were trained in the countries where the outsourcing companies are located (USA, Europe). In red biotechnology, off shoring and outsourcing can contribute to resolving the innovation

paradox as they may significantly reduce the costs of R&D (Srivastava 2002); the impact on overall employment and economic development are unclear (McCook 2005).

Red biotechnology: The role of the demand side

In red biotechnology, patients, health care professionals and government agencies are important players at the demand side of the production chain. Primarily because of their ability to influence the prices of drugs, the bargaining power of users is considered to be high (Gassmann et al., 2004). National governments increasingly constrain the prices of new products because of the rising costs of health care. This poses a challenge for firms because they increasingly need to show the economic value of their product. The personalisation of medicine will further increase the prices of products, but will reduce their use due to patient stratification. Also, a reduction of side effects should inherently be achieved. Diagnostics are vital to achieve these benefits. However, regulators often see them as putting yet more strain on health care budgets (Ernst & Young, 2008b). Costs that are saved by more effective use of medicines are not yet fully considered. This implies that the actual added value of diagnostic products is not ascribed to these products. Pressures on pricing will thus be especially challenging for diagnostic firms. Also with regard to the safety of biopharmaceuticals, firms feel an increasing regulatory burden (ibid). This is mostly due to increased demands concerning post-approval safety of products.

In influencing innovation processes, patients are represented by intermediary organisations such as patient organizations. Overall, studies indicate that it is important for patient organisations to be clear about their connections with industry, and not be seen as looking after the needs of the industry (Tait, 2007; Boon, 2008). However, with the emergence of personalised medicine, DBFs and pharmaceutical firms will increasingly try to create partnerships with patient organisations to save on marketing and sales (Ernst & Young, 2008b).

Red biotechnology: Regulation

Biotechnology is highly regulated (Gassmann et al., 2004). In medical biotechnology regulations on the safety, efficacy and quality of products are strict, as is regulation on the introduction of GMOs into the environment and its use in food products. Regulatory issues feature less prominently in industrial biotechnology, as the production normally takes place in contained environments.

In Europe, firms active in biotechnology need to deal with EU-level regulations as well as national regulations, which may have similar implications but this is not necessarily so. For instance in the case of research and development in the field of stem cells currently relatively much room is given to individual member states to formulate their own specific regulation. This in turn leads to a divergence of specific regulations across member states. Also, implementation of regulation by the individual member states often occurs slowly (EMCC, 2007). Also, there are currently differences in regulation between the US and EU. In the field of medical biotechnology, for example, a recent ruling of the European Patent Office (EPO) indicated that it will not be granting patents on inventions that are based on stem cells that have been obtained from human embryo's (Siva, 2009a). With this decision

the EPO deviates from the United States Patent and Trademark Office (USPTO). This US patent office overall issued about two-thirds of all stem cell patents worldwide (Papatryfon et al., 2006), which further illustrates the currently existing differences between the US and Europe.

Green biotechnology: Eco-efficiency/sustainability

A challenge for green biotechnology is to deal with developments and trends related to sustainability, climate change and biodiversity such as to limit deforestation, better mobilise ecological functions, to limit the use of chemical inputs, etc. (Trommetter, 2008).

The application of biotechnology in agrifood can have important positive contributions towards a more sustainable economy. In the agrifood sector the application of biotechnology has environmental implications for the primary production and for the food production process. In the latter case, the use of biotechnology improves resource efficiency and related emissions.

In the primary production sector (i.e. agriculture) biotechnology helps to increase production efficiency, reduces drug and antibiotic treatments in animal production (due to the use of – recombinant - vaccines) and reduces harmful emissions through the use of enzymes as feed additives (Zika et al. 2007). Primary production is one of the major contributors to environmental pressures in the EU (Tukker et al. 2006). Animal production accounts for a significant share and biotechnology applications are used to decrease this problem: e.g. lysine in pig feed leads to a reduction of nitrogen excretion and phytase in pig and poultry feed to reduction of phosphorus emissions (Papatryfon 2007). GM-crops have the potential to decrease the use of chemicals (pesticides) in crop protection; their impact must be evaluated on a case-by-case evaluation (ibid). New challenges for eco-innovations applying biotechnology are the further improvement of resource productivity and aiding in the decoupling of economic growth from environmental pressures. The use of biomass for so-called biobased (i.e. biomass) products helps to lighten the environmental footprint and enhance energy security.

Green biotechnology: advances in the adoption of agricultural biotechnology applications

The area cultivated to GM crops continues to increase rapidly from 40 million ha in 2000 to134 million ha in 2009 (James, 2010). There is a rapid growth in the number of countries where GM crops are cultivated (25 in 2009) – with rapid growth especially in developing countries and also the area where GM crops are grown is increasing. An even faster growth is in the “technology intensity” as measured in the number of GM crops with multiple GM or “stacked” traits. After a relatively slow start Brazil has now overtaken Argentina as the second largest grower of GM crops in the world. The only European country with more than 100,000 ha under GM crops is Spain (maize). This rapid growth has important implications for EU-countries for several reasons. First, it will be increasingly difficult to separate GM crops from non-GM crops in the agrifood chain. Second, increasingly also European farmers will miss out on productivity increases realised elsewhere in the world. Third, Europe would miss out on environmental benefits of GM crops such as reduced need for agro-chemicals. Fourth, there is also a risk of European technological capabilities falling (further) behind those of countries where GM crops are widely cultivated (including also India China, and Brazil).

Green biotechnology: Consumer acceptance and regulation

Notwithstanding this large variety of applications, less is known about its adoption in terms of new products as no information is available on products sold or used (Reiss et al. 2007). From the figures presented in box 2.1 (in chapter 2) it shows that its contribution to the European economy is the smallest of all three biotechnologies. European companies hold strong position in specific markets such as breeding and propagation material, veterinary products and feed additives. An exception are GM crops and the small impact partly could have been caused by the restrictive legislation in Europe on GM crop legislation and approval and labelling of genetically modified organisms in food which might have negatively affected the competitive position of European firms in this field.

However, European seed companies - that have strong positions in specific seed markets - have developed and are now using alternative biotechnological breeding strategies in which no natural barriers between species are being crossed – e.g. marker assisted selection, cis-genesis – which might be accepted by the European consumer and improve the companies' competitive position. These two related factors - market and regulation – are the main challenges for the green biotechnology industry in Europe. Other market related challenges for green biotechnology include the development of the world population and the needs for food and the growing demand for biomass for biofuels and as source for other industrial outputs (for the latter two: see the next section). In the food market health is an important trend; biotechnology research and specific biotechnologies are used for the development and production of these foods.

White biotechnology: Biomass as feedstock for the chemical industry

The most important trend in industrial biotechnology is the increased use of biomass as raw material for chemicals production. Currently the chemical industry almost exclusively relies on crude oil, biomass is only used to a small extent (< 10%). The use of 1st generation biomass feedstock (particularly corn and wheat) is very much under public discussion as higher commodity prices are a concern for net food importing developing countries and the poor in urban populations. Also they lead to higher costs and lower incomes for producers that use the feedstock for animal feed. Lignocellulosic feedstock is an alternative raw material for bioethanol and other chemicals; this so-called 2nd generation raw material is available in large quantities, can be harvested at any time of the year and can grow in nutrient-poor soils.

Biodiesel and especially ethanol production recently have got a boost by an increased demand of renewable energy sources mainly driven by environmental but also political considerations. For bioethanol very high growth rates of 25% are expected for the coming years. Important innovations are to be expected: 1) new types of enzymes for pre-treatment processes, especially hemicelluloses that can hydrolyse several types of hemicelluloses from a large variety of biomass species into sugars and 2) cheaper production processes of these (hemi) celluloses. The innovations in enzymatic pre-treatment methods will make lignocellulosic biomass (2nd generation feedstock) available for the production of bioethanol and other chemicals (Enzing et al., 2008a, b). Overtime, micro-organisms will

be able to turn biomass feedstock into a full range of chemical products (ibid). Most biomass-based chemical products are still more costly than the petroleum based alternatives. Companies are cautious in investing in the development of biomass-based products as the risk on insufficient return on investment is considered too high, even when there is a large potential market and the strategic importance for the company is high (ibid).

White biotechnology: Eco-innovation

Using biomass replacing non-renewable sources such as fossil oil in the chemical industry is often referred to as one of the major contributions of biotechnology to eco-innovation. However, also the use of biotechnological processes in the chemical industry (processing both fossil and biomass feedstock) for applications in a wide range of products contributes to more sustainable production processes. The biobased (i.e. biomass-based) economy is often used as a synonym for the biotech-based (i.e. use of bioprocesses) economy, also referred to as bio economy (see for instance OECD, 2009a).

The application of biotechnology in industry has a positive impact on resource (chemicals) and energy use, greenhouse gas emissions, emissions of other pollutants to water, air and soil, and on the generation of waste. The use of enzymes in downstream industrial processes (detergents, pulp and paper, textiles, leather) and the replacement of chemical process steps by bioprocess steps in the production of fine chemicals leads to savings in energy consumption (and thus GHG emissions, mostly CO_2), water consumption, and chemicals input. Often also the process time is reduced (Reiss et al., 2007). In the chemical industry the contribution of biotechnology to more sustainable production processes is the highest for the fine chemical segment, especially because of the shortening of production chains (Van Ast et al., 2004). In case these chemicals can be produced from waste streams the ecological gains are even higher. In biopolymers production, the use of energy and related GHG emissions are reduced, although depending on the oil-based polymer taken as a benchmark, the values differ. For PHA, environmental indicators show negative environmental impacts compared to oil-based polymers (Zika et al., 2007). The blending of transport fuels with bioethanol could help to decrease the relatively high environmental impact of this sector (21% of total emissions). The full climate change mitigation potential of industrial biotechnology ranges between 1 billion and 2.5 billion tCO_2e per year by 2030, compared with a scenario in which no industrial biotechnology applications are available (WWF, 2009).

White biotechnology: 'Bio refinery'

Often the concept of 'bio refinery' is used for the production of chemicals on the basis of biomass, analogous to petroleum refinery. Bio refinery is defined as the transfer of the efficiency and logic of fossil-based chemistry and substantial converting industry as well as the production of energy onto the biomass industry (Kamm et al., 2007). According to Kaempf (2005) bio refinery is still in its infancy stage: the existing starch based miles will be followed in 2011 by bio refineries that fraction residues in dry mills for new co-products from lignin. In about 2020 fully integrated industrial bio refineries will be operating, in which multiple feed stocks are fractionated into high value products for economics and

fuel production (ibid). Steinmetz and Menrad (2008) have made an inventory of bio refineries in Europe. They distinguish between green bio refineries, oilseed bio refineries, cereal refineries, forest based and lignocellulosic based refineries and multiple concepts and have identified in total 93 including five future bio refineries located in eleven European countries (form which they received a response). More than half are producing biofuels (ibid).

White biotechnology: Corporate venturing, off-shoring

Corporate venturing and offshore/outsourcing (see Red biotech) also appear to become common company practice in large and innovative companies in the white biotech sector. For instance DSM Venturing is an active investor in start-up companies that create innovative products and services in Life Sciences and Materials Sciences for supporting DSM's innovation and growth strategy. Besides financial support, DSM Venturing supports the start-up companies with DSM's knowledge, resources and networks in order to establish mutual benefits and learning and creative a supportive environment for open innovation.

4.1.2 Drivers for future innovation

In the SIW-II study of Van der Valk et al. (2010) on main drivers for future change in the nine sectors the main drivers for future changes in the biotech sector have been identified. Based on a number of expert workshops two sets of drivers have been identified that are most important for future developments in this sector: rapid advantages in S&T and demand side drivers. A third group of drivers – intermediate drivers - relate to the role of public sector: government, regulation.

Advances in S&T

Biotechnology continues to be characterised by rapid advances in technology. This applies to processes, products, tools and instruments. Particularly important are advances in genomics, metabolomics and proteomics, and in systems biology. But also information technology plays a very important role, e.g. for enabling faster and cheaper gene sequencing as well as advanced simulations (e.g. protein folding, proteomics, bioinformatics and organ simulations)[7].

Specific advances include the following:

- High throughput diagnostics using microarrays (lab-on-a-chip) are increasingly used in large scale DNA mapping
- New applications are emerging through the development of protein and metabolite microarrays
- Emergence of synthetic biotechnology (Box 3) as a new field and the standardisation of toolkits ("bio bricks")

[7] FP7 Project: Virtual Physiological Human http://www.vph-noe.eu/

- Use of stem cells (especially of the embryonic type and advances in the utilisation of adult stem cells and even "normal" cells like skin cells through "reprogramming techniques) has great potential for the development of new therapies
- Pharmacogenetics analyses the response of individuals to medicines and will allow for much more targeted therapies
- Genetically modified crops are rapidly taking off in recent years. New developments are the inclusion of multiple modifications (stacked traits) to address problems where a number of genes are involved – this allows dealing with problems such as drought or cold tolerance
- New types of GM crops to be used as efficient feedstock for biofuel production such as low-lignin trees and forage crops, but also the use of algae for the production of biodiesel
- Plant molecular farming exploits the potential of GM plants to produce useful substances such as proteins and enzymes.
- This can also be achieved using GM animals ("bio-pharming") or using animal tissue
- In agrifood the development of nutrigenomics applications allow the development of diets aimed at an individual's genotype.
- In industrial biotechnology new developments focus on second generation biofuels, which are not derived from the edible parts of agricultural crops and more generally on new biomaterials (e.g. bio plastics).

S&T advances allow two different developments: first the exploration of new areas of endeavour (moving the scientific frontier) and second the standardisation and automation of biotechnology processes and procedures. The latter has led to a rapid fall in the cost of biotechnology procedures, which can be seen as a driver in its own right.

Convergence of technologies: Innovation also often takes place at the interface of different fields of science or technologies. One example is the use of technologies used for computer chips and in ink-jet printing which is used in the development of DNA chips and can be used in organ printing as well[8]. Much is expected of developments that combine advances from computer science, biotechnology, nanotechnology and cognitive science. More specifically, the convergence of biotechnology and medical technology leads to new products for the growing health market (aging society); this includes bio-imaging, biomaterial implants, and in the future the possibility to 'print' body parts using 3-D printing technologies[9].

Cost reductions of DNA sequencing: While the first mapping of the human genome in the HUGO project (less than a decade ago) required a large international consortium several years of work it now looks possible to produce a genetic map of individuals at reasonable cost in the very near future. The dramatic fall in research cost is exemplified by the recent hype about the "thousand dollar genome".

[8] http://www.wired.com/rawfile/2010/07/gallery-bio-printing/all/1
[9] http://www.wired.com/rawfile/2010/07/gallery-bio-printing/all/1

This cost reduction further stimulates developments in the field of personalised medicine[10]. Yet, the sole sequencing of a human genome is getting cheaper and faster, but this is only the beginning. The real science and analysis is still in its infancy and deals with the workings, functions and interactions of genes. Research areas like epigenetics and nutrigenomics are analysing the effects of environmental influences on gene expression (i.e. DNA methylation)[11]

Alternatives to genetic modification and embryonic stem cells: Regulatory hurdles especially with regard to plant and animal genetic modification and the use of human embryonic stem cells have encouraged scientists to seek alternative procedures. These include for example the use of techniques of genetic modification in such a way that the final product does not contain or express genes from other organisms. In the area of stem cells researchers are looking for ways to use non-embryonic stem cells.

Demand side drivers and emerging markets

Economic growth: investments in biotechnology: Economic growth influences developments in biotechnology innovation in at least two ways: it influences demand for biotechnology applications, as well as the extent to which investments in biotechnology are made. The profitability of new, advanced products such as medicines and bio-based materials depends on the disposable incomes of consumers, but also on institutions that regulate demand such as health insurance companies and on government policies. Important in this respect is also the cost-effectiveness of biotechnology innovations.

Furthermore, the availability of capital is crucial to the development of the sector that is highly R&D intensive. Private (venture) capital for biotechnology (especially in medical biotech) is determined by expected profitability, which depends amongst others on market size (income growth and policies), on the protection of intellectual property rights (IPR), and the existence of functional capital markets. The concern in Europe is that capital markets and policies are more advanced in the USA which explains why European investments in biotechnology lag behind those in the United States. Public funding for biotechnology R&D is a necessary complement to private funding and here again the USA is investing more heavily than Europe (Ernst & Young, 2009).

Economic growth: disposable incomes and demand for innovations: Until mid 2008 most economic scenarios assumed an increase in disposable incomes in Europe, despite rapidly ageing societies. Others, such as Beck (2003), presented a more pessimistic view highlighting the limits to globalisation

[10] In 2009 a company completed the first individual genome sequencing for 48000 US dollar (http://singularityhub.com/tag/48000/) and another US start-up company has announced that it has managed to sequence 3 human genomes at an average cost of 4400 US dollar (some of the sequencings were more expensive and some cheaper). This does not include the costs for personnel and machines, only for chemicals (http://www.technologyreview.com/biomedicine/23891/). By 2030, the sequencing of a human genome could fall to 100 US dollar (or even below) and can be achieved within 1 hour time (or even less) (http://www.xconomy.com/%20boston/2009/05/05/nabsys-secures-4m-first-round-to-develop-electronic-dna-sequencing/)

[11] http://epigenome.eu/en/2,48,875

– based on political fragmentation, the fact that cheap energy is about to run out, that ageing societies are less dynamic and that, more generally, western societies may be approaching the limits to growth identified first by the Club of Rome in the 1970s. The financial crisis of 2008 has given more weight to the possibility that economic growth may be much lower in the coming decades than the previous ones. In this new context, the cost-effectiveness of biotechnology innovations will be ever more important. Especially in the EU a reduction of venture capitalists' activities is threatening biotech firm survival. Due to a decline of funds the UK has already lost its lead in available venture capital to Germany (Mitchell 2009b).

Acceptance of biotechnology: Public acceptance of biotechnology is a complicated issue with significant differences between application sectors and types of actors. In the medical sector biotechnology applications are generally very well accepted as they represent major improvements for patients (insulin case) – the exception being those applications and technologies where ethical issues such as the use of human embryonic stem cells or gene therapy are concerned. Acceptance of industrial biotechnology is also generally high as production takes place in contained environments. This contrasts with agricultural biotechnology where concerns about biosafety (e.g. out crossing of genetically modified plants to wild relatives) and food safety (consumption of GM products) are widespread. On the other hand there are environmental benefits to GM crops such as reduced reliance on agro-chemicals for plant protection, and the possibility to design new crops to better deal with harsh environments and climate change. Also genetic technologies for research purposes proof very valuable in agriculture and environmental science, e.g. in the context of biodiversity and finding new and wild plant species for cross/inbreeding to improve current plants (e.g. potatoes).

The introduction of new technologies in society has often been controversial and biotechnology has generated and continues to generate serious debates and controversies in Europe. There is a growing demand for transparency and stakeholder involvement in decision-making about investments in biotech R&D. This has been referred to by Wilsdon and Willis (2004) as the new trend towards "See-through-Science". Potential applications of biotechnology that can contribute to achieving sustainability challenges may face less public resistance, or may even be supported by public interest organisations. These applications can be found mostly in the field of industrial biotechnology and to a more limited extent in primary production through a reduction in the use of agro-chemicals.

Changing market characteristics: ageing and individualisation: Under the influence of economic, demographic, cultural, and lifestyle changes a number of developments in markets are taking place that affect the role and position of biotechnology.

Population ageing is an important, certain driver of developments in European societies. It leads to changing demand patterns both directly by ageing consumers and indirectly as governments are faced with the cost of care for an older population. Demand for products such as prosthetics and ultimately replacement or artificial organs as well as treatments to cure or delay dementia and other age-related diseases may drive developments in biotechnology R&D. An important shift in priorities is also the move from cure to prevention, with the latter increasing quality of life at lower costs. Biotechnology-

derived medicines to treat diseases on the other hand are also often very expensive to use. An example is monoclonal antibody drugs that require intravenous administration in hospitals.

Another important trend is individualisation of Western societies. Personal solutions in the form of diets and medicine are becoming increasingly important. In combination with a trend that populations Europe are becoming more ethnically diverse this leads to a growing segmentation of markets. The rise of niche markets, each with a different life style, and facilitated by the emergence of virtual communities (such as Facebook) has important implications for the development of new biotech products and services (e.g. "personal" genome services)[12]. In this respect convenience and experience are becoming important characteristics of new markets. Ageing consumers want healthy yet convenient products that provide specific experiences (in food, wellness, and care).

Intermediate drivers

Extent of Regulation: Biotechnology (at least in its early phase) was a radically new technology, the risks and impacts of which where highly uncertain. Moreover, ethical issues are very important to biotechnology developments and heavily influence regulation and policies. Regulatory frameworks governing risk and safety have been important in determining the development, diffusion and adoption of new biotechnology products and processes. In Europe the precautionary principle has been the basis for regulatory practice. It holds that when there is possibility of severe and irreversible harm, and in the absence of scientific or societal consensus the burden of proof is on the proponents of new actions – in this case the introduction of new technology. The emergence of new technologies calls for adjustments to be made to existing regulatory frameworks. These adjustments can subsequently have a large impact on further innovation in a certain field. Possible adjustments not necessarily imply an increase of the extent of regulation. To illustrate, in the field of medical biotechnology, developers of new medicines for so-called 'orphan diseases' (i.e. rare and neglected diseases) can receive protocol assistance from the European Medicines Agency (EMEA) to increase their changes of gaining marketing authorisation (EC, 2006). On the other hand, policy decisions and regulations with regards to biologics, used in original bio pharmaceutics and biosimilars, have been made so far on a case-by-case basis, further fragmenting the market and increasing uncertainty (Ernst & Young, 2009).

An important issue is the difference in the extent of regulation between countries. Some European countries (amongst others Germany and Austria) have very strict rules on human embryonic stem cell research (and PID), while other European and especially non-European countries have far less strict regulation. These differences in regulation could lead to competitive disadvantages, but also legal uncertainties. For example, will medications based on human embryonic stem cells be allowed to be imported into countries with strict regulation on stem cells? And will tissue engineered products be allowed to be sold commercially if organs as such are not allowed to be sold?

[12] http://www.wired.com/epicenter/2009/11/singularity-university-biotech-bioinformatics/

Government priorities: As one of the driving forces of regulation, government priorities are an important intermediary driver for future developments in biotechnology. In the case of biotechnology innovation, important possible priorities are achieving food and energy security, aiming for improving public health and the quality of life of citizens, and contributing to sustainable development. In the face of rising prices of energy and raw materials and in response to urgent issues such as climate change, concepts such as cradle-to-cradle are becoming ever more prominent. This has important implications in relation to the production of food and raw materials, especially in moving towards the bio-based economy.

Health care costs are rising across Europe and there is an increasing pressure on the healthcare sector and the health care insurance companies to lower costs. Bio-based medical technologies and pharmaceuticals are often rather costly, at least initially. Although they ultimately support more effective and efficient diagnostics and treatments and are also driving prevention, these long term impacts are often overlooked when deciding on health care investments. Differences in national health care systems within Europe, but also with the US result in fragmented and complex markets. The pressure on health care costs offers also opportunities for the development of generics and biosimilars.

Standards: The role of standards in the development and adoption of new technologies is related to the two previous drivers ‘extent of regulation’ and ‘government priorities’. Standards enlarge the market and create transparency for producers and users. In many fields the imposition of environmental, safety, or quality standards by government, or indeed by companies or industry associations in the form of self-regulation, can support innovation.

4.2 Sector scenarios

Scenarios have been developed based on two dimensions that have been selected as key drivers in the biotechnology innovation process: economic growth and regulation (see Van der Valk et al., 2010). Each dimension has a high and a low level of development, thus creating four scenarios. Regulation affects the range of products and services that are developed and allowed on the market. This driver was considered (during workshop with experts) to be most uncertain and also of large impact. Regulation can hamper the innovation process, but also stimulate specific developments leading to innovations. The different biotechnology application sectors have their own specific relevant regulations; therefore, the potential influence of regulation differs per biotech sub-sector. Low levels of economic growth will severely restrict the development of new biotechnology products and services. Competition will occur on the basis of incremental innovation, and for instance new combinations of existing innovations. In case of high levels of economic growth there is room for radical innovations; also innovation trajectories that are more long-term oriented and risky are becoming more relevant and feasible under this circumstances.

Scenario I: 'Loosing Momentum: GMO ban & basic healthcare'

Within this scenario, there is very limited growth of the biotech sector as a result of low investments and regulatory restrictions. New applications of biotechnology are very limited in number as well as in innovativeness. More controversial applications such as GM foods and human embryonic stem cell or gene therapies are banned by regulatory restrictions. The main barrier to non-controversial innovations, both in medical biotechnology and in industrial biotechnology, is the lack of financial means to fund innovation. In general, within this scenario innovation in Europe is hampered.

Scenario II: 'Cost-effective innovation'

Investments in biotechnology are limited and therefore cost-effectiveness has become the crucial consideration in decision-making on the development and adoption of innovations. The extent of regulation is limited, which implies that some new possibilities can be explored. This is however limited by the lack of investment funding.

Scenario III: 'Acceptable technology, sustainable innovations'

This scenario shows a situation where developments in innovation are potentially booming because of the high levels of investments made, but restricted in some application sectors by regulation. In this scenario, mainly developments within those innovation themes that are subject to more controversy will be limited. This would concern developments in for instance human embryonic stem cell applications, gene therapy (to some extent) and GMOs. At a global level, the prices of raw materials, foods and oil are likely to be high in this scenario, because of the economic prosperity that coincides with high levels of investments.

Scenario IV: 'New Horizons'

A wide range of new technologies, applications and services has been developed as a result of high investments and limited regulation. The effects on developments in agricultural and medical biotechnology are similar: limited regulation and high investments stimulate developments in all innovation themes that are relevant for these application sectors. There are opportunities for highly innovative small firms. Developments in industrial biotechnology may occur more slowly as sustainability standards are not strictly adhered to. However, because of the high oil prices due to economic prosperity, there are increased research and development efforts in the area of biofuels.

4.3 Future innovation themes and corresponding linkages with other sectors

Van der Valk et al. (2010) have identified a number of emerging biotech-based innovations themes that leading to new or improved products and processes in the three biotech subsectors.

4.3.1 Innovation themes in medical biotechnology

Medical biotechnology has the largest diversity of innovation themes: regenerative medicine and tissue engineering, pharmacogenomics and biomarker analysis, advanced drug delivery systems and bioinstruments.

Regenerative medicine and tissue engineering

In the near future developments in the field of tissue engineering will enable the production of structural tissues such as skin and bone tissue (New Zealand Ministry of Research 2005). Over time, developments in the field of stem cell research will provide opportunities to broaden the applications of tissue engineering. It is expected that these developments may even enable the production of fully engineered organs (ibid). Stem cells can also be used in therapies for the treatment of diseases such as Alzheimer and diabetes and as such hold an important promise for the future (Papatryfon et al. 2006). But the possible applications of stem cells for treatment are broader: very recently, British researchers have started the development of artificial blood using embryonic stem cells (Dijkgraaf 2009) and stem cells can also be used in toxicity testing (Chu 2007). At the end of 2008, Spanish surgeons transplanted the first tissue engineered full organ: a windpipe created from the patient's own stem cells (Macchiarini et al. 2008). While previously the use of embryonic stem cells was considered much more promising than the use of adult stem cells (Papatryfon et al. 2006), new developments enable a safer derivation of pluripotent stem cells from skin cells (Soldner et al. 2009). Efforts are also made to improve the extent to which stem cell differentiation can be influenced using small molecules (Papatryfon et al. 2006). Knowledge about this differentiation process is still limited (ibid), but improving[13]. Currently, Osiris Therapeutics, a US based medical biotech firm, has two mesenchymal stem cell based products in clinical trials, for the treatment of graft-versus-host-disease, Crohn's disease and knee cartilage regeneration (Mack 2009). At the beginning of 2009, the US based biotechnology firm Geron obtained an investigational new drug status for the treatment of spinal cord injuries (Alper 2009). This firm therefore has permission to start with clinical trials (Couzin 2009). This will be the first clinical trial of a product made up of human embryonic stem cells. Firms are thus increasingly targeting the markets that emerge due to technological developments and within the boundaries of regulatory frameworks. For further development of tissue engineering and regenerative

[13] See for example: http://www.scientificamerican.com/blog/post.cfm?id=adult-stem-cells-retain-cellular-me-2010-07-19, and: http://www.technologyreview.com/biomedicine/25632/?a=f

medicine large investments are needed. This development will therefore thrive in Scenario III and especially IV, where there is limited regulation.

The recent developments sketched above indicate that the potential market for stem cell-based medicinal products is large, and expanding with the further development of technology. Because of the former US ban on financing stem cell research, which was lifted in 2009, but is now contested in the courts, EU research may be in the lead at the moment. Further diffusion of the outcomes of research activities to firms is necessary to benefit from potential head start. For society at large, new developments in regenerative medicine and stem cells will open up revolutionary new ways of treating diseases such as diabetes.

Advanced drug delivery systems

New developments in drug delivery systems occur on the interface between biotechnology and nanotechnology. Research is conducted on capsules compiled of nanoparticles that can be used to deliver the medicinal product at the desired place as well as sustained release of the product once it has arrived. However, so-called nanotubes compiled of polymers are still disputed due to safety issues. In general the safety of 'nanomedine' innovations is still being researched.

Another new method of drug delivery entails the use of capsules that are sensitive to light or heat. To illustrate, Dutch multinational Philips, traditionally active in lighting, recently signed an agreement with US biotechnology firm Celsion for the co-development of a heat sensitive chemotherapy treatment (C2W 2009). Such innovations are the result of technological convergence of electronics, imaging technology and biotechnology.

Advanced drug delivery systems can be applied in a range of treatments, most notably cancer treatment. Their market is therefore particularly large. The application of drug delivery systems can contribute significantly to the effectiveness of treatments, and also to the reduction of side effects of treatments. Therefore, innovations in this field can contribute to the cost-effectiveness of treatments and can therefore be adopted in scenarios where economic prosperity is limited.

Pharmacogenomics and biomarker analysis

While developments in the area of pharmacogenomics have resulted so far only in a few products that have been marketed (the co-products HER2 and Herceptin are a well known example), expectations are high (Papatryfon et al. 2006). Biomarker assay devices are thought to contribute to the integration of DNA diagnostics in health care. Micro fluidics-based lab-on-a-chip technology (Box 5) can be utilised for this to circumvent the absence of required facilities in clinical labs (Sorger 2008).

While developments in lab-on-a-chip technology do not yet live up to expectations formulated a decade ago, this technology is still perceived to have the potential to radically impact the use of biomarkers in diagnosis and patient stratification (Sorger 2008). Furthermore, when analysing protein levels, these chips can also be used to monitor disease progression (New Zealand Ministry of

Research 2005) as well as to test food safety and in bio defence (Papatryfon et al. 2006). One of the most important barriers of translation of pharmacogenomics innovations into healthcare is that it is difficult to show their cost-effectiveness, among other things, because of scarcity of data (Gurwitz et al. 2009).

This innovation theme can also contribute to the cost-effectiveness of treatments; its market is potentially large as all diseases have some extent of genetic predisposition. On the other hand, firms developing personalised medicine may need to invest more in R&D, because diagnostics as well as therapeutics need to be developed. It is not yet clear if the increase in price that is the result of these increased expenditures will be mitigated by the costs saved due to increased effectiveness and safety of medicinal products (Gassmann et al. 2004). Therefore, development of this innovation theme is expected to depend on economic prosperity and evolve more rapidly in Scenario's III and especially IV, where high quality healthcare is an important priority.

4.3.2 Innovation themes in agricultural biotechnology

In agricultural biotechnology developments are expected to be less radical and more in line with past and current developments; the most notable innovation themes are related to the genetic modification of plants and animals and entail bio pharming and the further development of GM crops.

Bio pharming

As mentioned already above, the first applications of modern biotechnology were biopharmaceuticals that were produced in cells. More recently, plants have been discerned as a promising potential production system: 'bio-pharm'. Types of products that can possibly be produced in plants include proteins in general and more specifically antibodies and industrial enzymes, as well as vaccines (Papatryfon et al. 2006). The production of vaccines in plants can lead to advantages in speed and capacity of production and therefore the availability of vaccines in case of sudden increases in demand (Gijsbers et al. 2006; Murphy et al. 2007). The commercial activities in this field are still limited and mostly entail fundamental research. Main technological challenges are the so-called post-translational events including glycosylation (Papatryfon et al. 2006).

To enable rapid developments in this field, regulation on GM-crops in the EU needs to become more flexible. Opportunities for bio pharming are largest in Scenario IV 'New Horizons', where high quality healthcare has the highest priority and regulation on GM crops and animals is flexible. Due to the EU GMO ban R&D on this innovation theme has been limited in the EU. It could therefore be that US firms dominate the market for bio pharming that emerges within scenario IV and EU firms may not be able to compete with their US counterparts.

Further development of GM crops

Developments in the area of GM crops are progressing. Until now, the focus has mostly been on developing crops with one specific trait, but in the future these traits will increasingly be combined. GM

plants that have stacked traits are plants that have been modified in such a way that they display multiple traits such as pest resistance and herbicide resistance (Papatryfon et al. 2006). Plants could also be genetically modified to cope with drought. Stacking traits in practice is an extension of earlier efforts to enhance crops by a single modification and can lead to significant advantages in regard to yield and nutrition.

Because of the regulatory uncertainty in regard to GM crops in the EU, most large firms that are active in this field are US-based. It remains to be seen if EU firms will be able to benefit from new developments in this field when these developments are going to thrive in Scenario's II and especially IV. It could well be that the commercial benefits of the flexible regulatory environment that has formed in these scenarios mainly accrue to US firms. It also remains to be seen how large the local EU market for GM crops will be as there has traditionally been public resistance in this area. When relevant, benefits of GM foods for the consumer need to be made clearer.

Non-GM biotechnology for plant breeding

Genetic modification is only one of the set of modern biotechnologies that can be used for crop enhancement (COGEM 2006). Non-GM biotechnology for plant breeding forms a group of specific techniques that do not involve genetic modification as such; they include, among others, tissue culture technologies and the use of biomarkers.

Tissue culture techniques or micro propagation can be used to make reproductions of an individual plant from tissue. It thus enables cloning of a plant that has certain desired traits and is free of infections (Molecular plant biotechnology 2009). A technique that is frequently used is 'anther culture', which enables the production of pure homozygous 'diploid' plants. Such plants are composed of two sets of the same gene sequence and thus have identical copies of each gene. Undesired mutation can be excluded using this technique. Molecular marker techniques can be used to monitor genetic variation and select certain plants based on biomarker prevalence ('marker assisted selection'). These techniques require further development before they can be cost-effectively applied. Tissue culture technologies and biomarker-assisted selection significantly speed up the process of developing a crop with specific desired traits, without using actual genetic modification. Also there are techniques that use genetic modification during the development process of a new crop but the actual product does not contain any mutated genes or foreign genetic material (COGEM 2006).

Developments in the area of non-GM biotech breeding will thrive in Scenario III, where sufficient investments can be made to further develop these techniques and GM plant breeding is inhibited by the high extent of regulation. EU research institutes are believed to have an excellent scientific base in the area of non-GM biotechnology breeding techniques. In general, non-GM biotechnology breeding would increase the efficiency of crop production in a way that is accepted by consumers. However, EU regulation is restrictive when GM crop breeding is concerned. There are concerns that in the EU the breeding of crops enhanced using non-GM biotechnology will also be restricted, while this is not the

case elsewhere (for instance in the US and Asia). Therefore, the EU risks to fall behind in these developments as well, after already lagging behind in GM-crop breeding (COGEM 2006).

4.3.3 Innovation themes in industrial biotechnology

In industrial biotechnology innovations are to be expected in the fields of bio plastics, biofuels and bio refineries.

Renewable bio plastics

The development and application of bio plastics is an important trend in the development of the knowledge-based bio-economy (EU2007DE 2007). The market share of bio plastics is estimated to be about 20 % in around 2020 (New Zealand Ministry of Research 2005). Bio plastics contribute both to a reduction of the dependency on oil for producing plastics, and to a reduction of waste as products made of bio plastics are biodegradable (MacRae 2007). As such, these products can contribute to achieving a more sustainable society. Because of this, the forecast of the development and introduction of bio plastics has not been an issue of much public debate (Herrera 2004). On the contrary, in the future developments in the field of bio plastics may even be supported and stimulated by NGOs striving for sustainability. This is however yet to be seen. Around 2030, it may have become possible to imprint bio plastics and thereby make extensive use of them in electronics (MacRae 2007). They may also play an important role in the production of lab-on-a-chip kits. It may well be that production facilities of bio plastics will largely be located in China, thereby boosting its economy (ibid). An appealing feature of bio plastics is that they may serve a dual purpose: after use as for instance packaging material they may, by use of certain enzymes, be converted into biofuels. This opens up new markets and may for instance especially be promising for application in the military sector (Waltz 2008). One important aspect that may limit the adoption of renewable bio plastics is their cost-level compared to normal plastics. This could reduce the size of the market for these products. Standards imposed to achieve a transition towards a sustainable society can help to overcome this barrier. The adoption of bio plastics can contribute to reducing emissions as well as energy consumption in general (WWF 2009). This is the case in Scenario III, where, under the influence of strict sustainability demands, this transition is realised using industrial biotechnology innovations.

Biofuels

In the US, bioethanol development is strongly supported by the government. Also because of this the US is leading over Europe: the direction of EU policies on biofuels remains unclear due to the negative evaluation of first generation biofuels with respect to their environmental and economical sustainability (Sheridan 2008). While the US is said to have a clear vision and roadmap this is lacking in Europe and this could significantly slow down developments in this field as industry awaits more certainty (ibid).

Venture capital investments in sustainable energy technologies do show a decreasing support of biofuels that are produced at the expense of food production (Huggett 2008). In response, the investments in alternative sources for biofuels production, such as algae (Box 6) and crops containing

cellulose is raising (ibid). These second generation biofuels are especially promising in regard to their potential contribution to emission reduction (WWF 2009). Especially expectations about the use of algae for the production of biofuels are high, but it is not yet clear if this process for the production of oil will be economically viable (Waltz 2009). Genetically modified non-food crops may also be an important source for the production of biofuels. In comparison to the acceptance of these crops for use in food products, their use in fuels may face less resistance (MacRae 2007).

Developments within the innovation theme Biofuels are booming in Scenario III, where there is a full transition towards a sustainable society. One of the risks is that extensive production of biofuels will restrict the total area of land that is available for the production of foods. Developments in the EU are currently lagging behind those in the US because of the US priority of energy security and their political strive for decreasing oil dependence. Biofuels can replace fossil fuels used in transportation (WWF 2009).

Bio refineries

Bio refineries are considered to be the petroleum refineries of the future. A variety of feed stocks can serve as inputs to the refinery and, similarly, a range of products can be produced, e.g. biofuels, bio plastics, and chemicals. Second generation bio refineries are even able to process non-food, lignocellulosic feedstock, but these more advanced bio refineries are still in the R&D phase (OECD 2009a). Recent developments in R&D also concern marine bio refineries, in which algae are used. Developments in plant breeding and more specifically in making crops more suitable for use in bio refineries will lead to more competitive prices for biofuels and biochemical in the future (ibid).

Second generation and marine bio refineries are still in a relatively early phase of development and are therefore only likely to be realised in Scenario III and, to a lesser extent because of a lack of attention for sustainability, in Scenario IV. First generation bio refineries can be relevant in all scenarios, but are more likely to be overtaken by next generation refineries in Scenario III. The EU has a favourable competitive position in the chemical industry, but is currently lagging behind in regard to development of bio refineries. While the scientific position of the EU in the field of bio refineries is quite strong, private investments and the supply of raw materials are both limited. Investments are however needed to deal with difficulties related to realising refineries of a sufficient scale. Because of their potential contribution to sustainability, bio refineries are generally accepted, especially when non-food feed stocks are used (Biopol 2009).

4.4 New requirements for sectoral innovation

Van der Valk et al. (2010) have identified the potential barriers and requirements for the above innovation themes to develop into successful products for (new) markets and more effective production processes. They have been grouped in five sets: physical infrastructure, knowledge and skill requirements, organisational change and firm strategies, institutional change and regulatory issues and structural change.

Physical infrastructures

Biotechnological innovations require new infrastructure and equipment both in the R&D phase and in the production phase. For instance, at the R&D phase expensive facilities may be required e.g. to contain biohazard risks or elaborate procedures followed to avoid out-crossing of GM crops. But in general the cost of biotechnology R&D work are becoming lower rapidly, driven by the automation and high throughput sequencers[14]. At the production of innovative products stage the effects of automation and miniaturisation can also be observed. While there are products and processes that traditionally require large-scale investments, such as bio refineries or pilot plants for bioprocessed chemical products. In certain parts of industry, there is a trend towards more modular and smaller production units.

Skills requirements and the knowledge base

The biotechnology sector is highly dynamic and requires continuous investments in the development of new skills and competences. The skills issue is very important as a sound scientific and technical understanding of biotechnology (and of the different specialisms in this broad sector) is of key importance. Due to the variety of technological developments within the field of biotechnology and the rapid pace with which these developments take place, it will be increasingly difficult for individual firms to determine which technological opportunities to seize. A key capacity is the ability to interpret and understand the development in other fields of science, especially in nanotechnology, informatics and cognitive science. It is expected that radically new applications will emerge at the interface of different S&T fields following the emerging technologies model. In this sense, 'being able to create innovative synergy' may become increasingly important (European Monitoring Centre on Change, 2008: p. 15).

Many biotechnology start-ups are driven by a single big idea. A core asset for any such company is the ability to judge business developments and especially to generate business models on how to turn scientific insights into products and services that earn money in the marketplace. Because of the decline of available capital for biotechnology, especially in Europe, skills for identifying and serving new markets will become increasingly important.

As biotechnology is a highly regulated sector affected by several important legislations that pose challenges and opportunities for business, researchers and managers alike need to learn about new legislations and their impact on their sector. This requires, among others, an understanding of law, ethics and consumer behaviour.

[14] The Economist (June 17, 2010) reports that the cost of DNA sequencing in 2010 are about a one hundred-thousandth of what they were ten years ago

Firm strategies and organisational change

Collaborative R&D and open innovation have been common in modern biotechnology even since its emergence in the 1980s (McKelvey 2000). The first biopharmaceuticals firms were fully integrated, e.g. were involved in preclinical and clinical R&D as well as marketing and sales. Over time, at least in Europe, a shift occurred towards other business models that were less capital intensive and provided the firms with a shorter time-to-market. These models include developing and licensing out platform technology and commercialising services (Willemstein et al. 2007) and thereby focusing on a limited, specific part of the value chain (European Monitoring Centre on Change 2008). More generally, with the increasing importance of large datasets for drawing conclusions on for instance genotype-phenotype interaction (due to the emergence of pharmacogenomics); firms may also establish their business on maintaining such datasets (McKelvey 2008). Due to developments in the field of personalised medicine significant shifts in business models may also be necessary as blockbuster markets are not likely to be available for such products (Siemens 2006).

Bio plastics (and more generally biomaterials) and biofuels were indicated to be important emerging innovation themes. While they are both considered to be promising, until now most attention has been given to the development of different kinds of biofuels, including biodiesel and bioethanol. This is especially the case in the US, whereas in Europe a biomaterials roadmap has also been developed. The two markets for industrial biotechnology can however also be combined, as the more fundamental building blocks are similar. Because of this, firms can make use of the growing attention, especially in the US, for biofuels to also develop biomaterials and enter the market with bio plastics (Waltz 2008). The main disadvantage that seems to be holding firms back from investing heavily in the development of bio plastics is the time line of returns on investment: the advantages of investing in bio plastics may not become apparent in the short term but may be large in the long term (Herrera 2004; Katsnelson 2005). For bio plastics to become a competitive alternative for normal plastics, the prices of bio plastics need to be as low as possible. To share the costs of R&D, firms that want to enter this emerging field increasingly make use of collaborations with other firms or research institutes, as has also been a trend in pharmaceutical biotechnology in the past decades (Katsnelson 2005). Overall, the investments in the field of bio plastics by European firms are lagging behind the investments by US firms. European investments might be boosted in the future, because of future regulation making the use of bio plastics mandatory. Such regulation is more likely to be formulated in Europe than in the US (Herrera 2004). This would significantly reduce the uncertainty faced by firms that decide to invest in bio plastics. EU policies to stimulate the development and uptake of biofuels may also be implemented.

Institutional change and regulatory issues

In some specific areas of research, such as non-GM biotechnology breeding techniques EU research institutes have a strong position in terms of scientific excellence. However, other aspects limit the extent of translation of the scientific findings into product development trajectories. One important

aspect is the institutional context in EU countries. Specific institutional issues emerge in the field of medical biotechnology, in regard to biofuels policy, in regard to GM and non-GM biotechnology plant breeding techniques and EU-level harmonisation.

Especially in the case of innovations that are of a more radical nature, the developments in the stringency and rigidity of regulations may be of significant influence on their future progression. An example is the use of stem cells in therapy, which is currently being researched. Emerging positive attitudes toward stem cell research and development in the US, as supported by the Obama, but now contested in the courts, could be at the expense of developments in the EU, with the UK as a leading country in this field, as firms choose a favourable location for their research (Siva 2009a).

An IPR issue that may lead to deviations between the USPTO and the EPO in the near future could be the increased broadening of human gene patents, to for instance also include claims for antibodies that have not actually been produced (Hashimoto & Aida 2008). More generally, obtaining a patent in the EU is more costly than in the US (Lawrence 2008). Furthermore, in the past years the first patents of medicinal products derived from biotechnology expired. This gave rise to the opportunity of introducing biosimilars onto the market. At this moment a difference between the US and Europe has become apparent: biosimilars are still absent in the US, because of the fact that guidelines for their market approval have not yet been implemented in the US. In Europe, an increasing number of biosimilars is entering the market (Aggarwal 2008). It is as yet unclear what the effects of this apparent difference between the US and Europe will be in the future. National and EU-level regulatory developments in the field of biosimilars may have a large impact on the potential success of such products and their predecessors that are facing patent expiration (see Schellekens (2009)). A suggestion to resolve this debate would be to make the cell cultures available that have been used for producing the original product, and let these be used by others who want to produce generics after patents have expired.

Targets have been set for expanding the use of biofuels in the EU, i.e. to 5.75% in 2010. The EU Biofuels vision document prepared by the Biofuels Research Advisory Council (2006) mentions a target for 2030 of 25% of CO2 efficient biofuels in the transport sector as “ambitious and realistic”. For biofuels the key question is what their net effects on greenhouse gas emission reduction will be: these depend critically on the energy use in the production feed stocks and on the efficiency of biofuels production (production pathways and technologies) – also in relation to other renewable energy sources. As a result in the EU there is still much uncertainty with regard to policies on biofuels. In the US, reducing oil dependency is perceived as the main driver for developments in the field of biofuels, while in the EU improving sustainability has highest priority. This creates a disadvantage for first generation biofuels in the EU. While these products do serve the US objective of reducing oil dependency, they do not help to achieve EU sustainability targets. Therefore, first generation biofuels a subject to much criticism in the EU, which also has impact on the perception of biofuels in general. It may therefore also slow down developments in second generation biofuels in Europe (Sheridan 2008).

As discussed above GM technology has not been accepted widely in the EU. New technologies in plant breeding allow researchers to use GM techniques while resulting in products that do not contain any “foreign” genes. The status of these products is still unclear. At any rate these new technologies will blur the once sharp distinction between GMO and non-GMO, and as such will require a response from policy makers.

Several issues have emerged in the analysis of the new innovation themes that could benefit from harmonisation at the EU-level. First of all, there is a need to harmonise legislation on highly innovative therapies such as gene therapies and products deriving from tissue engineering across EU member states (Aldridge 2009). In the current situation, individual member states have the opportunity to complement EU-level directives with their own more specific and possibly highly diverging regulations, which creates uncertainty for firms working in these fields. Furthermore, this divergence between member states could decrease the overall attractiveness of the EU as a place for doing business in these highly innovative areas that are part of medical biotechnology. Secondly, to gain more benefits of developments in pharmacogenomics, some extent of harmonisation of content of bio banks and processes of data storage is needed (Gaisser et al. 2009). This would facilitate the linking of individual bio banks, resulting in more comprehensive data sets. In the current situation knowledge that could lead to promising new applications of pharmacogenomics is highly fragmented (Enzing et al. 2009).

Structural change

The biotechnology sector is highly dynamic and in a constant process of structural change. Changes worth noting include concentration, possibilities for de-concentration, and the effects of convergence and open innovation.

In the last decade the agricultural biotechnology sector has gone through a process of concentration. As the regulatory framework for the application of GM crops in Europe remained quite strict a number of life science companies (notably in Europe) have scaled down their activities in agricultural biotechnology or left the field altogether. This has turned the fear of opponents of biotechnology that the technology would end up in the hands of a few multinational life science companies into a self-fulfilling prophecy. At present there a few main players left and Monsanto (which has kept up its investment in biotechnology) has emerged as the clear winner (Business Week 2008). Overall, it is difficult for small firms to survive and grow in this field, as they have difficulties bringing their inventions to the market. Reasons for this are a lack of funds to cover regulatory and R&D costs, a lack of a marketing infrastructure or a lack of high-yielding production system (OECD 2009a). Because of these issues most small firms will use the exit strategy of being acquired by large established firms. In medical biotechnology concentration due to M&A activity also occurs, albeit to a lesser extent than in agricultural biotechnology.

An important model in biotechnology has been and continues to be the venture capital based high tech start-up company – sometimes set up as a spinout from universities or research institutes. At a certain stage, typically when the biotechnology start up has a promising technology or product, or

when it is unable to fund costly clinical trials it is acquired by a large multinational enterprise. With the end of the blockbuster model and falling cost of a number routine research procedures the potential for small biotechnology companies to develop products and processes for small niche markets may well increase. It would however still depend on the availability of start-up capital. Also, with the emergence of personalised medicine established pharmaceutical firms have to adapt their marketing and sales forces, as this development signals the end of the single large markets for pharmaceuticals that can be targeted by a single large marketing and sales force. Venture capital is also increasingly important in industrial biotechnology – especially biofuels development has attracted many investors in recent years.

Technological convergence implies that innovation is increasingly taking place at the interface of different technologies. It will lead to changes in the sector with novel types of companies emerging that seek to combine and integrate knowledge from genetics, medicine, computer science, materials science and nanotechnology, mathematics and modelling, cognitive science, etc. This will lead to radically new combinations of technologies and to innovative products and services. It also promotes more open innovation processes as no company alone can cover the broad set of knowledge required.

4.5 Sectoral innovation policy in a scenario framework

From the future developments presented above, Van der Valk et al (2010) have selected a number of important issues that are relevant from a policy perspective. These issues can be subdivided into those that are of direct economical importance and those that are important from a societal perspective. In general, developments in modern biotechnology are very much affected by regulation, which was the reason to include this as one of the two main drivers for developing the scenarios.

To promote innovation in the ‘Loosing Momentum’ (Scenario I) major initiatives would be required to boost both investment and demand, as well as to remove regulatory barriers. But since these low levels of economic growth restrict government budgets the support of investments will be quite difficult. Scenario II (‘Cost effective innovations’) is characterised by low levels of regulation and low levels of economic growth. With limited government budgets for support, policy options here should concentrate on encouraging private sector investments through a variety of means such as the promotion of networks of actors, facilitating the exchange of knowledge between universities and companies, etc. Scenario III (‘Acceptable technologies, sustainable innovations’) is characterised by high levels of regulation and high levels of growth. This focuses investment on green and other broadly acceptable innovations. Here governments should focus on selective support of key innovations, working closely with private companies in public-private partnerships, to ensure desirable and acceptable outcomes. In Scenario IV (‘New horizons’) regulatory barriers are low and high levels of economic growth will spur the development of a wide variety of different technologies and innovations. In this scenario government policy should concentrate on its role as a watchdog to keep abreast of potentially risky developments. As this is the most dynamic of the four scenarios

governments should also develop capacity in foresight to identify key trends and developments before they actually occur.

Past developments of GMO regulation have significantly shaped sectoral developments in agricultural biotechnology. As a result of strict regulation on GMOs only a limited number of firms are still active in the EU. For the future this raises the question about the status of products derived through non-GM biotechnology breeding technology: are they considered to be genetic modification after all, or not? In other countries this is not subject of discussion, while in the EU it is currently an issue. This lack of clarity makes firms and investors hesitant to engage in the further development of these techniques (COGEM 2006). If EU firms face yet another ban this would further threaten the application of biotech research in the EU. Developments in agricultural biotechnology worldwide are booming, while in the EU they are very limited at the moment. This can imply that it will be increasingly more difficult for the EU to guarantee that foods do not contain GMOs. Now when the EU level it has been decided to make regulation on GMOs more flexible, this will be even more difficult. Past experiences show that public perception and acceptance of GMO-derived foods can have a large impact on the evolution of the sector and competitive position of firms. This indicates the importance of on-going communication about developments, and more specifically also about the potential advantages of new products for consumers. In medical biotechnology these are often very clear while this is not the case in the area of GM foods.

Another controversial issue is the simultaneous use of patents and plant breeders' rights in agriculture. A choice should be made in the EU on which of these types of intellectual property rights should prevail. At this moment this decision is left to the European Patent Office (EPO), but it is considered to be a fundamental decision to be made by the EC. If the EU decides to embrace developments in GMOs in the future, what will the effect on the agricultural sector in the EU be? Will the EU agricultural industry be able to take up the opportunities? What can be done to support them in improving their competitive position compared to for instance their US counterparts?

In some scenarios, developments within the medical biotechnology sector are evolving rapidly and their potential in terms of profitable trajectories for innovation is difficult to overlook. Simultaneously, the investments that need to be made by firms to take part in these developments are often large. This raises the questions: 'What new business models may emerge as a result of the different S&T and demand side drivers and what business models are more likely to result in profitable firms? How can 'smart business models' be defined?'

Building on this issue, and in the light of the growing convergence of biotechnology with other sectors, it needs to be noted that it will be increasingly important for managers and employees of biotechnology firms to be able to identify opportunities for innovation arising because of this convergence. Also, managers and employees should be better able to foresee environmental, ethical and societal implications and developments that are relevant for their R&D activities.

In several of the innovation themes especially GMOs, bio pharming and biofuels, policy developments in the EU have been uncertain. In some cases, decisions have been made that later on have been withdrawn again. Furthermore, a frequently heard criticism in regard to EU policies is that they are complex and static. This has a direct impact on the R&D investments of firms in the EU. In the scenarios, regulation in the EU could be more or less extensive but regulation should at least provide clarity. This also applies to government funding programs: in technology fields such as biotechnology where research and innovation are lengthy processes, it is important to be consistent: either stimulate developments for a longer period of time, or do not stimulate developments at all.

Firms and research institutes working in biotechnology could benefit from more harmonisation across member states, for instance in the field of stem cell research. But on the other hand, ethical issues are dealt with on the level of the individual member state. Furthermore, this issue of harmonisation is also relevant for the EU and US. Especially in more controversial innovation themes in medical biotechnology the different EU member states make use of the opportunity to develop their own regulation in addition to EU level regulation. This raises the questions: ‘How to more effectively and efficiently manage different levels of regulation: national (member state-level) and EU level? And: Is it desirable and feasible to harmonise more?

Especially in medical biotechnology, the call for cost-effectiveness and cost reduction is profound. During the past years, as is also reflected in the innovation paradox in pharmaceuticals, new medicines have only become increasingly expensive to develop. It is as yet unclear if developments in emerging innovation themes will improve the cost-effectiveness. Simultaneously, public healthcare systems are under pressure everywhere because of the ageing of societies. These two trends reinforce each other. Full centralisation of decision making on reimbursement of medicines is neither feasible nor desirable for instance due to differences in the prevalence of diseases among countries. To deal with the issue of cost-effectiveness in innovation in medical biotechnology a more centralised approach does seem to be necessary. A way to approach this issue is to develop an EU framework for the evaluation of the cost-effectiveness of medicines that can be further specified in individual members states to take parameters into account that are specific for the different member states. Costs of unemployment and other, more indirect costs should also be included in this framework.

Related to the previous issue, decision-making on the marketing authorisation of diagnostics occurs within the different EU member states, while marketing authorisation for biotechnology-derived medicines occurs on the EU level (at the EMEA). With the further emergence of pharmacogenomics and personalised medicine, where diagnostics and medicines are developed *in tandem* (Van Merkerk and Boon, 2007), this difference in registration procedures may become more problematic for firms. Thought should be given to how to address this issue.

Earlier in this report the shortcomings in the translation of research into applications in the EU were noted. This shortcoming is evident in a number of fields, for example in the development of bio refineries. Establishing public-private partnerships was indicated as a possibility to help resolve this lack of translation of science to innovation. In the US, large public private consortia have already been

set up. In the EU similar initiatives would be useful to share the risks of bio refinery development. Joint investment programs are needed, as a reasonable sized demonstration plant requires a large investment[15]. Such an initiative may even take shape in a EU-wide master plan for bio refinery development). Important decisions for instance on where to build the plant and how to obtain sufficient feedstock to serve as inputs for the bio refinery are then taken on the EU level and actions can be coordinated. More coordination between the different DGs of the EC will be needed to do this.

[15] For a reasonable sized demonstration plant this investment can amount to 2 billion euro.

5 Drivers and barriers to innovation: market and regulatory factors

5.1 Introduction

The SIW-I study identified a number of key drivers of innovation. These drivers are: financial constrains, human resources and skills, knowledge creation and diffusion, cooperation between firms, networks, demand factors, competition, innovation culture, regulation and taxation (Reinstaller and Unterlass, 2008). A number of key drivers, not sufficiently explored in SIW-I, are included in a study performed under SIW-II. In this study (Montalvo et al, 2011a) the influence of two key drivers – market and regulation – on the innovativeness of firms is explored in more detail. In addition a number of factors in the innovation system and their effect on innovation has been studied.

In the study, data collected from two different sources are being used: a company survey and CIS4 data on the biotech sector. A main contribution of the study of Montalvo et al (2011a) is that - based on a survey under European biotech firms - it provides insight in how the companies themselves perceive the relation between regulation-related and market-related factors on the innovativeness of the firm. The rate of response was 7.5%, resulting in 33 usable cases that have been included in the analyses. The size of the firms captured in the overall survey that covers all nine sectors in SIW-II, resulted to be 60.9% small, 15.9% medium and 23.3% large firms. Above 80% of the respondents in the firms addressed were in medium and high ranking management levels. The majority of small firms in the sample reflects the biotech industry structure, with relatively many SME's and a few large multinational companies.

The quantitative analysis - using both data sources - was done in order to test the relationships of dependence in the biotech sector between innovation outcomes, innovation activities, market factors and regulation. The types of innovation (innovation activities) used in the study, are those included in the Community Innovation Survey 2008: products, services, manufacturing methods, logistics, support activities, management systems, lay out changes, relations with others, design, sales. A new variable was created that is a composite of all types of innovation. For regulation a list was made based on a literature search of several types of regulation that affect the biotechnology sector. Concerning the market related factors two additional factors were used as compared to the SIW-I study: the optimisation of costs and efficiency in firms and global openness to trade. A number of CIS4-based outcome indicators were used (competitiveness, brand image, social benefits, company growth, technical risk).

The overall analysis that explored the relative importance of market-related factors and regulation for innovation showed that eight of the 39 factors that have been analysed are highly significant: two of them are market-related (increase market share and faster response to customer); none of them deals with regulatory issues. Regulation shows to be not that relevant for innovation in the biotech sector; the regulation-related factor 'Meet regulation and standards' is positioned on a 19th - and non-significant - position. The biotechnology sector is not an exception in this respect as compared to the

other sectors in this SIW-II study: for only two of them (Aerospace and Electrical and Optical Equipment) regulation and standards is a significant factor influencing innovation. However, the factors 'Information from Government' might very well concern also regulatory issues, as government is the actor that develops and maintains regulation. Other factors that are important for innovation in the biotech sector are collaboration and difficulties in finding collaboration partners, improved production flexibility, employees' satisfaction and reduced labour costs.

5.2 Market-related factors affecting innovation

In the study of Montalvo et al (2011a) a large number of market-related factors and their relation with innovation have been analysed. These market-related factors include: oil and energy prices, demand in Asia/Eastern Europe, supplier power (cost structure), client power (cost structure), customer preferences, aging population, inputs and components prices, incumbents market position, market structure, optimisation and efficiency, labour costs outside EU, market expansion, heterogeneity customer base and global finance crises.

The analysis shows that that high-oil prices are an important driver of innovation in the biotech sector. This variable is highly positively correlated to the innovation types: 'innovation in management systems' and 'supporting activities'. This is very much in accordance with what was found in other studies and especially applies for the white biotech sector where second and third generation biofuels are being developed as alternative to fossil fuels (Enzing et al., 2008c). Also customer preferences and market structure (industry consolidation, market concentration) were found to be drivers of innovation. This also applies for increased demand for products and inputs in Asia and Eastern Europe, supplier power to influence firms' costs structure, incumbents' current market position and pace of innovation in firms' business type. The increased demand for products and inputs in Asia and Eastern Europe and supplier power to influence firms' costs structure are positively correlated to 'innovation in supporting activities' and 'layout of production organisation' (the latter only with increased demand for products and inputs in Asia and Eastern Europe). The market structure, was found to be positively correlated with several types of innovation, especially 'layout of production organisation', Similarly, client power to influence firms' costs structure and incumbents current market position are also positively correlated to innovation. These outcomes confirm the important role of demand side factors that are directly related to the client itself and is in accordance with what one can expect from the type of biotech companies that were involved in the survey: high-tech firms working on a business to business market in close contact with their clients i.e. other companies in the biotechnology innovation chain.

Aging of population that was indicated as an important driver, especially for the health-biotech sector in the SIW-I study (SYSTEMATIC, 2007) but also in the foresight study of SIW-II (see chapter 3), was not found to be a driver of innovation in the biotech sector. This difference in outcome could very well be explained by the sample of companies that participated in the survey. Most of them are small biotech companies and these type of companies do not produce for a consumer market and thus for them this specific market trend (aging population) is not relevant for them. Mostly they operate in a

business-to business market and sell technologies and services that can be used by many different companies in the red, green of white biotechnology. Also the prices of raw materials and component prices (e.g. food prices), and market expansion were not found to be a driver. This could be explained by the same arguments as those mentioned for 'aging population'.

5.3 Regulation affecting innovation

The influence of regulation in biotechnology innovation processes is rather ambiguous: it can both positively and negatively affect the innovation process in the biotechnology sector. Publications of biotechnology organisations and consultants document this (Ernst &Young, 2007; 2008, EuropaBio 2008). As an example: the regulation in the field of stems cells, GMOs and animal testing restricted the development and use of specific technologies, but also stimulate the development of alternative and less-controversial technologies.

In the SIW-II survey companies were asked to evaluate the effects of specific regulations on innovation in their firms. Most types of regulations included in the SIW-II survey are formulated in a rather generic way and or not technology or product specific: environment, labour, agriculture, workforce safety, health, IPR regimes, public procurement, price, interoperability-compatibility (between old and new standards), communication, occupational, animals protection and European regulations, etc. Two more specific legislations were included (REACH, GMO).

The analysis shows a rather poor association between regulation and innovation in the biotechnology sector. It was found that only 'labour regulations' and 'interoperability-compatibility (between old and new standards) 'are highly significantly correlated to innovation in biotech firms. When analysing in more detail to what type of innovation the two regulations correlate, it was found that this was to 'layout changes of production organisation'. In addition, 'labour regulations' is highly correlated to the innovation type 'design of a good or service' and 'sales or distribution methods'. This finding was not reported in literature on innovation in the biotechnology sector, mostly probably because it has never been investigated. However, it could be that these outcomes are not specific for the biotechnology sector. It might very well be that they are more representative for small firms that have to deal with labour regulations and the compliance with these regulations leading to the development of procedures that have a positive effect on the efficiency of their innovation processes.

IP regulation is positively associated to the innovation type 'industrial relations' and European regulations to 'product innovation' and 'innovation in supporting activities in the sector'. The latter is in line with the argument that the Community Patent and European Patent Litigation Agreement are urgently needed (Europe INNOVA, 2008) and literature in the field (Anderman, 1998). The correlation analysis also suggests a positive association (but only moderately significant) of the workforce safety regulations to innovation in 'supporting activities' and 'layout changes of production organisation'. Here, again, the outcome could very well be that these general regulations are not specific for the biotech sector but apply for all small (high-tech) firms that have to deal with these types of general regulations.

Overall, the outcomes of the analysis do not lead to strong conclusions on the effects of specific regulations on innovation in the biotech sector, except for the IP and EU regulations.

5.4 Other system factors affecting innovation

In addition to the analysis of market-related factors and regulation and their effect on innovation, a group of factors have been included in the analysis that have been identified in previous studies and literature as important drivers and barriers to innovation. In the study of Montalvo et al (2011a) three groups of factors have been included that are important components of the innovation system - business environment, collaboration and innovation and innovation culture – and their specific role as driver or barrier in innovation processes in the biotechnology sector has been investigated.

5.4.1 Business environment

The specific business environment factors that have been selected for the study are: business opportunities, duration of R&D, growth opportunities (collaboration), R&D costs, availability of human capital, opportunities to secure benefits, technical risks, capital risks, pioneering advantages, consumer acceptance and willingness to pay and losing know-how control (collaboration)[16].

The analysis suggests that all factors of business environment are drivers of innovation in the biotech sector; especially R&D costs have very large influence on innovation, followed by growth opportunities arising from collaborative innovation projects, business opportunities and consumer acceptance and willingness to pay. Although not reported by the literature, the survey results suggest that the likelihood of losing know-how control in collaborative innovation projects is also perceived as a barrier for innovation in the biotech sector. The results of the correlation analysis suggest that costumers' acceptance and willingness to pay is strongly correlated with innovation in the biotech sector. This factor is correlated with a number of types on innovation 'innovation in industrial relations', 'design' and 'manufacturing methods'.

Additional analysis of a number of factors dealing with access to capital and knowledge resources show that access to capital and access to information are drivers of innovation in the biotech sector, which confirms what is found as main characteristics of the biotech sector as a capital and knowledge intensive sector. The correlation analysis suggests a positive correlation between two access variables - 'access to information' and number of innovation to the market - and the innovation types 'innovation in supporting activities' and 'innovation in management systems'.

[16] Regulatory uncertainty was also included as a business development factor, but we have addressed this in Section 4.3.

5.4.2 Collaboration and open innovation

Collaboration, especially with knowledge provides (such as public R&D organisations) and with other companies in the chain (suppliers, customers) are important factors for successful innovation, especially in high tech sector such as the biotech sector. The ability to combine internal and external information is a crucial new source of competitive advantage (Rigby and Zook, 2002), Montalvo and Koman (2011) have analysed the role of a number of factors in innovation in the biotech sector. Most actors (suppliers, public research organisations, universities, customers) show to be a driver in innovation. The correlation analysis suggests that innovation of biotech firms is highly positively correlated to collaboration with suppliers, competitors and customers, while the association with collaboration with universities is only moderately statistically significant. Collaboration with suppliers is highly positively correlated to the innovation types 'innovation in industrial relations' and 'design'; collaboration with competitors is highly positively correlated to 'innovation in sales or distribution methods', 'design' and 'management systems'; while collaboration with customers is positively correlated to 'innovation in services' and 'layout of production organisation'.

Compared to the rest of the sectors in the SIW-II study, firms in the biotech sector work have a more easier collaboration and open innovation with all actors. The largest mean difference is reported for collaboration with PROs and universities, while there is only a slight difference in the mean value compared to all sectors for collaboration with customers.

5.4.3 Innovation culture

Under 'Innovation culture' the role of the following factors on innovation in the biotech sector has been studies: team diversity, multi-lingual employees, problem-solving teams, minimize opposition to change, value new skills/abilities and participation in improving activities. The results show that the value of new skills / abilities is positively correlated to the innovation type 'innovation in layout of production organisation'. In addition, correlation analysis also suggests a strong correlation to 'supporting activities' and to 'innovation in management systems'. Moreover, the correlation analysis suggests that innovation is also highly positively associated to team diversity, problem-solving teams, minimize opposition to change and participation in improvement activities. Minimize employee's individual opposition to change and innovation is positively associated to innovation in logistics, delivery or distribution, in supporting activities, in management systems and in layout of production organisation. Similarly, assembling problem solving teams to ensure a creative atmosphere is positively associated to all the abovementioned innovation types except logistics, delivery or distribution. Finally, team diversity and participation in improvement activities are positively associated to innovation in design and industrial relations, respectively.

The outcomes of the study of Montalvo et al. (2011a) show that although regulation is widely acknowledge as an important aspects issue for the biotech sector, it in general does not have any significant impact on innovation in the biotech sector, except for IP and EU regulation that are positively associated to some types of innovation. It also showed that – although the biotech sector is

characterised as a science driven and capital intensive sector, which was confirmed by the outcomes of the study – especially market related factors show to be of importance for successful innovations. Customer preferences, clients' power, markets in Asia and market structure are crucial aspects for successful innovation processes in the biotech sector.

6 Horizontal issues

In the SIW-II project in a number of studies so-called 'horizontal issues' dealing with innovation and innovation performance have been addressed. These issues include: technological specialisation, high growth companies ('Gazelles'), organisational innovation, eco-innovation and lead markets. In most of these studies the biotechnology sector was also involved. A summary of the most important results of these studies is presented in this chapter. The Gazelle study (Mitusch and Schimke, 2011) and the Organisational innovation study (Rubalcaba et al., 2010) did not make a specific analysis on the level of the SIW-II sectors; these two issues will not be addressed in this chapter.

6.1 Technological specialisation

The study on impact of technological specialisation on economic performance (Grupp et al., 2010) defined national specialization as the weight of the sector in a country, relatively to the weight of the same sector in the world. The study measures the specialization patterns using patent data and evaluates the distribution of the sectoral patenting activities of that country relatively to the rest of the world's patenting activities in that sector. A country with a strong specialization in a specific sector measured through patenting activities could represent technological excellence in this sector. National specialization patterns are driven by the economic dynamics of a sector; but depend also on the specific innovative activities of the companies in the sector, on the valorisation activities of public research organisations in the field and also on policy factors such as supportive (national/regional) technology transfer instruments. Calculations on the relation between technological specialisation and economic performance could not be made for the biotechnology sector, due to unavailability of data on the biotech sector in the CIS4 database[17].

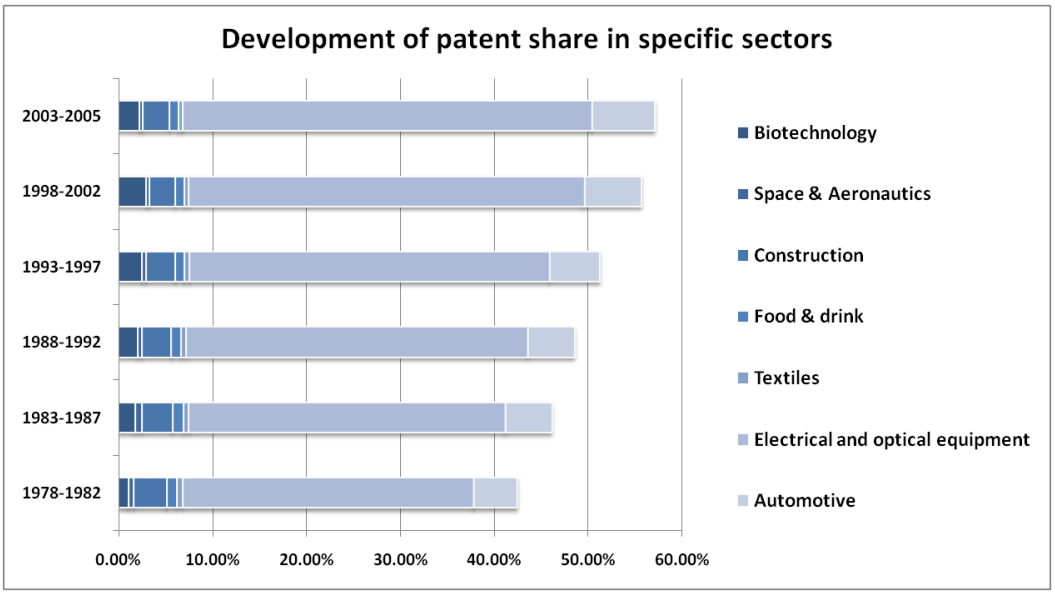
Patent activity output

Biotech belongs to the top 5 of the set of seven selected sectors (from the nine the SIW-II study focuses on) when it comes to patenting activities (1987-2005, EU27 plus CN, IN, JP, US). Most patents are generated in the sector electrical and optical equipment (nearly 39%). About 6% of the patents are held in the automotive sector, 3% in the sector construction and about 2% of the patents are held in the biotechnology sector, 1% in the Food sector. The relative technological advantages in the biotechnology sector are mainly concentrated in Belgium and Denmark.

The following figure (taken from the report of Grupp et al, 2010) illustrates the development of the sectoral performance in patenting between 1978 and 2005 in the seven sectors. The biotechnology sector shows the strongest increase in this period; also electrical and optical equipment and automotive shown an increase. The patent share in the sectors construction and textiles decreases, that of food & drinks stays rather stable and space & aeronautics shows so specific development path.

[17] As a proxy for the biotech sector, Grupp et al. (2010) calculated performance figures for the chemical sector.

Figure 6.1 Development of patent share in specific sectors



Source: Grupp et al., 2010

Europe versus other regions

The study of Grupp, et al. (2010) suggests that Europe as a whole still lags behind the main international competitors, in terms of investments and capacity to drive new technological trajectories. It is the case of health-related technologies, entering a new paradigm, for which the US leadership seems to be uncontested, because of, among other factors, policy priorities and larger investments in biotechnology and ICT for medical equipment.

The study even shows that Europe has a strong disadvantage in pharmaceuticals and biotechnologies. The technological specialisation profile of Europe (EU27) is oriented towards consumer goods, civil engineering, industrial processes, agricultural and food apparatus and several sub-fields of the broad areas of machinery, mechanics and transport. Except for pharmaceuticals and biotechnologies, Europe is also highly de-specialised in the broad area of technologies related with electronics and electricity. The US technological profile is more distinctly oriented towards biotech and pharmaceuticals, together with electronics (mainly Information Technology) and medical engineering. This pattern – Europe weak, US strong - strongly persists over time. But also other global players like India, while still exhibiting relatively modest patenting activity, are sharpening their biotechnological profiles. India is strongly specialised in pharmaceuticals and organic chemistry and exhibits technological advantages in biotech, agriculture and food products and, though to a lesser degree, information technology. Also Japan shows some strength in biotech, but it lags far behind. China shows no clear specialization pattern.

Within Europe

The most dynamic economies (the EU Innovation Leaders according to the European Innovation Scoreboard 2009) are also specialised in these large and fast growing technology fields of consumer goods, civil engineering, industrial processes, agricultural and food apparatus and several sub-fields of the broad areas of machinery, mechanics and transport.

Within Europe most patents in the biotechnology sector have been applied in the EU15. Nevertheless most EU15 countries are under-specialized in biotechnology. The exceptions are Denmark and Belgium that show technological advantages in this sector. Especially, Denmark has a technological leadership in biotechnology over the whole period of investigation (which is probably mainly due to the patenting activities of the companies Novozymes and Danisco, worldwide leaders in enzymes). Although France and Germany remain under-specialized in this sector their patenting performance increases continuously. The patenting activities of the New Member States are very low; there are only a few countries like Estonia, Hungary and Lithuania, who gain comparative advantages in the last decades.

Specialisation - excellence

However countries with a high number of patent applications do not necessarily have high quality patent quality, as measured by patent citations. Several authors (Trajtenberg, 1990; Harhoff et al. 2003) have showed that the more citations a patent receives, the higher the value of the patent. This implies that when investigating technological specialisation through patenting, also the quality level of the patents should also be taken into consideration. This analysis shows that the two values (number and citation value of patents) are positively related in a country, there are also countries with high patent specialization and low citation specialization, and low patent specialization and high citation specialization. In the biotechnology sector are Denmark and Slovakia are outstanding: both are +/+ performer with high specialization and high citation values in period I and II[18]. Finland and Italy are among the -/- performers, for all periods. Countries which have higher specialization values, but lower citation values is only Estonia (in the first period). There are no notable -/+ performers. Grupp, Malerba et al. (2010) mention Denmark as an example of consistent good combination of technological specialisation and “high quality” of specialisation, particularly in the fields of biotechnology and food & drink. According to them Denmark has not only a high technological specialisation in both sectors, but also may have future technological advantages.

[18] Countries which have positive or negative values in both specialization patterns are called +/+ performer or respectively -/- performer. The focus, however, lies on countries which have positive specialization patterns, but negative Citation Index-values (+/- performer) or the other way round (-/+ performer). There are three selected time periods (I: 1994-1996, II: 2000- 2002 and III: 2003-2005)

Technical specialisation and collaboration

Because of the important aspect of collaboration in open innovation processes, also the relationship between technological specialization and collaboration during the creation of knowledge was investigated in the study by Grupp et al. (2010).

Based on co-inventorship data (the team that has been working on the patent and owns the patent) the aggregated data for the SIW-II sectors present an increasing numbers of linkages; however this phenomenon does not hold for all the sectors. There are a number of sectors where the network connections are decreasing and this especially accounts for the biotechnology sector where almost all numbers fall in the period between 1994-1996 and 2000-2002.

Table 6.1 Network connections in biotech ownerships of patents

Network connections	1994-1996	2000-2002	Relative growth
EU15-EU15	864.34	791.15	0.47
EU15-NewEU	2.17	3.37	0.80
EU15-NonEU	77.63	24.27	0.16
NewEU-NewEU	3.00	2.14	0.37
NewEU-NonEU	0.35	0.00	0.00
NonEU-NonEU	1,128.61	108.40	0.05

Source: Grupp and Malerba, et al., 2010

In order to control for the increasing numbers of patents, a calculation was made of the change in the share of patents generated in collaboration compared to the overall amount of patents between the two time periods. Hence, a value of 2 indicates that double the amount of patents was generated by collaboration with other organisations from the first to the second period. In base of biotechnology there is negative growth figures (column 4 in the table). The overall analysis including all sectors shows that the increasing connectivity is largely driven by a change in the propensity to co-operate.

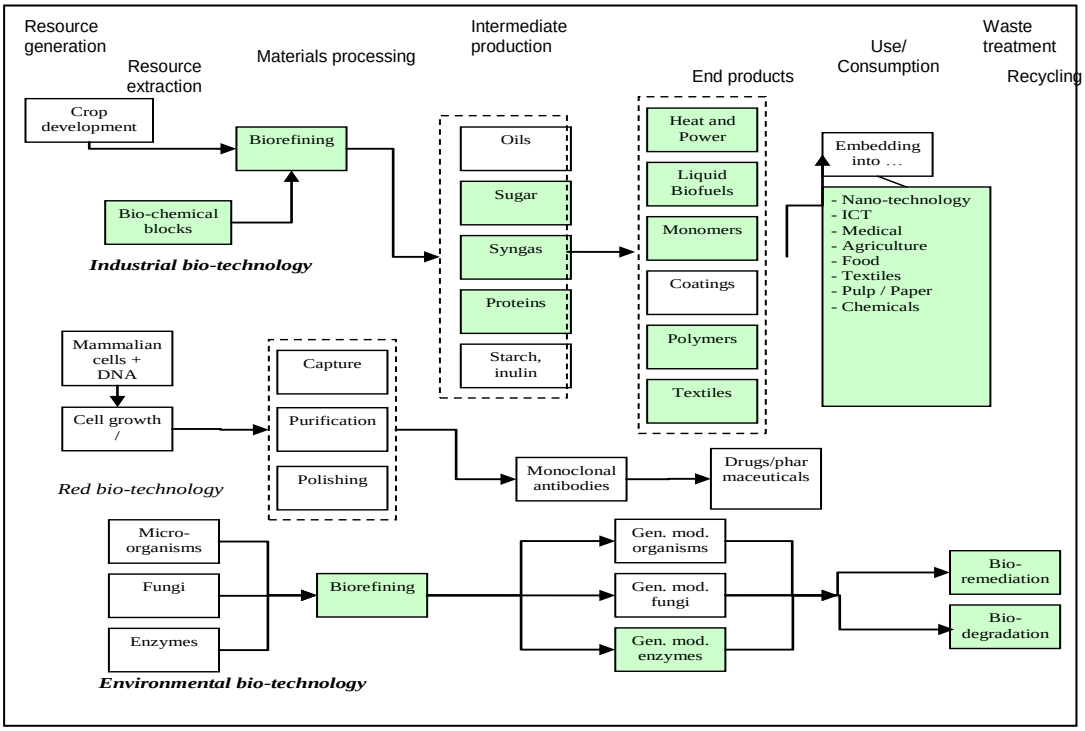
Additional analysis of the relationship between the degree of specialisation and the positioning in the collaborative network between countries also shows a decreasing number of connections in the biotechnology sector. Germany is a central player in Europe for the whole network; especially in the second period it holds most of the connections to the EU15 countries and to the New Member States. Beside Germany, the United Kingdom also plays an important role in the first period, but this importance changes in the second period. Furthermore, nearly all collaborations from New Member States to non-EU countries disappear. Taking into account the specialisation, it can be observed that most of the strong connections in the first period exist between specialised countries (Belgium, Denmark, United Kingdom and United States). The loss of linkages in the United Kingdom (UK) in the second period may be caused by the country lower specialisation in the ‘biotechnology’ sector, and the increased specialisation in the USA.

6.2 Eco-innovation

The study of Montalvo et al. (2011b) provides a detailed examination of the potential for eco-innovation in the nine SIW-II sectors. The study provides a sectoral overview of emerging eco-innovations, the impact of regulation and the current and potential applicability of eco-innovations in the nine SIW-II sectors. The main results of this study for the biotechnology sector are presented in this section. Montalvo at al. (2011b) focus their study on the white biotech sector. As was already concluded in chapter 2, the biotech subsector is considered to be one of the key enabling technologies with most potential for sustaining European competitiveness (Rammer et al. 2010). This subsector is an enabler of technological change and innovation processes in a wide range of sectors (Enzing et al., 2007a) as it provides important inputs for innovations in downstream sectors (such as healthcare, food, agriculture, energy, textile, pulp and paper, environmental remediation). These applications are expected to result in a significant share of the "bio-economy" in relation to the economic output of nations (Enzing et al. 2008a, OECD 2009a).

Montalvo et al. (2011b) have identified the critical blocks for eco-innovation in the white biotech sector, including the environmental applications of biotechnology; those areas where biotechnology applications could have a role as enabler of eco-innovation are highlighted (figure 6.2).

Figure 6.2 Value chain of the biotechnology sector and perceived critical blocks for eco-innovation



Source: Montalvo et al. (2011)

Because of the enabling nature of this sector the contribution of the sector to climate change and the exact environmental consequences of biotechnology activities along the value chain cannot be precisely predicted (Zika et al., 2007). Already some critical issues have been identified (e.g. see

Enzing et al., 2007b), but studies about long-term climate change related effects and sustainability performance of the whole sector are not yet available. More critically, the resource intensity of the biotechnology sector as a whole is poorly studied (Zika et al., 2007).

Montalvo at all (2011b) argue that current definitions of industrial biotechnology explicitly relate it to its application to environmentally friendly production methods and technologies (biobased economy) but hardly take into account its own environmental impacts (referring to for instance Festel, 2010). The environmental benefits of biotechnology-based processes in terms of cost reductions and less energy and materials consumption compared to chemical processes are counterbalanced by the substantial amounts of resources when calculated on a per-molecule basis – particularly for water consumption: for instance Graedel and Howard-Greenville (2005) estimated that 1 kg of synthetic organic material produces 100 kg of waste water.

Notwithstanding the examples for eco-innovation in the industrial biotech, Montalvo et al. (2011b) argue that there is no clear evidence that eco-innovations are inherently more or less environmental-friendly than alternative technologies (using Graedel and Howard-Greenville, 2005). It often depends on the application area: biotechnology is favourable when it replaces environmental-harmful or resource-intensive chemical or physical processes in a cost-effective way (Kircher, 2010). Certain bio refinery mechanisms aiming to produce bio-chemical substitutes are more efficient in terms of energy and resource consumption and produce less waste (Woodley, 2008) and bio-catalyst processes operating at lower temperatures, produces less toxic waste and fewer emissions (Gavrilescu and Chisti, 2005). But also some bio-leaching processes do avoid the release to the air of acid gases (e.g. arsenic trioxide) but leave unsolved the generation and disposal of carcinogenic compounds (e.g. ferric arsenate) (Whiteley and Lee, 2006).

Montalvo et al (2011b) mention a number of recent studies for the BIO4EU-project that have signposted a number of opportunity areas that are expected to drive eco-innovation in this sector. The studies present a detailed account of applications, prospects and market potential of industrial biotechnology among other application areas up to the year 2005 (see: Enzing et al., 2007; Reiss et al., 2007; Zika et al., 2007). The study of Enzing et al. (2007) attempted to present the environmental issues of 10 selected industrial biotechnology applications namely: bioethanol, biopolymers, cephalosporin, enzymes for detergents, enzymes for fruit juice processing, enzymes for pulp and paper, enzymes for textile processing, lysine, riboflavin and biosensors. However, lack of aggregated data made this task rather difficult.

Regulation and eco-innovation

For the case of industrial and environmental biotechnology literature on the impact of regulation on innovation is restricted to a number of application areas (e.g. bio-fuels, bio-materials, etc.). It is envisaged that the DG Energy's Biofuels Directives and Biomass Action Plan will constitute an important boost to the biobased economy (Jarekrans, 2008). According to Reiss, et al. (2007), for the case of bio-fuels quota obligations in EU member estates are considered as potential drivers of

innovation in the sector. France and the UK have strict obligations for the oil companies to offer certain blends in an ever higher percentage of bioethanol as a fuel every year. The Netherlands and Germany started obligations in 2007. In the UK the Renewable Transport Fuels Obligation encouraging investments in renewable fuels (Arthur D Little 2009b). For the case of biomaterials, in Germany the Packaging Ordinance comprises a new distinct regulation for certified compostable packaging made from biodegradable polymers. These products are exempted during the market introduction phase until the end of the year 2012, giving room to innovation (Reiss et al., 2007). The OECD (2009b) suggests that the use of biotechnology for chemical production (renewable chemicals) is likely to continue to increase, driven by rising energy costs, new chemical legislation (e.g. REACH in Europe), and increasingly stringent environmental regulations.

The relevance of standards (and its interoperability) as drivers of innovation may be important given the application of industrial biotechnology in a number of sectors. An example of a promising standard convergence is the American ASTM 6400 standard for compostable plastics and Europe's EN13432 standard on biodegradability, which could potentially contribute to supporting the international deployment of bio-based materials. Environmental performance standards based on life cycle analysis (LCA) methods (e.g. ISO 14044-2006) are expected to be a driver for eco-innovations in industrial biotechnology, especially when lower carbon footprints are rewarded in the market (OECD 2009a).

The biotechnology sector is seen as one of the key enabling technology areas with large potential to contribute to eco-innovation and sustainability. Like in other fast changing sectors that are science based, regulation lags behind technological developments. Thus we could expect that direct regulation hardly drives eco-innovations in the biotechnology sector. This statement is confirmed by our survey results, where the relative lack of associations found between environmentally motivated regulations and all kind innovations considered. The exception to this is the regulation on Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH). This could be expected as Biotechnology despite oriented to handling living material is also strongly supported by all kinds of enabling chemicals.

Opportunities for eco-priority areas

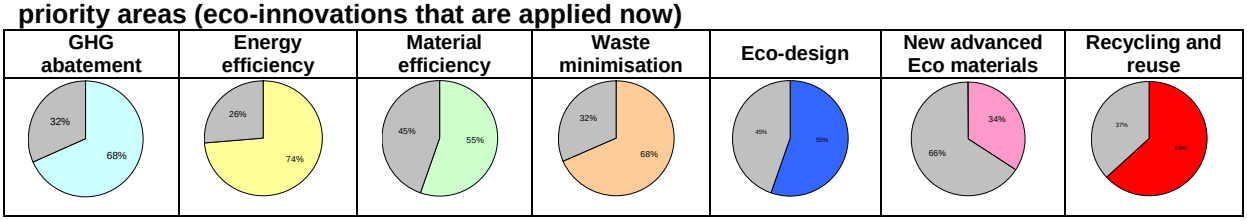
Montalvo et al. (2011b) analysed – based on survey data under a group of 1819 firms developing eco-innovations for the nine SIW-II sectors – the eco-opportunities of seven eco-priority areas (greenhouse gas abatement, energy efficiency, material efficiency, waste minimisation, new advanced eco-materials, eco-design, recycling and reuse). This analysis they made on the sector level consists of three parts. The first part presents the survey results dealing with the eco-innovation opportunities that are now being used for each eco-priority area. The second deals with potential eco-innovation opportunities that could be but are not (yet) used. Third part presents - based on the results of these two – the potential for eco-innovation in the biotech sector. The results are presented in pie charts: in each pie chart the coloured area represents the contribution to a priority area from an eco-innovation being applied (current) or from those that could be applied (not currently applied). The grey area represents the missed applicability. The addition of both percentages represents the potential for eco-

innovation in relation to an eco-innovation priority area: this is the reported value. The reader should keep in mind that the potential for eco-innovation should be understood as a relative measure, that is, the current applicability plus the applicability of eco-innovations that could be applied now but are not being applied in the sector.

Current applications

Figure 6.3 below presents the results for the eco-innovations applied now. The current contribution of biotechnology eco-innovations to a particular eco-innovation priority area is lead by the energy efficiency field, with 74%. This is followed by GHG abatement and recycling and reuse (68% and 63%, respectively). New advanced eco-materials is the category with the less contribution (34%).

Figure 6.3 Contribution of biotechnology eco-innovations to different eco-innovation priority areas (eco-innovations that are applied now)

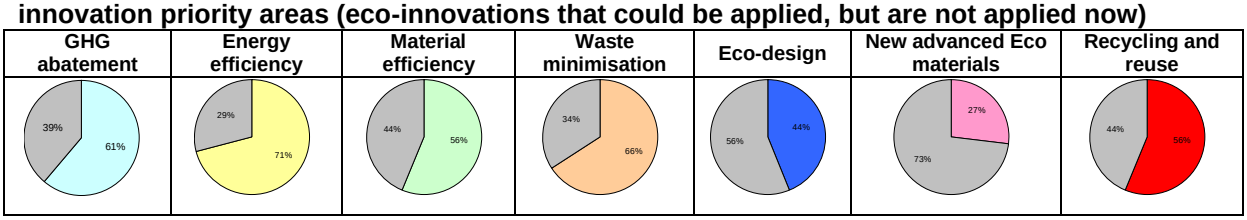


Source: Montalvo et al. 2011b

Not currently applied

Figure 6.4 presents the results of for the eco-innovations that could be applied now, but are not applied. The results are rather similar as the previous table: energy efficiency (71%) at the top and new advanced eco-materials at the bottom of the list (27%). In most cases the potential contribution of those eco-innovations that could be applied but somehow are not applied equals the same amount as in the table above. The previous suggests that the potential contribution could be twice as much as the current one.

Figure 6.4 Additional contribution of biotechnology eco-innovations to different eco-innovation priority areas (eco-innovations that could be applied, but are not applied now)



Source: Montalvo et al. 2011b

Potential for eco-innovation

The potential contribution of biotechnology eco-innovations to each eco-innovation priority area expressed in percentage is the sum of the percentages in the collared areas as presented in the two figures above.

Table 6.2 Potential of biotechnology in eco-innovation priority areas

GHG abatement = 129%	*Material efficiency = 111%*
Energy efficiency = 145%	New advanced eco-materials = 61%
Waste minimisation = 134%	Recycling and reuse = 119%
Eco-design = 99%	

Source: Montalvo et al. 2011b

Montalvo et al. (2011b) indicate that eco-innovation opportunities of biotechnology linked to new eco-materials are manifold but the penetration rate is still low. For example, bio-based products are established in higher value business segments in the chemical industry, but these are still represent a niche of about 6% of the total products (Festel, 2010). For the specific case of bio-polymers, a recent study suggested that their share in comparison to general polymers is only 2%, but the annual growth of this market in Europe (for 2003 - 2007) has been around 50% compared to 38% at a global scale (Shen et al., 2009). Technology and price competition from other well established technologies, economies of scale, competition among bio-technological platforms in terms of energy source (from biomass itself in refineries vs. from sunlight and carbon from atmosphere), and cost advantages constitute a major issue to overcome for the entire supply chain of many industrial biotechnology eco-innovations (OECD, 2009b). Cooperation and licensing in specific areas of application such as renewable chemicals are on the rise and could help to leapfrog the current vs. the potential contribution of biotechnology eco-innovations to new eco-materials (Montalvo et al., 2011b).

6.3 New lead markets

The SIW-II Lead market study (Dachs et al., 2011) concludes that lead times for new innovation designs in biotechnology are long and uncertainty is high in the biotechnology sector. Positive experience with certain products on the Lead Market will subsequently reduce uncertainty abroad (demonstration effect) and may facilitate the transfer of new products and processes to other markets. Moreover, positive experience with a specific product or process on the home market will reduce potential consumer fears concerning new biotechnology applications (e.g. for GM food products, human embryonic stem cell research) and enhance acceptance abroad. A Lead Market at the forefront of a trend will offer other markets the answers to their open questions and deliver solutions to counter their reluctance. On-going communication and information about technological improvements and advantages arising from application on the Lead Market will enhance the exportability to other markets. Further export potential may arise from a harmonisation of the currently divergent regulatory framework at the EU-level (Dachs et al., 2011).

Technological developments in biotechnology require both, public and private high investments in R&D. European investment in biotechnology R&D is lagging behind implicating competitive disadvantages compared to USA. Additionally, upcoming countries such as China, India as well as South Korea and Singapore are emerging competitors in this field as scientific powers and investment in agricultural, medical and industrial biotechnology rises. Within Europe, countries with favourable conditions in terms of demand specialization, relative price level, high export orientation and foreign direct investments as well as favourable market conditions in a specific sector are mainly Western

European countries, in particular France and UK. In terms of technological advantages, patent analysis (Grupp et al., 2010) indicates that most of the EU countries are under-specialized in biotechnology with the expectation of Denmark and Belgium. These two countries have comparatively high potential to exploit new market opportunities and establish a Lead Market position possessing relative advantages in several fields (Dachs et al., 2011).

7 Policy analysis and conclusions

This report on the biotechnology sector provides specific insights in the pervasive character of biotechnology as it is applied in many different industrial sectors. It illustrates how the specific sectoral innovation systems work in each subsector and the current trends, future drivers and bottlenecks in each subsector.

As biotechnology is not an industrial sector for which national and international statistics bureaus (such as Eurostat) collect information data availability on the biotech sector is rather poor and proxies have to be used, which have their disadvantages as the results have to be interpreted with caution. However there is growing interest of national and European policymakers in collection of data on the biotech sector and most are also used in this report.

Our results illustrate a variety of innovation strategies in the biotechnology sector. In fact it shows that biotechnology is not one industrial sector, but deals with the development and use of biotechnology in a wide range of sectors. The innovation strategies differ considerable per subsector and also between the different types of companies in the sectors (DBF's, large production and marketing firms). Policy should account for this complexity and create favourable framework conditions by fostering the innovative capacities of firms in the different subsectors in a more general sense.

A challenge in the biotechnology sector is the shortage of highly qualified personnel especially engineers and technicians in specific application oriented and industry-relevant areas such as bioprocess engineers (in the chemical sector) and qualified personnel with comprehensive knowledge of the industry and professional experience in all aspects of biotech business making such as capital raising, regulatory affairs, marketing, etc.

A main challenge in the biotech sector is the sufficient access to funds. The sector is known as knowledge and thus capital intensive. The financial crises has had severe impacts; this might be a reason for that the survey results show that a lack of funding hampers innovation in this sector. There is a need for more risk capital, seed financing and general research funding at all stages. This financial support is needed for start-ups as well as for existing companies moving to more innovative products.

Sustainability in general and resource efficiency in particular is a key issue for the biotechnology sector, with most potential in the white biotech, but this issue is also addressed in the red and white biotech. In the white biotech sustainable production models are gaining importance, but the most promising development is the use of biomass for the production of chemicals and materials. As Europe still has a strong position in the science base in the field of bio-based production processes and a strong enzyme and chemical industry, strategies should be developed on how to keep and further improve these strengths with Europe. Therefore it is important to continue the already on-going efforts and initiatives on the European level. Establishing public-private partnerships may help to stimulate the translation of science to innovation and share the risks of bio refinery development. Joint

investment programs are needed, as a reasonable sized demonstration plant requires a large investment. Such initiative can be integrated in a EU-wide master plan for bio refinery development; coordination between the different Directorates-General of the European Commission will be needed to implement this.

The results of the study describe the current development with respect to globalisation and offshoring. The study shows that in biotechnology, especially in the pharmaceuticals, Europe as a whole lags behind the main international competitors, in terms of investments and capacity to drive new technological trajectories. It is the case of health-related technologies, entering a new paradigm, for which the US leadership seems to be uncontested, because of, among other factors, policy priorities and larger investments in biotechnology and ICT for medical equipment. The international character of the biotechnological innovation process in the red biotech sector, combined with a strong market and strong R&D competences in the USA and lower labour costs in Asia, asks for developing new strategic niches for a European red biotech sector. European policy could stimulate that the benefits of these internationalization processes spread among all groups affected by the process and support initiatives for developing alternative strategies for European red biotech.

Finally, a more general note in regard to policies to stimulate developments in biotechnology must be made. Prior research has shown that EU countries employ a mixture of generic and specific policy instruments to stimulate biotechnology activity. Furthermore, it was shown that the use of these two types of instruments and regulations should be well balanced (Enzing and Reiss, 2008). This adds to the complexity of the development of effective policies to stimulate biotechnology. The current reality is that countries have their own strategies and corresponding policies to stimulate biotechnology developments. Moreover, regional policy making is of growing importance. These policies address a range of issues, among others stimulating networking and cluster development and public-private partnerships. Overall this calls for more, socio-economic research that supports the (further) development of policies, which would result in so-called ‘evidence-based policies’. Such evidence-based policies may facilitate priority setting in innovation policy making within Europe.

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Annex – Overview of SIW deliverables

Overview of the deliverables from the Europe INNOVA Sectoral Innovation Watch

Deliverables can be downloaded from www.europe-innova.eu

Task 1 Innovation Performance Sectoral Reports

Ploder, M., C. Hartmann, E. Veres, B. Bertram (2010) Sectoral Innovation Performance in the Automotive Sector, Final Report Task 1, Europe INNOVA Sectoral Innovation Watch, for DG Enterprise and Industry, European Commission, June 2010, revised December 2010

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Task 3 Market and Regulatory Factors

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Task 4 Horizontal Reports

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Task 5 Input and Output Papers

Mitusch, K., C.A. Tran, J. Stohr, F. Montobbio, L. Cusmano and F. Malerba (2010) National Specialisation Report, Input Paper to the workshop ´Tomorrow's innovative industries: Regional and national specialisation patterns and the role of the regional business environment', Task 5, Europe INNOVA Sectoral Innovation Watch, for DG Enterprise and Industry, European Commission, May 2010

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Final Synthesis Report

Montalvo C. and A. van der Giessen (2011) Sectoral Innovation Watch – Synthesis Report, Europe INNOVA Sectoral Innovation Watch, for DG Enterprise and Industry, European Commission, December 2011.