Progress

Priorities for Addressing **O**pportunities and **G**aps of Industrial Biotechnology for an efficient use of funding **res**ource**s**

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About PROGRESS

PROGRESS is a coordination and support action for the European Commission and aims to support and accelerate the deployment of Industrial Biotechnology (IB) in the EU industry by identifying high-value opportunities for IB and proposing actions to address them successfully. In order to achieve this overall aim, we first provide a comprehensive and dependable information base (including modelling and simulation approaches) to enable plausible estimations about the future of IB in the EU in the short and medium term. Second, in collaboration with stakeholders, we elaborate a future scenario and a common vision for IB in Europe containing the most promising value chains, related R&D&I needs and required policies for IB in Europe. Based on these steps, we provide strategic advice for research, industry and policy making regarding potential issues and topics for collaboration, future policy programmes, the required technological infrastructure, capabilities, and economic structures. A main focus is to identify opportunities for collaboration between EU member states and to propose actions to increase awareness and incentives for such collaborations. For more information, see www.progress-bio.eu

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Content

1 Scope and structure of the deliverable

This deliverable documents the results of Task 2.3 of the PROGRESS project. The aim of this task was an in-depth assessment of the selected value chains in Task 2.2, by collecting additional indicators (e.g. patent analysis, additional market data) and document analysis (i.e. trend reports, market reports, sector studies etc.) as well as selected expert interviews.

It turned that all not data generated in the PROGRESS project in this phase, could be matched to the selected value chains. Hence, the following report is two-fold.

Section 2 summarizes a unique assessment in the PROGRESS project by analysing the use of biotechnological methods within production at firm level across industries in representatives samples for IB. Based on data from the European Manufacturing Survey (EMS) with a sample of over 3,000 firms from eight European countries (Germany, Austria, Spain, Croatia, Denmark, the Netherlands, Switzerland, Republic of Serbia), a reliable picture can be drawn of the share of the companies in an industrial sector that have adopted biotechnology (e.g. biocatalysis, bioreactors) and genetic engineering methods in their production processes, or plan to do so in the near future. This provided an interesting picture of the adoption patterns for biotechnological and genetic engineering methods as tools within the production.

Section 3 adopts a value chain perspective as it allows the simultaneous analysis of market needs, of innovation potentials as well as the identification of (missing) European competencies and concrete bottle-necks for innovation and commercialization.

Six value chains for an in-depth analysis have been selected:

- Flavors & Fragrances,
- Production of biopharmaceuticals,
- Enzymes,
- Lignocellulosic ethanol
- Bio-based plastics
- microbiomes for food and healthy nutrition

For all six value chains the VC analysis is structured in a similar manner and will contain the following chapters.

- Description of the value chain (including actor groups, applications)
- Technology and Innovation Potential
- Economic analysis, containing
- Patent analysis
- Market trends
- Actors and activities along the value chain
- Framework conditions

2 Biotechnology and genetic engineering methods on the shop floor in European manufacturing

This chapter summarizes the analyses of the current sectoral diffusion of industrial biotechnologies in European manufacturing industries. We outline the adoption patterns of biotechnological and genetic engineering methods in the production processes of different industries. Within the framework of the broader project, the key objective is to provide the context to further develop roadmaps and actions. Therefore, we describe the current importance of biotechnology and genetic engineering methods used as tools in production. We do not address the importance of biotechnologically modified products used as input in production.

2.1 Database and key indicators

The following analysis is based on data from the European Manufacturing Survey (EMS). EMS allows an integrated analytical approach at firm level, and includes all the variables needed in one database to provide the sound overview described above.

European Manufacturing Survey

EMS is organized by a consortium of research institutes and universities across Europe.1 EMS surveys the utilization of techno-organizational innovations in manufacturing at the level of individual manufacturing sites and the thereby achievable performance increases in the manufacturing sector. The concept of EMS is to monitor process and product innovation as well material and immaterial innovation at the level of individual firms using fact-based indicators. The roots of the EMS can be found in the German Manufacturing Survey, first developed in 1993 by Fraunhofer ISI. From 2001 onwards, this survey was extended to a continuously growing number of European partners and developed into the European Manufacturing Survey (EMS). Fraunhofer ISI coordinates the consortium.

EMS is conducted as a written or online survey by each partner in his/her country. In each country, the survey comprises a large random sample of manufacturing firms with at least 20 employees covering the whole manufacturing sector. Manufacturing or plant managers are asked to fill in the questionnaire. To ensure comparability, the questionnaire is translated into the respective national language and pretested in each participating country. Currently, a database is available from six survey rounds in 2001, 2003, 2006, 2009, 2012 and 2015.

Data sample and country coverage

1 For detailed information about the EMS consortium and its national partners, see http://www.isi.fraunhofer.de/isi-en/i/projekte/fems.php.

The latest *European Manufacturing Survey* (EMS) 2015 was carried out in 11 European Member States. **Eight countries** were selected for our study (compare Table 1): Germany, Austria, Spain, Croatia, Denmark and the Netherlands as well as Switzerland and Serbia. This limitation was due to national sample sizes as well as the coverage of process sectors. Selecting these eight countries ensured the coverage of a wide range of manufacturing and market contexts.

The selected countries account for a total sample of 3,089 enterprises with at least 20 employees across European manufacturing industry. This large firm-level data set allows in-depth analyses of the utilization of biotechnology and genetic engineering methods in eight different national industries. Two specifics of the data set have to be taken into account when interpreting the data: First, the data represent the manufacturing sector in the selected countries but cannot claim to cover the whole European Union or Europe in all its variety. Second, for Serbia, the EMS data cover the industrial provinces of Vojvodina and Central Serbia, but not the Kosovo province.

EMS data allow differentiation by country, sector and size class – as well as by companies producing different batch sizes and products with a different degree of complexity.

Table 1: Description of the EMS 2015 sample by country and firm size

	Country sample		Firm size (number of employees)				
			20 to 49	50 to 99	100 to 499	500 and more	Total
Country	%	N	%	%	%		%
Germany	39.8%	1,231	47.0%	23.3%	26.5%	3.3%	100.0
Austria	7.5%	231	51.2%	18.7%	26.9%	3.2%	100.0
Switzerland	24.2%	749	50.4%	23.7%	22.7%	3.2%	100.0
Croatia	3.4%	104	52.1%	17.2%	27.4%	3.2%	100.0
Serbia	9.1%	280	71.2%	13.2%	14.0%	1.6%	100.0
The Netherlands	4.5%	140	52.9%	25.3%	19.0%	2.8%	100.0
Denmark	8.3%	257	38.0%	22.0%	33.7%	6.3%	100.0
Spain	3.1%	97	83.7%	5.3%	9.4%	1.6%	100.0
Total	100.0%	3,089					

Source: *European Manufacturing Survey* 2015, eight countries, compiled by Fraunhofer ISI. Weighted data

The data represent a meaningful basis for analyses due to their representativeness and the wide range of information covered. Regarding the objectives of this study, we are convinced that the advantages offered by the EMS database far outweigh its limitations. To overcome the limitations of some national sub-samples, an adjustment weighting is applied to the analyses. The EMS data sample is weighted to align it with the actual firm sizes and industry structures in the respective countries. The size of the data set remains the same. A summary of the weighting factors is displayed in the appendix (Annex 1). As a result, the weighted data of each country represent the structure of the manufacturing sector.

Table 1 above shows the firm sample distribution across the analysed country data.

Key variables

In order to map the diffusion of biotechnology in industrial production, we used answers to the EMS question “Does your company use biotechnology / genetic engineering methods (e.g. catalysts, bioreactors) (y/n)?” We display the share of companies in the relevant country/sector that uses biotechnology applications as a percentage of all companies in the relevant country/sector.

In addition to those already actually using biotechnology/genetic engineering, we can also display the shares of firms planning to integrate them in production by 2018. In addition, an indicator of investments in improved biotechnology since 2012 can be used as well. This helps to capture the dynamics of biotechnology utilization within manufacturing firms. The sub-question “Has the technology in use been upgraded since 2012?” identifies whether firms reinvested in the technology in the three years prior to the survey. Reinvestment can be regarded as an indication for a major development in the technology. Moreover, it might also indicate that the utilization of biotechnology in a company, country or sector is considered successful and provides actual benefits for the company.

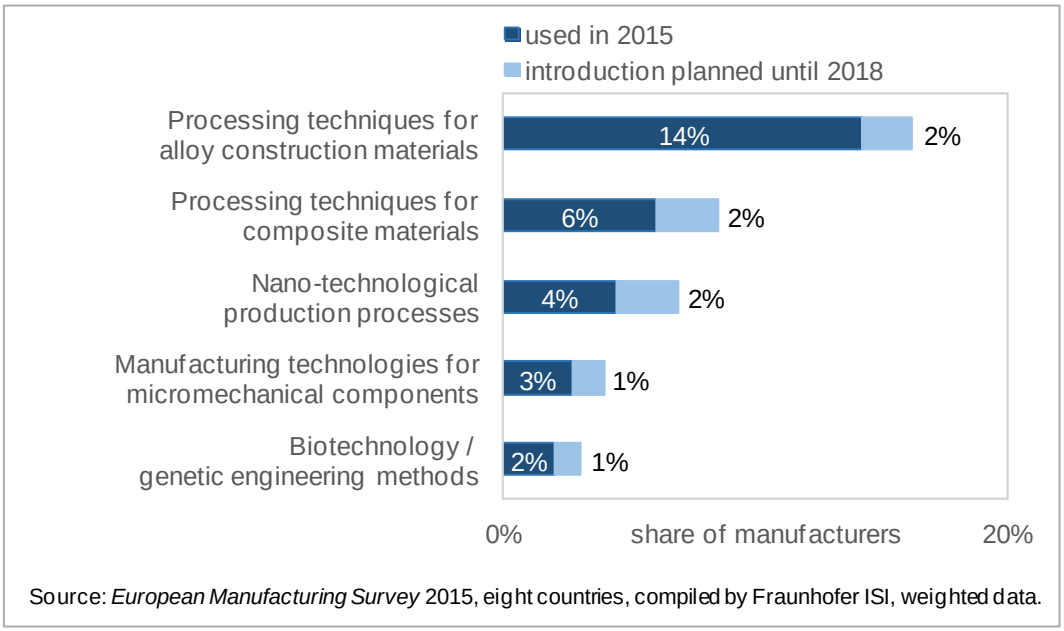
A set of basic structural information (e.g. firm size, sectoral affiliation) can be used to analyse structural features. EMS also includes detailed variables covering aspects like manufactured product complexity and innovative behaviour.

2.2 Adoption of biotechnological methods in production

An overall analysis of the eight selected countries shows that, in general, biotechnology and genetic engineering methods such as catalysts, bioreactors are rarely used in European industrial production. Less than 2 percent of all manufacturing firms in the analysed countries use these technologies in their production processes. Moreover, no major increase can be expected until 2018. Only around 1 percent of all manufacturers plan to introduce biotechnology or genetic engineering methods in their production.

Regarding the interpretation of these results it has to be remarked that the shares reflect the diffusion of biotechnology as a method in production and thus the share of manufacturing firms able to handle biotechnological processes. Considering the long and complex value chain of biotechnological products, certainly more firms are using biotechnological products or biotechnologically modified, novel bio-based materials. But this issue is not the focus of these analyses.

Figure 1: Shares of manufacturers using biotechnology or genetic engineering methods or planning to do so until 2018 compared to other key enabling technologies in production



Source: *European Manufacturing Survey* 2015, eight countries, compiled by Fraunhofer ISI, weighted data.

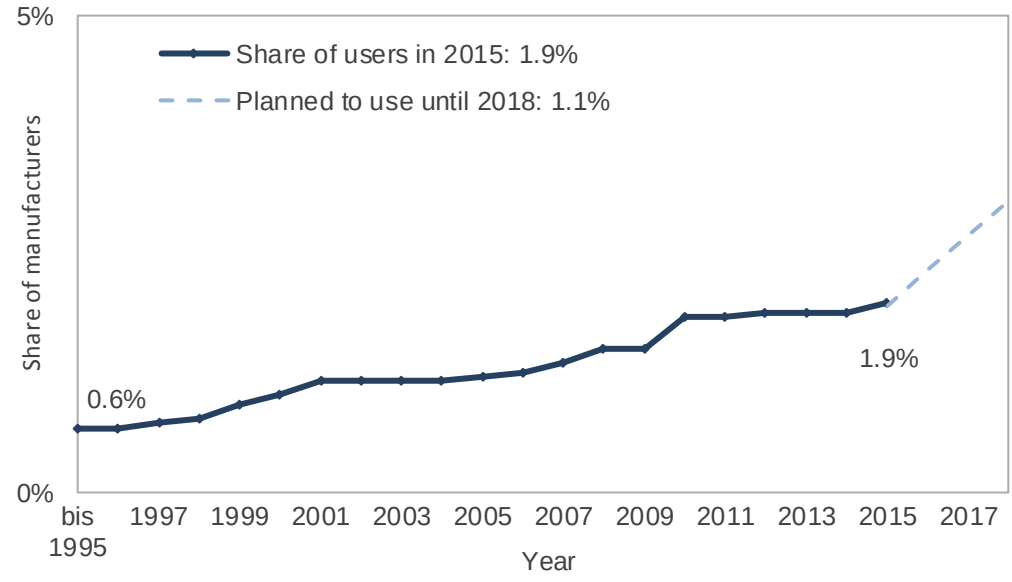
Further analyses show – as Figure 1 displays – that the diffusion rate of *biotechnology and genetic engineering methods* is low in comparison to the diffusion of other key enabling technologies. For instance, around 4 percent of manufacturing firms in the analysed countries use *nano-technological production* ***processes*** *(e.g. surface processing),* around 6 percent *processing techniques for composite materials such as carbon fibre or fibreglass*, and 14 percent of manufacturers use *processing techniques for alloy construction materials such as aluminium, magnesium, titanium alloys, etc*. This picture is not expected to change in near future. For the other analysed technologies, a higher share of firms plans to introduce them. In summary, it seems that biotechnology and genetic engineering methods still have very specific uses in production. The anticipated further diffusion through European remains a future prospect.

However, most firms that have introduced biotechnology are using these technologies to a significant extent in their production. 83 percent of users indicated at least partial or even extensive utilization compared to the most reasonable potential utilization. Only 17 percent used it for an initial trial only. Further analyses also reveal the dynamic nature of biotechnology and genetic engineering methods. 68 percent of users had made reinvestments since 2012 to improve the used technology. It is reasonable to assume that only firms that have had good experiences with these methods and that stand to benefit from using biotechnology are eager to reinvest in improved technology. Additionally, up-

grading can also mean that firms want to profit from the latest technological developments, resulting in either a better performance of existing processes or in completely new application domains. In comparison, reinvestment was reported by around 60 percent of users for the other key enabling technologies. This is still a high share, but not statistically significant. Thus, biotechnological methods do not show remarkably higher dynamics than other high-tech technologies.

2.3 Diffusion over time

Figure 2: Shares of manufacturers using biotechnology or genetic engineering methods in production or planning to do so until 2018



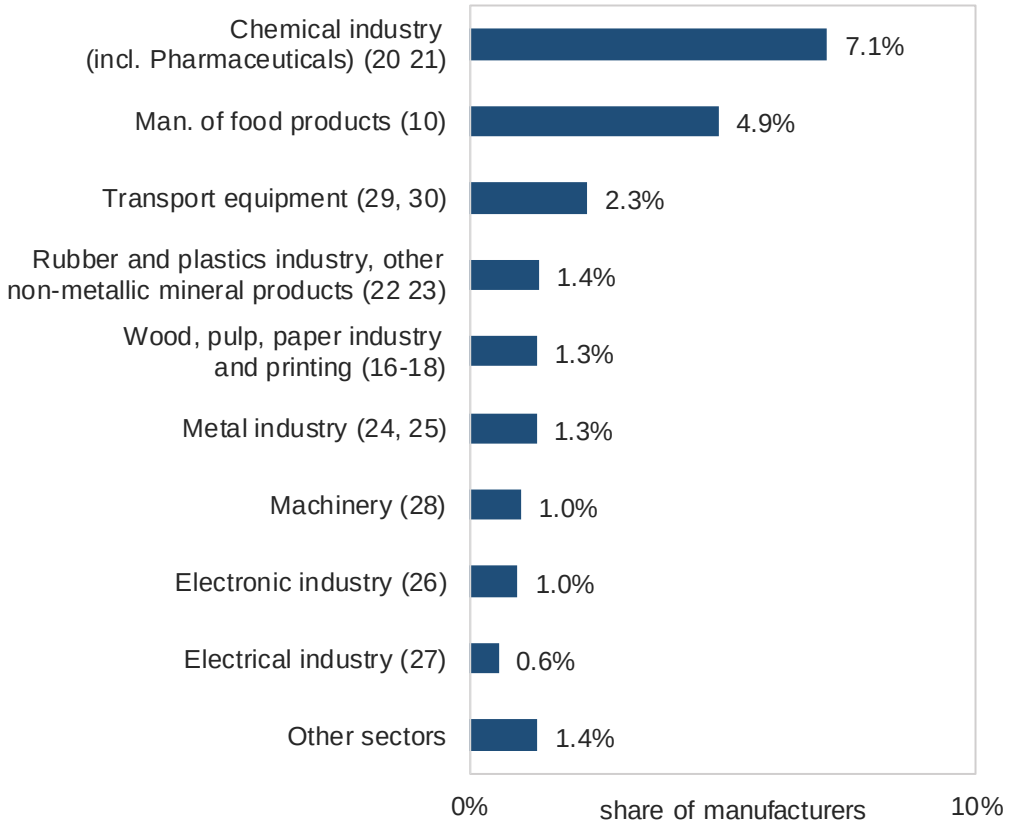
Source: *European Manufacturing Survey* 2015, eigth countries, compiled by Fraunhofer ISI, weighted data.

A chronological perspective provides more insights into the diffusion dynamic. As Figure 2 shows, looking at the diffusion dynamic over time reveals that biotechnology and genetic engineering methods only began to be adopted more than episodically by manufacturing firms within the context of their production in the mid 1990s. In 1995, less than 1 percent of all manufacturers were using these technologies. By 2010, this share had risen to 1.8 percent. Diffusion then stagnated and reached a level of 1.9 percent among all manufacturers in 2015.

1 percent of the production managers surveyed in 2015/2016 reported plans to adopt biotechnological or genetic engineering methods in production in 2018. However, it has to be expected that not all firms will realize these plans so that less than 3 percent will actually have introduced these kinds of technology in 2018.

2.4 Diffusion within industrial sectors and regions

Figure 3: Diffusion of biotechnology by sector (share of manufacturers) in manufacturing industries



Note: figures in brackets refer to NACE, rev. 2

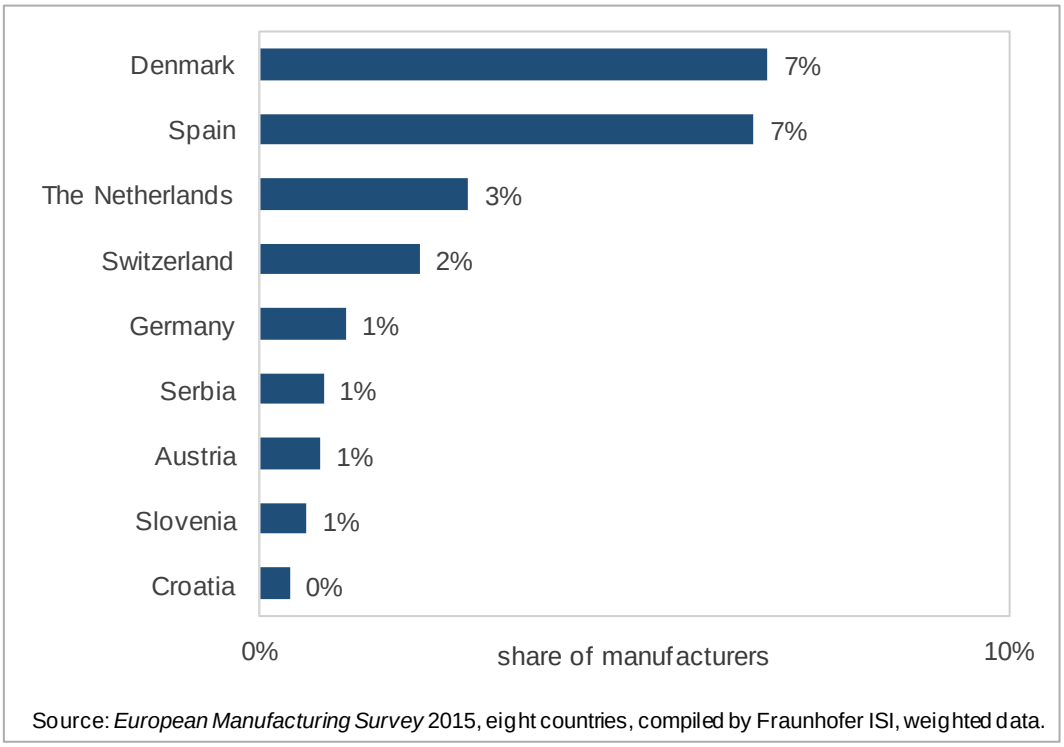
Source: *European Manufacturing Survey* 2015, eight countries, compiled by Fraunhofer ISI, weighted data.

Large differences become visible when looking at the diffusion in the different industrial sectors, as shown in Figure 3. There are two main sectors with a relevant share of manufacturers using biotechnological processes: the chemical industry, including pharmaceuticals, as well as the food industry. While 7 percent of the chemical manufacturers apply biotechnology, 5 percent of food product manufacturers do so. All other industries hold a share of approximately 1 percent only on average (ranging from 0.6 percent to 2.3 percent).

To sum up, specific process producers are applying biotechnology to a significant degree. Additionally, first relevant attempts can be found among producers of transport equipment. However, a broader utilization in discrete part production is not detectable. The chart illustrates the limited relevance of biotechnology for the remaining industrial

sectors. So far, biotechnology is not commonly applied to the entire manufacturing industry, but rather a technology that is used for specialized products and applications in chemical industries and by food manufacturers. The remaining industrial sectors hold shares between 0.8 percent and 1.5 percent and are hardly relevant for biotechnology.

Figure 4: Share of manufacturers using biotechnological processes by country



Source: *European Manufacturing Survey* 2015, eight countries, compiled by Fraunhofer ISI, weighted data.

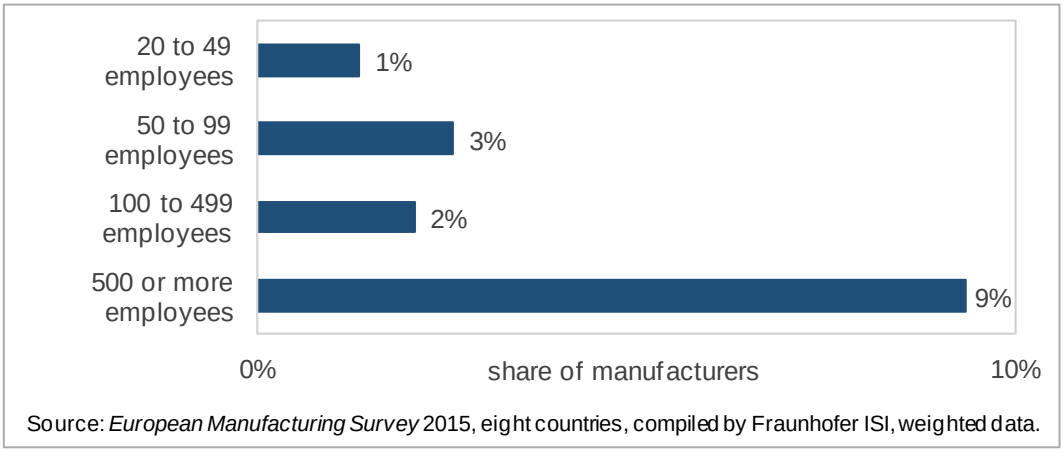
There are also large differences in applying industrial biotechnology among European countries. Figure 4 shows that only Denmark and Spain feature significant shares of manufacturers using biotechnological processes. In Denmark and Spain, 7 percent of all manufacturers apply biotechnology. All the other analysed countries have much smaller shares, ranging from 0.4 percent in Croatia and 1 percent in Germany to 2 percent in Switzerland and 3 percent in the Netherlands.

Here, it has to be remarked that the reported figures are relative shares and provide the total average for each country. Moreover, for interpreting the result it has to be taken into account that the manufacturing landscape differs considerably between the countries. Consequently, Spain with a relatively large food sector shows more activities than for instance Germany with its relatively large machinery and metal industry. Moreover, the results are very much in line with other existing indicators that outline the leading position of Denmark as well (e.g. Key Enabling technology Observatory 2015). However, the relative importance of German manufacturing biotechnology users for Europe is hidden in this figure as it does not reflects the relative greater size of German manufacturing.

2.5 Diffusion over different firm size classes

Apart from differences by industrial sector and country, there are also differences in terms of company size. Figure 5 illustrates the utilization of biotechnology related to the number of employees.

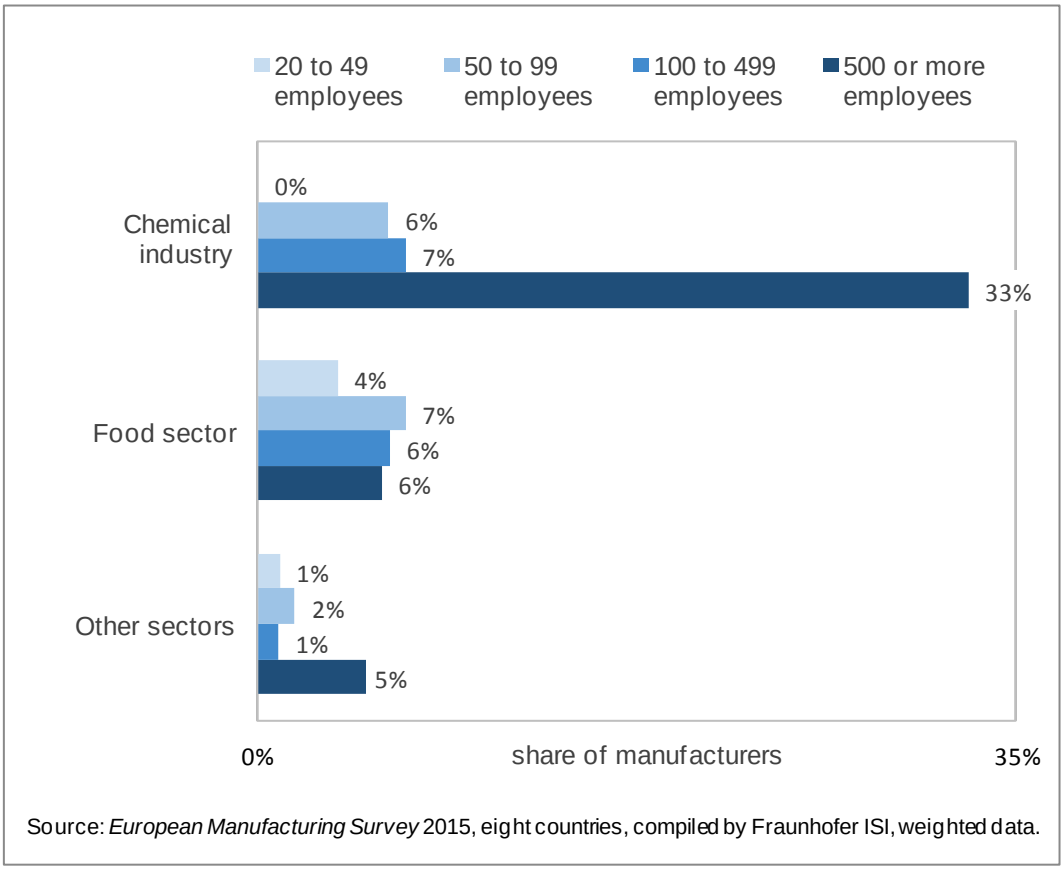
Figure 5: Share of manufacturers using biotechnology by company size



Source: *European Manufacturing Survey* 2015, eight countries, compiled by Fraunhofer ISI, weighted data.

Again, there are large differences between company types. Small and medium-sized companies hold shares between 1 percent and 3 percent, whereas 9 percent of large companies apply biotechnological processes in their production. The share of biotechnology among large companies is considerably higher than among small and medium-sized enterprises. However, medium-sized firms between 100 and 499 employees do not use this kind of technology more than small firms with less than 100 employees. This result indicates that biotechnology is mainly used by large or very large companies. It should be perceived as a technology that is not applied or cannot be applied by typical SME-structures.

Figure 6: Share of manufacturers using biotechnology by company size and sector



Source: *European Manufacturing Survey* 2015, eight countries, compiled by Fraunhofer ISI, weighted data.

This finding is specified by analysing the effect of company size in relation to the most important sectors of biotechnology. For Denmark and Spain, a respectable 12 percent of large manufacturers (with 500 or more employees) use biotechnology in production. As shown in Figure 6, 33 percent of large manufacturers apply biotechnology in chemical industries in the eight countries. This relationship between firm size and adoption rate only differs in the food industry, which shows less variation between the different company sizes in the shares of users. Consequently, we can conclude that biotechnology is mostly used in niches and predominantly by large companies. However, applications are also accessible to smaller firms in the food sector. A more general use by a larger number of manufacturers seems possible here.

Summarizing the findings above, we conclude that biotechnology is used for specialized products in industrial manufacturing and is applied in several industrial niches. As the figures illustrate, there are marked structural differences concerning the diffusion of biotechnology in terms of industrial sector, company size, and region. Biotechnology is significantly relevant for chemicals including pharmaceuticals, the food industry and pre-

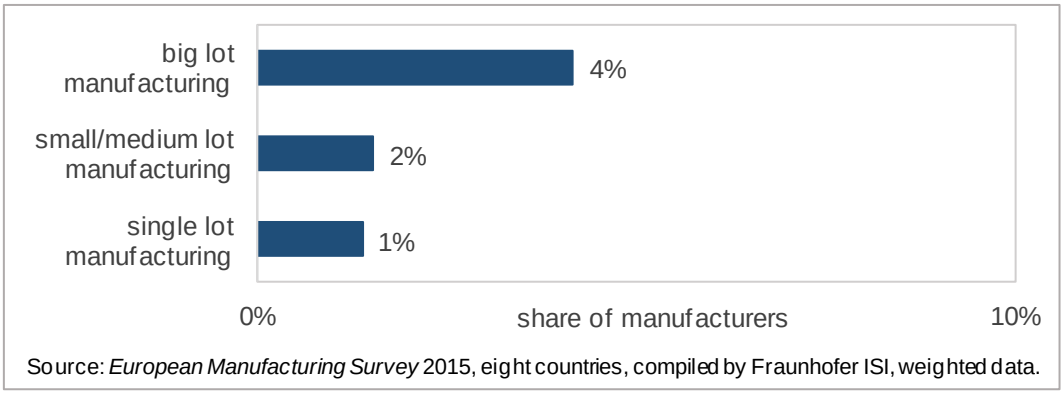
dominantly for large companies. Regarding the regional aspect, biotechnology is particularly relevant in Spain and Denmark, while the six remaining countries do not play an important role in its diffusion.

2.6 Corporate characteristics and innovativeness of industrial users

Corporate characteristics play an important role in terms of the firms' behaviour. It becomes obvious that the utilization of biotechnology is also strongly driven by production characteristics. As Figure 7 illustrates, single lot as well as small/medium lot manufacturers hardly use any biotechnological processes (approx. 1 percent). In contrast, 4 percent of the manufacturers producing large lot sizes apply biological production processes. This indicates that biotechnology is used more for continuous production instead of often changing user specific products. This general trend holds true, even when analysing only food and chemical industry firms or only Denmark and Spain.

The diffusion of biotechnological methods is not linked to the complexity of the main product produced by the manufacturers. There is no difference between manufacturers of simple products, medium-complex products or complex products concerning the application of biotechnology. There is the same average share of approximately 2 percent of users in each of these groups. Biotechnology seems to address other degrees of complexity than the one usually surveyed. Consequently, it can be concluded that the complexity of applying biotechnological methods is rooted in the technology itself rather than in its integration in production processes. Additionally, it seems that the firms can only achieve actual benefits from applying biotechnology at a certain scale of production and with a specific investment.

Figure 7: Share of manufacturers using biotechnology by batch size



Source: *European Manufacturing Survey* 2015, eight countries, compiled by Fraunhofer ISI, weighted data.

The specialization of those manufacturers adopting biotechnology becomes even more obvious if we analyse their innovation activities. 48 percent of the manufacturers using biotechnological or genetic engineering processes are product innovators. This means that these manufacturers introduced a totally new product or a much improved one to

the market over the last three years. In contrast, 57 percent of non-users are product innovators. These shares do not differ significantly in terms of statistics. The results suggest that manufacturers using biotechnological or genetic engineering methods in their production are not more innovative than non-biotechnology users regarding their product innovation. Consequently, the utilization of biotechnology, is not directly linked to product innovation in industrial manufacturing. This finding demonstrates again that biotechnology is not specific to very product-innovative manufacturers, but is a specific application for niche industrial processes and products.

This relationship becomes even more apparent when the share of innovators is analysed for the biotech users in Denmark, Spain and for the two main biotech using industrial sectors (chemical and food industry). Taking only Denmark and Spain into account, we observe a 61 percent share of biotechnology users belonging to the non-innovators, whereas 53 percent of non-users were non-innovators. In the chemical industry, only 49 percent of users are product innovators, while 62 percent of non-users are innovative. In contrast, in the food sector, 63 percent of users are product innovators, while only 55 percent of non-users are innovative. Both differences are not statistically significant. However, these results suggest that biotechnological methods do not seem to foster innovative processes for chemical firms, whereas they are more closely linked to product innovation for firms in the food industry.

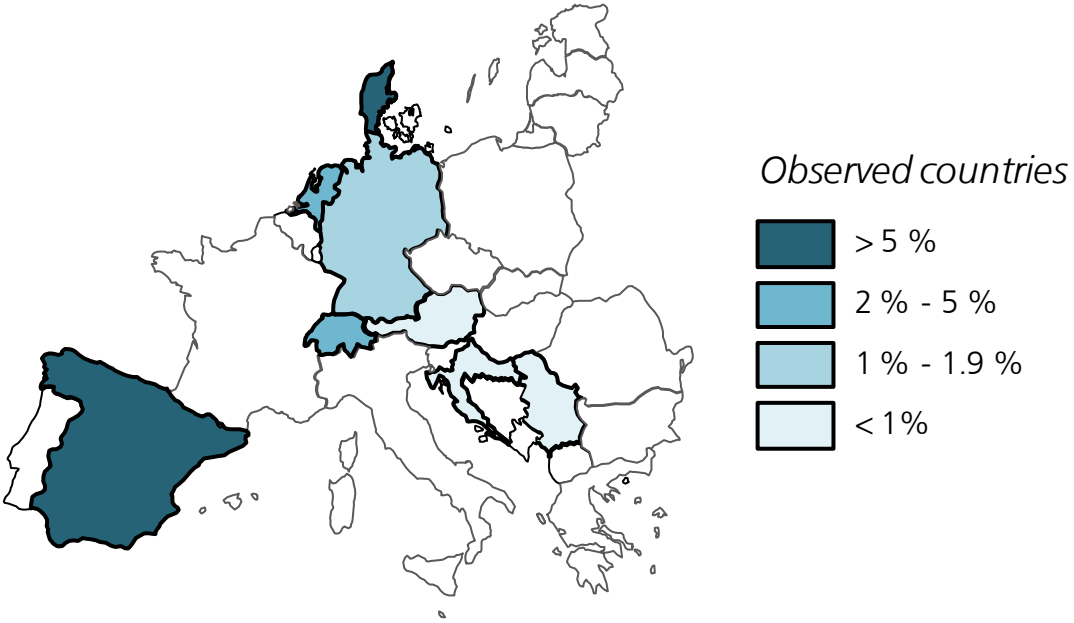
Firms belonging to other sectors are even less innovative when using biotechnology; only 38 percent of them introduced products to new markets. In contrast, 57 percent of the non-users in these sectors are product innovators. These results support the assumption that biotechnology is not directly linked to innovativeness for most manufacturing industries although it is viewed as a key enabling technology. This relationship is even clearer, if the leading markets of industrial biotechnology are analysed in more detail.

2.7 Summary and perspectives

Summarizing the findings of this chapter based on our empirical analysis of eight selected European countries, we conclude that biotechnology has not diffused widely through European manufacturing industries. Although the other four key enabling technologies have not diffused very widely either (between 3 and 14 percent), biotechnology has the lowest diffusion share in manufacturing industries. Overall, only 2 percent of all manufacturers apply biotechnological processes in production. Consequently, biotechnology is (still) used mostly in niche production processes. Over the 20 years from 1995 to 2015, its share rose by 1.5 percentage-points, from 0.5 percent to 2 percent. With respect to this development, we assume that there will be no relevant increase in the share

of manufacturers using biotechnology in the near future, although 1 percent of all manufacturers stated they plan to introduce biotechnological processes during the next three years. Thus, it cannot be expected that biotechnology will be applied beyond industrial niches in the near future. In fact, biotechnology is used for specialized products and applications only, and should not be regarded as a solution for the entire manufacturing industry.

Figure 8: Diffusion of biotechnology (share of manufacturers) in manufacturing industries for eight selected countries in continental Europe



Nevertheless, biotechnology is particularly relevant for chemical industries including pharmaceuticals as well as food manufacturers. These two sectors hold shares of 7 percent and 5 percent, respectively, of manufacturers applying biotechnological and genetic engineering processes in production. These technologies are also more often used for large lot production than for small or single lot productions. Moreover, more large companies are applying biotechnological processes than small and medium-sized ones. Approximately 9 percent of the analysed European manufacturers with more than 500 employees apply biotechnology within their production processes. In contrast, SMEs range between 1 and 3 percent. Therefore, we conclude that biological technologies may require more extensive resources and structures that are only provided by larger companies and in large lot process productions. The finding that large companies focus more on biotechnology is especially valid for the chemical industry. Every third large chemical manufacturer uses biotechnology or genetic engineering in production processes. In contrast, this size effect is not observable for food manufacturers. Here, there is only a

small gap between the share of SME and the share of large companies using biotechnology.

Another important finding is the relationship between using biotechnology and innovativeness in manufacturing. Although biotechnology is considered one of the key enabling technologies and consequently understood to be innovative, there are no indications that innovative manufacturers are more likely to apply biotechnology in their production. In fact, the group of non-innovators was more likely to use biotechnological processes in their production than the group of innovators. Only in the food industry are users of these technologies slightly more innovative.

This result supports the view that biotechnology is not (yet) directly linked to innovation in manufacturing industries. So far, it is a technology for specialized processes and niche products in manufacturing and is not an indicator of innovativeness. It seems that many technological applications are not yet feasible for production processes. Moreover, biotechnological and genetic engineering methods are applied at an earlier stage in the value chain or are part of input products rather than tools in the production of manufacturing industries. When developing further roadmaps and actions to foster these technologies in Europe, this differentiation has to be taken into account.

Finally, we observe strong regional differences concerning the diffusion of biotechnology in manufacturing industries across Europe. In our analysis, we looked at eight European countries: Germany, Switzerland, Austria, Denmark, Spain, Croatia, Slovenia and Serbia. There are only relevant shares of manufacturers applying biotechnology for Denmark (7 percent) and Spain (7 percent). In this context, we have to consider that these higher shares do not result from a different industrial structure. Instead, this finding illustrates that the chemical and food manufacturers in these countries are focusing on different products which results in the higher diffusion. In contrast, the other countries hold shares below or around 1 percent. Only Switzerland and the Netherlands have higher shares of 2 percent and 3 percent, respectively, and are in the middle of the observed countries (see Figure 8). Therefore, we can state that biotechnology is also focused very strongly on single European regions.

These findings have to be reflected regarding the specifics of Industrial Biotechnology and its use in value chains. In conclusion, it has to be stated

- that, first, industrial biotechnology is traditionally and firmly rooted in the production of fermented food and beverages (e.g. milk products, bread, beer, wine) and therefore is used in food companies of all sizes,

- that, secondly, the chemical industry holds a central role in the deployment of biotechnology for industry: This sector is leading in the biotechnological production of a broad range of different product groups of B2B and B2C products, from bulk to specialty and fine chemicals, of which some can only be produced by biotechnological methods (e.g. biopharmaceuticals). Moreover, large chemical companies have built up the interdisciplinary competencies required to successfully develop and scale-up a process from the laboratory to commercial production, and have the financial capacity to set up dedicated production facilities, which have been specifically designed for biotechnological production processes with related high investments.

All in all, these results underline that IB will in the near future mainly be applied in firms with specific competencies, concentrated in a few industrial sectors. Although the number and share of the companies in the respective sectors may seem to be comparably small, it must be emphasized that the share of value added by biotechnological production may be much larger. Moreover, IB has a clear enabling character for a broad range of industries through the provision of services, processes and products in often long value chains, and through its potential to form new value chains usually based on renewable resources.

Apart from these results it has to be reminded that many non-manufacturing SMEs fulfil important roles in the value chain. Regarding Industrial Biotechnology these SMEs are active in R&D and/or services. Without having their own production activities, they provide biotechnological R&D services or test cutting-edge innovative approaches in early R&D and pilot stage levels which are later taken over by larger firms and developed to production maturity. This study however focuses on manufacturing industry. Thus, consequently these SMEs are not regarded in this study. .

Annex

Annex 1: Weighting factors (proportional weighting to sample size) by country

	Weighting factor					
Country sample	mini-mum	05 percentile	median	95 percentile	maximum	number of cases
Germany[1]	0.22	0.50	0.90	1.71	3.24	1,236
Switzerland	0.35	0.55	0.96	1.62	4.02	749
Serbia	0.15	0.31	0.55	2.49	2.49	280
Denmark	0.43	0.53	0.99	1.47	2.71	257
Austria	0.30	0.36	0.83	1.78	3.74	231
The Nether-lands	0.44	0.44	0.84	1.99	4.42	140
Croatia	0.13	0.20	0.61	3.18	3.59	104
Spain	0.07	0.12	0.48	4.04	4.04	97
Total	0.07	0.40	0.90	1.98	4.42	3,094

Note: (1) For the German sample, no weighting factor can be calculated in five cases as the regional affiliation was missing. Thus, these cases are excluded from the analyses.

Source: *European Manufacturing Survey* 2015, eight countries, unweighted data

To calculate the weighting factor, national statistics of each country on the manufacturing sites were used to weight the EMS survey sample according to size (taking into account 2 to 4 firm size classes) and industry structure in the manufacturing industry (taking into account 7 to 13 industry groups, NACE Rev. 2, Division 10-33) in the respective country. Eurostat data could not be used for this purpose as these do not contain such data at the level of manufacturing sites. In addition, the number of strata for calculating the weighting factors depends on the size of the national EMS data set. The attempt was made to be as accurate as possible when grouping, as well as avoiding zero cells or cells with fewer than five cases.

3 Value Chain Analysis

The field of Industrial Biotechnology is highly heterogeneous, e.g. with respect to the stage of maturity in innovation and commercialisation, the type of products or processes and their respective uses and applications, the amount and type of biomass feedstock needed and the level of competition with existing (fossil-based) products and processes. Against this background, a value chain perspective was chosen in the PROGRESS project. This perspective allows the differentiated, but integrated analysis of market needs, innovation potentials and the identification of (missing) European competencies and concrete bottlenecks affecting innovation and commercialisation. Six value chains with a high potential for innovation and for significant economic impact were selected which represent the heterogeneity of IB.

The selected value chains are:

- Lignocellulosic ethanol
- Bio-based plastics
- Enzymes (with specific reference to laundry and dishwasher applications)
- Production of biopharmaceuticals
- Biotechnologically produced flavours and fragrances
- Microbiomes for food and healthy nutrition

The value chain perspective allows the simultaneous analysis of market needs, of innovation potentials as well as the identification of (missing) European competencies and concrete bottlenecks for innovation and commercialization. For that purpose the VC analysis is structured in a similar manner and will contain the following chapters.

- Description of the value chain (including actor groups, applications)
- Technology and Innovation Potential
- Economic analysis, containing
    - patent analysis
    - market trends
    - actors and activities along the value chain
- Framework conditions

Main sources for the analysis were the collection of indicators (e.g. patent analysis, market data) and document analysis (i.e. trend reports, market reports, sector studies etc.)

as well as selected expert interviews. For the patent analysis Data on international patent applications according to the WIPO patent database were used. For that purpose, for each value chain a search strategy be using either IPC classes or keywords in conjunction with IPC classes was elaborated by Fraunhofer ISI experts.[2]

3.1 Lignocellulosic ethanol

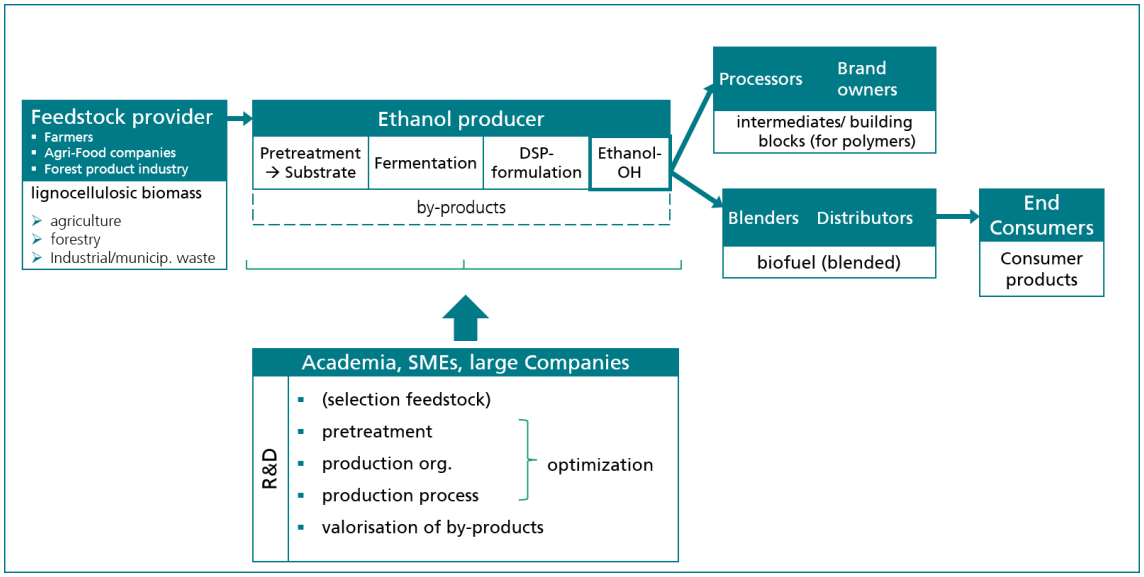
3.1.1 Description of the value chain

Bioethanol, and prospectively biobutanol, are biofuels based on biotechnological processes to convert biomass. Until now, first generation bioethanol dominates, which is derived from sugar or starch typically provided by food or feed feedstocks (e.g. sugar beet, sugar cane, wheat, corn, grains, etc.). However, the demand for greater sustainability calls for new technological approaches and diversified biomass sources for the production of biofuels. This particularly applies to biofuels produced from lignocellulosic or cellulosic biomass, originating from non-food feedstock. Lignocellulosic biomass is an abundantly available raw material, which includes agricultural residues (e. g. corn stover, bagasse, straws, husks), forestry residues (e. g. leaves, sawdust, cutter shavings), dedicated energy crops (e. g. switch grass, alfalfa, various weeds), waste paper and other organic residual materials.

Figure 9 illustrates various steps in the value chain of the lignocellulosic ethanol. It consists of feedstock providers, ethanol producers, after which it is subdivided into commercial blenders and distributors of bioethanol who distribute it to the end consumer on the one hand, and processors of intermediates and building blocks, which are derived from by-products, on the other. A critical component of the lignocellulosic ethanol value chain are R&D&I activities of academia and private sector companies developing and providing technological solutions for the pre-treatment of biomass and the subsequent conversion processes, thus removing barriers for the adoption of the lignocellulosic ethanol technology. Individual aspects of the value chain will be discussed in more detail in the following sections.

[2] For biopharmaceutical production, no useful delineation could be conducted as it appeared to be difficult to distinguis between patents for research and production of biopharmaceuticals.

Figure 9: Value chain of lignocellulosic ethanol



3.1.2 Technology and innovation potential

There are various technological hurdles along the entire value chain for the production of lignocellulosic ethanol. One of the major technological challenges represents the production process of the second generation ethanol. Generally, there are two ways to produce biofuels from lignocellulosic biomass: biochemical and thermo-chemical. However, the production costs of lignocellulosic ethanol based on the thermo-chemical pathway are currently not competitive with first generation ethanol. Since this is a largely fully developed technology, existing for a couple of decades, there is little room for cost reductions through technological improvements and learning processes (Eggert et al. 2011). The bio-chemical pathway is therefore much promising in terms of technological and cost reduction opportunities. Although this technology has meanwhile been proved to be effective, it is still not fully developed. Hence, there are still considerable efficiency improvement opportunities through technological learning and innovation activities.

Via the biochemical pathway, the lignocellulosic biomass is converted by means of hydrolysis and fermentation to ethanol. Prior to these main processes in the fermentation pathway, the lignocellulosic biomass, which consists of three main components (cellulose, hemicelluloses and lignin), must be pretreated.

Pre-treatment is necessary to separate cellulose and hemicelluloses from lignin for their subsequent conversion to sugars[3]. There are different pretreatment methods, which include physical, chemical and biological processes or combinations of these. The most widely used pretreatment technology is steam explosion, which reduces the size of biomass and initiates the breakdown of hemicelluloses and lignin. The process requires a lot of energy and creates by-products, which subsequently hamper the downstream fermentation. Some pre-treatment technologies are at an early development stage, like ionic liquids or biological pre-treatment using fungi (IRENA 2016). Current pre-treatment processes are still not cost-effective, since they incur high investment and operating costs, and have some efficiency drawbacks in terms of achieved yields. Therefore, technologies to improve yields of cellulose and hemicelluloses while limiting adverse effects of inhibitors to the enzymatic hydrolysis process need to be developed further.

Following the pre-treatment, cellulose and hemicelluloses may be hydrolyzed to simple convertible sugars in a hydrolysis process. There are two major hydrolysis ways: chemical, using acids; and enzymatic, using enzymes. Overall, enzymatic hydrolysis, which converts lignocellulosic biomass to convertible sugars, offers lower energy use and milder operating conditions than chemical processes, as well as a greater potential for higher yields and lower costs. However, the process itself is not well understood yet, so the potentials of higher yields and lower costs have not been fully realized so far. The identification and/or development of new enzymes are essential for this stage of the conversion pathway to achieve these goals. Enzymes, used in the hydrolysis process, represented until recently a substantial cost factor, making the conversion economically less efficient. In the last few years, a considerable progress in optimizing pre-treatment techniques has been made, resulting in lower enzyme use. The enzyme production could be increased in scale, which would lead to further cost reduction. According to IRENA, further technological and production improvements could enable up to 90% cost reduction of enzymes (IRENA 2016).

In the next stage the sugars - hexose (6-carbon sugars) and pentose (5-carbon sugars) - produced by hydrolysis, are converted by using microorganisms (bacteria and yeast) into ethanol and various by-products. A cost-effective fermentation depends largely on the ability of microorganisms to ferment C5 and C6 sugars. A considerable progress has been already achieved in engineering microorganisms, yet their sensitivity to inhibitors and the production of unwanted by-products remain serious problems. After the fermentation, ethanol is separated by distillation and dehydration. The residual lignin and other

3 Different lignocellulosic feedstocks have a different composition of lignin, cellulose and hemicelluloses, which influences the efficiency of pre-treatment and hydrolysis step. Straw and grassy feedstock have a lower lignin content, which makes their pretreatment easier (IRENA 2016).

components (e.g. unreacted cellulose and hemicelluloses, used enzymes and microorganisms) are left over at the end of the distillation. The recycling, up-grading and development of value-added co-products from residues (e. g. residual lignin, used enzymes) pose another challenge, which targeted R&D&I and technological breakthroughs can respond to. There is also a need for alternatives to the current separation technology, enabling lower energy and water consumption, which is currently a subject of ongoing research.

Furthermore, a possible consolidation of processes within the biochemical pathway, such as simultaneous saccharification and fermentation would offer another opportunity to achieve significant processing cost savings and should therefore be another important subject of targeted research.

For the competitiveness of advanced biofuels the access to low cost and good-quality feedstock is of great importance. Feedstocks used for the production of the lignocellulosic ethanol in the European facilities are manifold, ranging from agricultural residues like wheat straw and corn stover, through energy grasses, recycled wood, wood residues, to wastes. The type of feedstocks used depends largely on the specific biomass endowment of the region where the facility is located (e.g. straw in Central Europe and woody biomass in Northern Europe). The most important supply sources of the lignocellulosic biomass are the agricultural sector providing straw, energy grasses, agricultural residues and the residual biomass resources from the forestry (e.g. timber plantations, wood chips, residual wood). Other locally available biomass resources, like landscape care biomass (e. g. vegetation covered areas along the traffic routes), municipalities' wastes (foliage, vegetation residues from public parks and gardens, organic residual materials) and manufacturing industry wastes (wood wastes, wastes of the pulp and paper industry, wastes from food processing or from the textile industry) can also contribute to a sustainable supply of biomass. However, the valorization of wastes for the production of biofuels as well as other bioindustry applications has until now taken place on a small scale in Europe, due to unresolved problems related to the collection and pretreatment of wastes.

Collecting, transport and storage of the feedstock represent one of the main challenges for the production of lignocellulosic ethanol. At present, the existing biomass supply and logistics systems in the EU Member States are not sufficient to supply large volumes of high-quality biomass, so that much efforts have still to be done to develop a cost-effective and sustainable feedstock provision infrastructure. As a consequence of the lack of a well functioning logistical model, biomass supply remains a considerable cost contributor (Valdivia et al. 2016), accounting for 40-70% of total production costs, depending on the feedstock type.

Another serious problem for the production of lignocellulosic ethanol is the seasonal nature of the availability of the biomass. Potential technology solutions include pre-treatment of the biomass to increase its energy density and reduce susceptibility to degradation, like torrefaction or pelleting. Another possible solution could be the adoption of conversion processes able to use a mix of different feedstocks throughout the year depending on availability (IRENA 2016).

The existing infrastructure barriers, which limit a reliable supply and provision of feedstock, are another considerable obstacle to a commercial production of advanced biofuels. Many of the commercial plants are experiencing technical difficulties related to receiving, handling and processing large quantities of feedstock (IRENA 2016). The development of new collection, storage and transport systems, as well as specialized equipment for production sites, would help overcome these difficulties.

3.1.3 Economic Analysis

3.1.3.1 Patent Analysis

The sustainable production and uptake of biofuels largely depend on the technological breakthroughs, enabled by significant public and private investments in R&D. The US, Canada and many European countries as well as emerging economies such as China, Brazil and India are increasingly involved in the research and development of sustainable biofuels.

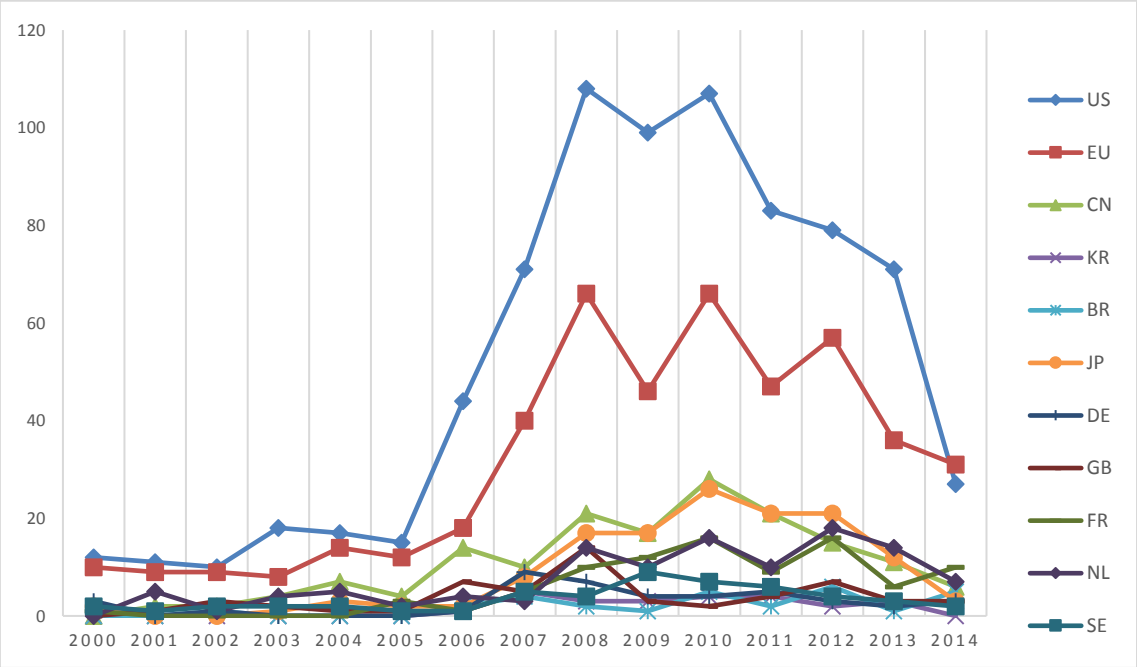
Patents are often used as an indicator for comparing and monitoring trends in innovative output of a specific technology across countries. When examining transnational patent applications[4] for cellulosic ethanol, one can observe a steep surge of world patent applications between 2005 and 2008 (see Figure 2). It was mainly the result of considerable increase in public targeted support for research and development of sustainable biofuels. The global patent applications for cellulosic ethanol grew between 2005 and 2008 with an average annual rate of 84% with the US, EU and China contributing most to this growth. Patenting activities in China rose significantly since 2002, following major patent reforms as well as changes in regulations regarding intellectual property, created under government funding (Albers et al. 2016). Overall, the number of world patent applications in cellulosic ethanol increased nearly eightfold between 2000 and 2010. The total number of patent filings over the last available 5 years (2009-2014) in the EU equals to 60%

[4] Relevant patents were identified by using keywords “cellulose” and “ethanol” in combination with select patent groups using data from the WIPO Statistics Database. Moreover, the IPC code C12P007-10 was used without keyword search.

of the level of the US in the corresponding period. Following the financial crisis, the drop of oil prices and shifting policy support, the growth rate of patent applications is slowing down since 2008 with a sharp decline after 2010.

During the time of rapid increase of patenting activities between 2004 and 2008, an average growth of the US cellulosic ethanol related patent filings amounted to 59% per year, while the EU achieved average annual growth rates of 47%. After this unprecedented growth, the number of the patent filings was falling between 2008 and 2014 at an annual rate of 21% for the US and 12% for the EU. China also experienced a steep decline in patenting activities within this time span of -19 % yearly, after achieving average growth rates of 32% between 2004 and 2008.

Figure 10: Transnational patent applications for cellulosic ethanol

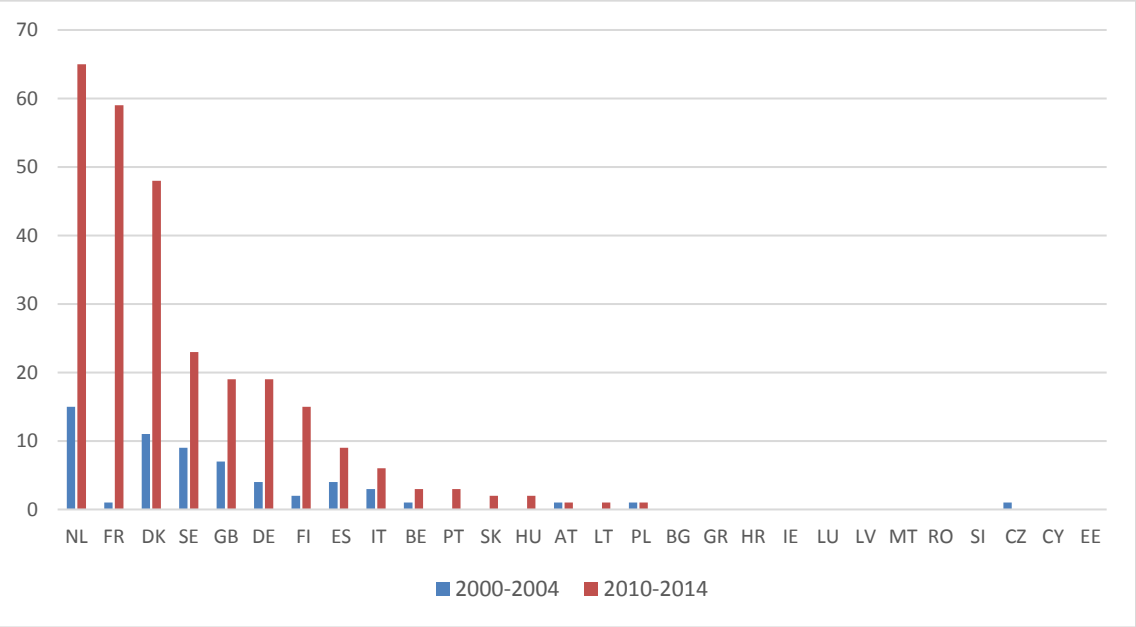


Source: Fraunhofer ISI based on WIPO

Within the EU, countries with the highest levels in terms of cellulosic patent filings are Netherlands, France, Denmark, Sweden, Great Britain, Germany and Finland (Figure 11). Overall, most EU countries with registered patenting activities in this field of technology showed a significant growth in patent applications. According to the data available, France achieved the most marked rise since 2000-2004, when it filed only one single patent for cellulosic ethanol to the WIPO, compared to 2010-2014, having filed 59 patents in total. High increases are also observed for Netherlands and Denmark (by factor 4,3), Germany (by factor 4,6), Finland (by factor 7,5), Great Britain (by factor 2,5), whereas the patenting output of Italy and Spain was in 2010-2014 approx. two times

bigger than in 2000-2004. The level of patenting activities in cellulosic ethanol of another group of EU countries including Belgium, Portugal, Slovakia, Hungary, Austria, Poland and Lithuania remains very low, with less than 5 patents each during 2010-2014. A large group of EU countries comprising many Eastern European countries and Greece exhibits no patenting activities at all in this field of technology.

Figure 11: Transnational patent applications for cellulosic ethanol in the EU countries



Source: Fraunhofer ISI based on WIPO

3.1.3.2 Market trends

The global ethanol production has increased significantly since 2000, with the United States and Brazil as major ethanol producers contributing 57 and 27 per cent each to the world production in 2016. At the same time, the United States and Brazil have been the world's largest consumers of bio-ethanol, followed by the EU. Between 2007 and 2016, the production of ethanol in the European Union grew by an average rate of 10,3% annually. Although this makes the EU one of the fastest growing regions in the world, its share accounted for only 5% of the global production in 2016. Following the economic and financial crisis in 2008-2009, the ethanol production stagnated in most countries. The largest volume of the ethanol production relates to the first generation (1G) bio-ethanol produced from food- and feed-based biomass.

In recent years, a lot of progress has been made with the deployment of early commercial plants, specializing on second generation ethanol production via hydrolysis and fermentation. Due to government support mechanisms, the private sector activities in developing and producing advanced biofuels increased considerably in the last decade. Lignocellulosic ethanol production using agricultural residues and some energy crops, both via hydrolysis and fermentation as well as syngas fermentation routes, has already reached early commercial phase. The technology using woody biomass (forest residues, short rotation forestry and coppice) is still mainly in the demonstration stage (IRENA 2016).

Globally, there are several first-of-a-kind commercial-scale lignocellulosic ethanol plants, most of which are in the process of commissioning or ramping up to full scale operation. Current installed production capacity for advanced biofuels is estimated at around 1,3 billion litres per year, accounting for a share of only about 0,05% of the global liquid transport fuel demand (IRENA 2016).Table 1 reveals that the US account for 35% of the total installed capacities for second generation ethanol production, followed by China and Canada. This development is primarily the result of the stimulating effect of government support mechanisms for advanced biofuels and the introduction of advanced biofuel mandates in these countries (see section 3.1.4). Since the EU's biofuel policy has been largely technology neutral so far, i. e. stakeholders are free to choose any technology or feedstock to meet the target, no additional incentives were provided to make the production and use of second generation ethanol more attractive. This led to much lower production capacities of second generation ethanol in the EU as a whole, compared to the US, China and Canada. Accordingly, only a small fraction of renewable ethanol (5%) was produced from lignocellulosic and other non-food feedstocks in Europe in 2016.[5]

Table 2: Second generation ethanol installed capacities

Region	2G Ethanol Installed Capacity (million litres)	Percentage of World Total
United States	490.4	35%
China	340.2	24%
Canada	303.5	22%
European Union	130.8	9%
Brazil	125.7	9%

[5] ePure: Statistics: http://epure.org/resources/statistics/

World (2015)	1 390.5	100%

Source: UNCTAD 2016

The market for advanced biofuels is still not sufficiently developed. The main barriers to expand to commercial scale are mostly associated with a significant risk and high costs of technology investments along with a limited access to finance – including venture capital – as well as uncertain future market and policy developments. Amongst other hurdles constraining the commercial growth of advanced biofuels are persistent low oil prices, high production costs, poor technology diffusion, insecure and technologically immature supply chains as well as production concepts (Gregg et al 2017, IRENA 2016, European Biofuels 2016).

Currently, the biofuel markets in Europe are rather fragmented as a consequence of different national regulations, sustainability requirements and support programs. This can generate an increasing uncertainty among producers and consumers, making the development of a successful European biofuel market more difficult.

Since the potential for reducing GHG emissions of lignocellulosic ethanol along with other advanced biofuels is quite promising, there are very optimistic expectations concerning favorable market prospects for them. Subsequently, global biofuel demand is expected to increase steadily in the future according to most scenarios, although the extent to which the demand increases depends on assumptions about policies, biofuel availability and costs. So far, most market outlooks are based on the assumption that the renewable energy policy goals in the transport sector and the CO_2 reduction targets are achieved. For example, provided that specific environmental goals are met and additional market mechanisms aimed to increase the market share of renewables are implemented, the IRENA REmap estimates that global demand for advanced biofuels could reach 124 billion liters per year by 2030, contributing about 25% to the total biofuels production (IRENA 2016). The WEO new policy scenario assumes that the share of advanced biofuels in 2035 would make up to 18% (67 billion liters) of the total biofuel production globally (IRENA 2016). Thereby, the deployment of advanced biofuels is expected to largely take place in the OECD countries, reaching an average share of 27% of all biofuels used there. Under the assumption that that the EU would meet its target of 10% renewable energy in transport, Bio-Tic (2015b) expects a considerable growth of lignocellulosic bioethanol market from 4 billion Euros in 2013 to around 14.4 billion Euros (13.1 million tonnes) in 2030. This growth should be mainly driven by the 2G generation bioethanol, which is expected to fully substitute 1G bioethanol by the end of this time period. However, the Bio-Tic study also points out the high uncertainty associated to future evolution of the bioethanol market.

The OECD/FAO (2016) is more pessimistic about the development of demand of bioethanol. Based on different information about prices, consumption and EU market share, the market is expected to grow from 3.7 billion Euros between 2013 and 2015 to 4,3 billion Euros in 2025 (in contrast to around 12,5 billion Euros in the Bio-Tic scenario). Moreover, the OECD/FAO expects for Europe a market share of lignocellulosic ethanol of only 0.7% of the total biofuels market in 2025, equating to around 0.03 billion Euros.

In any event, the future market opportunities of lignocellulosic ethanol will depend mainly on stable and long-term-oriented policy interventions aiming at stimulating technological learning and reducing risks. Implementation of a broad technology deployment policy would be critical to create a competitive market for both high-value and low-value bio-based products and their by-products in Europe.

3.1.3.3 Industry Structure and actors

The majority of the lignocellulosic ethanol production facilities in Europe are at pilot and demonstration scale, being operated with the purpose to test and validate the technology and to prove its economic viability.

High production costs, perceived high risk of investments as well as various technological challenges make a competitive production of advanced biofuels at commercial scale difficult. Continuous technological developments are still necessary to improve efficiency and to reduce costs. At the end of 2017, SEKAB in Sweden is the only cellulosic ethanol plant in the EU (Table 3), which is operating at commercial scale, (E4Tech 2017). Based on spent sulphite liquor from wood, it produces ethanol as a by-product of lignin processing. The ethanol is mostly for chemical use and not for fuels. Due to financial problems of the parent company, the world's first commercial scale cellulosic ethanol plant Beta Renewables in Crescentino, Italy was shut down at least temporarily in October 2017, after having operated for 4 years.[6] A number of commercial scale cellulosic ethanol plants within the EU are either under construction (Energochemica in Slovakia), or in planning stages (Enviral, Clariant in Slovakia, St1 in Finland, Clariant in Romania). Relative cost advantages and a high potential of biomass resources make Eastern Europe a particularly attractive location for the commercial production of lignocellulosic ethanol using proven technologies.

These developments in Europe for lignocellulosic commercialization are rather similar in other world regions. Currently, in the US there are changes in industry structure with prominent firms like DowDupont planning to leave the market, while others increasing

[6] Currently (as of December 2017), it is not sure whether and by whom the necessary investments can be provided to finance the facility.

their activities (e.g. Enerkema, Raizen, POET-DSM).[7] Moreover, it has to be noted that various synthetic biology firms that were active in the second generation biofuels market some years ago (Amyris, Solazyme) left these markets or were bought up (e.g. LS9).[8]

One of the difficulties that any commercial plant faces is the assurance of a long-term feedstock supply. Signing long-term agreements is particularly challenging in Europe due to a large number of different agricultural enterprises[9]. Moreover, both in Europe and the US, farmers are often not aware of economic benefits they could obtain from utilizing marginal land for the growth of non-food energy crops as well as from the sale of agricultural residues for value added processes and need to be educated in it (Valdivia et al. 2016).

3.1.4 Policy and Framework Conditions

As mentioned above, policy and an effective implementation of policy measures play a significant role in encouraging the development of sustainable biofuels. Because of missing cost competiveness compared to fossil fuels, biofuel policies have been the main driver for the development of the second generation biofuels in the United States, Member States of the European Union, Canada, China, and many other countries. From 2000 onwards, various instruments have been introduced, designed to support the production and consumption of biofuels, like blending mandates[10], tax exemptions, loan guarantees, targeted subsidies and other tax privileges.

Until recently, demand for biofuels has been mainly driven by blending mandates. However, policies did not differentiate between the first generation and advanced biofuels until a few years ago. Since then, some countries have shifted their policy towards the promotion of advanced biofuels, including the US, China and the European Union.

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[7] http://www.biofuelsdigest.com/bdigest/2017/11/02/breaking-news-dowdupont-to-exit-cellulosic-ethanol-business/

[8] https://www.technologyreview.com/s/524011/why-the-promise-of-cheap-fuel-from-super-bugs-fell-short/

[9] For example, to assure a 300 kton per year supply of corn stover, it is necessary to reach an agreement with more than 20 000 farmers, whereas in the US it can be achieved with just 150 farmers (Valdivia et al. 2016).

[10] There are currently 64 countries (as of 2016) with established or planned biofuel mandates (Innovation Outlook, IRENA 2016).

Within the European Union, the Renewable Energy and the Fuel Quality Directives provide a legal framework for the renewable energy. They outline an overall renewable energy policy for the EU countries to reach the 20% renewable energy target of final energy consumption by 2020. To lower the EU's dependency on fossil energy and to reduce greenhouse gas emissions from transportation, the Renewable Energy Directive required that at least 10% of energy used in the transport sector should originate from renewable sources. The Member States tried to reach this goal mainly through the use of the first generation biofuels. Due to the raising concerns with regard to the possible detrimental effects of the increasing demand for first generation biofuels, the EU approved in 2015 an amending directive[11], limiting the share of energy from food-based biofuels to 7% of the final consumption in transportation. To stimulate the development of advanced biofuels, they were allowed to be counted twice with regard to their energy content towards the target of 10%. Member states were expected to achieve the share of 0,5% of advanced biofuels in the total transport fuels. However, as these regulations are not binding, they have not provided a sufficient incentive to promote advanced biofuels production and consumption in the EU Member States so far.

In November 2016, the European Commission published a formal proposal for the revised Renewable Energy Directive (RED), called RED II, which should come into force on January 1, 2021. The new directive sets out an overall binding target for the EU of 27% renewable energy share by 2030. The renewable transport fuel mandate should progressively increase from 1,5% in 2021 to 6,8%[12] in 2030. To overcome existing deficiencies regarding the compliance with sustainability criteria, and to promote the development and commercialization of advanced biofuels after 2020, the Commission additionally included an obligation to gradually increase the share of blending for advanced biofuels, coming from non-food feedstock (listed in Annex IX[13]), like agriculture, forestry and industrial residues as well as bio-waste, from 0,5% in 2021 to at least 3,6% in 2030. In the aviation and maritime sector, advanced biofuels can be counted 1,2 times their energy content towards the 6,8% mandatory goal. Following the sustainability guidelines, the Commission requires that feedstocks, which have low indirect land use, should be given priority and be supported more strongly for the production of biofuels. To minimize direct and indirect negative effects, resulting from the use of food-based biofuels, their contribution to the overall renewable energy target should be capped at 7% in 2021,

11 http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32015L1513&from=EN

12 Please note that this share relates only to fuel and not to energy used as in the current Directive.

13 http://ec.europa.eu/energy/sites/ener/files/documents/1_en_annexe_proposition_part1_v6_0.pdf

gradually decreasing to maximal 3,8 % by 2030. To facilitate the development and commercialization of more advanced biofuels, the contribution of conventional low-carbon biofuels, which are derived from feedstocks, like animal fat, used cooking oil and molasses, should be reduced to the 1,7% limit. According to the Commission, the deployment of new advanced biofuels would save around 70% of GHG emissions[14].

The EU countries have some flexibilities in timing and policy design to reach these goals. Some EU countries have already shifted their policy towards the promotion of advanced biofuels. For example, Italy belongs to one of the first European countries, which adopted biofuel blending targets and introduced a mandatory quota for advanced biofuels. The Danish government pursues the goal of phasing out fossil fuels by 2050 and the promotion of advanced biofuels is a very important step towards it. Sweden invests considerable funds in the research and development of advanced biofuels with a particular focus on the second generation ethanol. Due to the strategic pricing policy of the Swedish government through high taxation on fossil fuel based products, biofuels have become highly competitive.

Overall policy has a key role, if barriers to competitive production of lignocellulosic ethanol should be overcome. Hence, policy instruments are intensively discussed. The consensus is that it is important to design policies that support activities along the entire value chain, including biomass production in agriculture and forestry, distribution, production, retail and the end-use of ethanol (Eggert / Greaker 2014; Gregg et al. 2017). Policy should be therefore broadened to promote a better integration of the whole value chain and an orientation towards more value-added products.

For that purpose, the following policy areas and instruments are identified as most important (Eggert et al. 2011; Eggert / Greaker 2014; Gregg et al. 2017): adjustment of fossil fuel prices to the level which would approximately reflect the external costs incurred through pollution and land degradation; public support for all kinds of R&D&I activities; and, access to capital. On the demand side, substantial investments in the necessary infrastructure are still required to facilitate the transformation of the car fleet to a flexi-fuel standard and to avoid a “blend wall” (Eggert / Greaker 2014).

[14] https://ec.europa.eu/energy/sites/ener/files/documents/1_en_act_part1_v7_1.pdf

Table 3: Pilot, demonstration and commercial plants for lignocellulosic ethanol in the EU

Company name	Country	Feedstock details	Technology Status	Biofuel production capacity (million litres/yr)	Start-up year	Project status
Aalborg University Copenhagen	Denmark	Wheat straw, cocksfoot grass	Pilot		2009	Operational
BioGasol / Estibio	Denmark	Straw, various grasses, garden waste	Demonstration	5	2013	Planned
Inbicon	Denmark	Wheat straw	Demonstration	5	2009	On hold
Inbicon	Denmark	Straw	Pilot		2003	Operational
Inbicon	Denmark	Straw	Pilot	1	2005	Operational
Chempolis Ltd.	Finland	Non-wood and non-food lignocellulosic biomass such as straw, reed, wood residues etc.	Demonstration	6	2008	Operational
St1 Etanolix	Finland	Sawdust	Commercial	10	2016	Operational
Abengoa Bioenergy	France		Demonstration	51		On hold
PROCETHOL 2G	France		Pilot		2011	Operational
Clariant	Germany	Wheat straw	Demonstration	1	2012	Operational
Beta Renewables	Italy	Straw, energy grasses	Demonstration	51	2013	Operational

Borregaard	Norway	Sulfite spent liquor from spruce wood pulping	Commercial	20	1938	Operational
Borregaard	Norway	Sugarcane bagasse, straw, wood, energy crops, other lignocellulosics	Demonstration		2012	Operational
SEKAB	Poland	Wheat straw and corn stover	First commercial	63		On hold
Beta Renewables, Energochemica	Slovakia	Wheat straw, switchgrass, rapeseed straw, corn stover	Commercial	70	2017	Under construction
Enviral, Clariant	Slovakia	Wheat straw	First commercial	63	2019	Planned
Sekab	Sweden	Spent sulphite liquor from wood processing	Commercial	18	2004	Operational
St1 (NEB, NEOT, UPM, KaVo)	Finland	Sawdust, recycled wood	Commercial	50	2020	Planned
Clariant	Romania	Agricultural residues	Commercial	63	2020	Planned

Source: based on database of IRENA and own research, own compilation.

3.2 Bio-based plastics

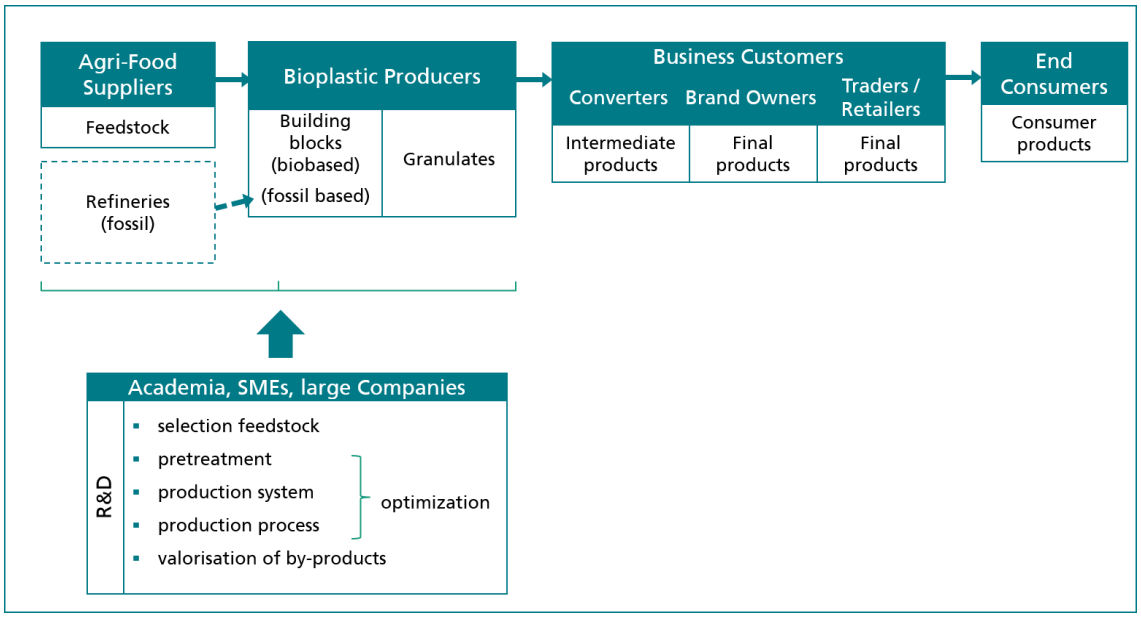
3.2.1 Description of the value chain

Bioplastics (bio-based polymers) represent an important product segment for IB. The term ‘bioplastics’ refers to the raw material used (biomass instead of fossil fuels), or to production methods (biotechnology instead of chemical synthesis) or to biodegradability. In the PROGRESS project the term bio-based plastics is used for plastics, which are – at least partly – produced from renewable biomass as feedstock and there is a biotechnological step in the production. They may be either biodegradable or durable.

The bio-based plastics value chain of IB (Figure 12) comprises high-volume products in Business-to-Business and Business-to-Consumer markets, which the public associates with bioeconomy or industrial biotechnology and therefore has a signalling function for other IB-based developments.

The bioplastics value chain may consist of a feedstock supplier that converts the feedstock directly into bioplastics. Alternatively, it can include intermediate steps where a building block such as lactic acid is formed and then converted into granulates (PLA). The following steps along the value chain may include compound formulation; although some plastics can also be used directly without compounding. The final processing step is the conversion of granulates/compounds into consumer products by business customers.

Figure 12: Value chain for bio-based plastics



3.2.2 Technology and Innovation potential

Regardless of their potential benefits, only a limited number of bioplastics have been developed to commercial scale (e.g. PLA) and they are not suitable for all desired application areas. Therefore, there is a general need for further R&D&I in order to develop bioplastics with desired properties for a variety of applications and uses. This includes identification and characterisation of promising sources (besides food crops such as corn, wheat or soy) of biomass feedstock to produce bio-based plastics (e.g. waste streams, lignocellulose or plant-based proteins) in order to identify candidates with promising properties and functionalities for the identified market opportunities. Furthermore, green chemistry and/or fermentative production processes have to be developed and optimised, especially with respect to (bio-)catalysts, yield, bio-plastic quality, cost-competitiveness, and sustainability of production (related detailed R&D&I needs are described below). This requires intensified cooperation between chemists, microbiologists, (bio-)process engineers and material scientists. In order to fulfil their innovation and technological potential, the scale-up of production processes, to reach a critical mass for a given bio-based plastic, becomes a key issue. This will help achieve economies of scale and address different market segments and applications.

Plant based proteins serve as an excellent example to illustrate the innovation potential of bioplastics. These proteins, from new sources (besides corn, wheat and soy) could be used as a source of raw material for bio-based plastic products, possibly biodegradable. Potato and rice have been tested as potential promising sources for bio-based plastic production leading to gluten free food packaging bioplastics. However, there is a need for further R&D&I to improve mechanical and water absorption properties of plant protein based bioplastics.

The majority of bio-based plastics are produced industrially from food crops (as mentioned above). Due to the food-first principle, there is a need to additionally exploit non-food feedstocks, e.g. lignocellulose, whole plants or crop plant residues from food crops (e.g. straw), specifically grown non-food crops (e.g. Miscanthus, switchgrass), industrial waste streams (e.g. from food processing, such as whey), CO_2, or municipal waste fractions. Bio-based plastics based on non-food feedstocks have not reached commercial scale and there are still a number of R&D&I issues to be solved due to a number of technological complexities and high production prices. For example lignocellulose is being investigated as an abundant non-food feedstock for the manufacturing of bio-based plastics. A major fraction of lignocellulose is lignin, which is used mostly as an energy source. For wood as the most dense lignocellulosic material, the following challenges exist: Upscaling of current steam explosion installations to the sizes required for large

industrial applications, improving the yields of hemicellulose separation at steam explosion, efficient separation of cellulose from lignin and glucose production from cellulose. Additionally, it would be necessary to overcome hurdles posed by the structural heterogeneity of lignin and the presence of impurities. Eventually, potential lignin-derived products could be hydrocarbons, phenols, macromolecules and oxidized products.

Another non-food based biomass example is cashew nut shell liquid (CNSL). This, a relatively underused by-product/waste stream of cashew nut production that has not yet been widely used for bio-based plastic production. Phenolic compounds, which could be used in resins or composite materials, could be derived from CNSL, thus valorising this by-product and contributing to a circular economy. CNSL-derived products could be used in paints and surface coatings for improvement of colour range, minimize oxidation, improve adhesion to surfaces.

Generally, it has to be noted that the boundaries between the previously clearly separated areas of bioplastics on the one hand and petrochemical plastics on the other hand are becoming increasingly blurred as natural-fiber reinforced petrochemical plastics, chemically reinforced biocomposites as well as petrochemical plastics with bio-based proportions (for example Bio-PET30) are gaining importance. Moreover, some new bioplastics are expected to enter the market as Bio-PVC, Bio-PP and PEF (Aichinger et al. 2016 based on IFBB 2015; European Bioplastics 2017).[15]

3.2.3 Economic analysis

3.2.3.1 Patent analysis

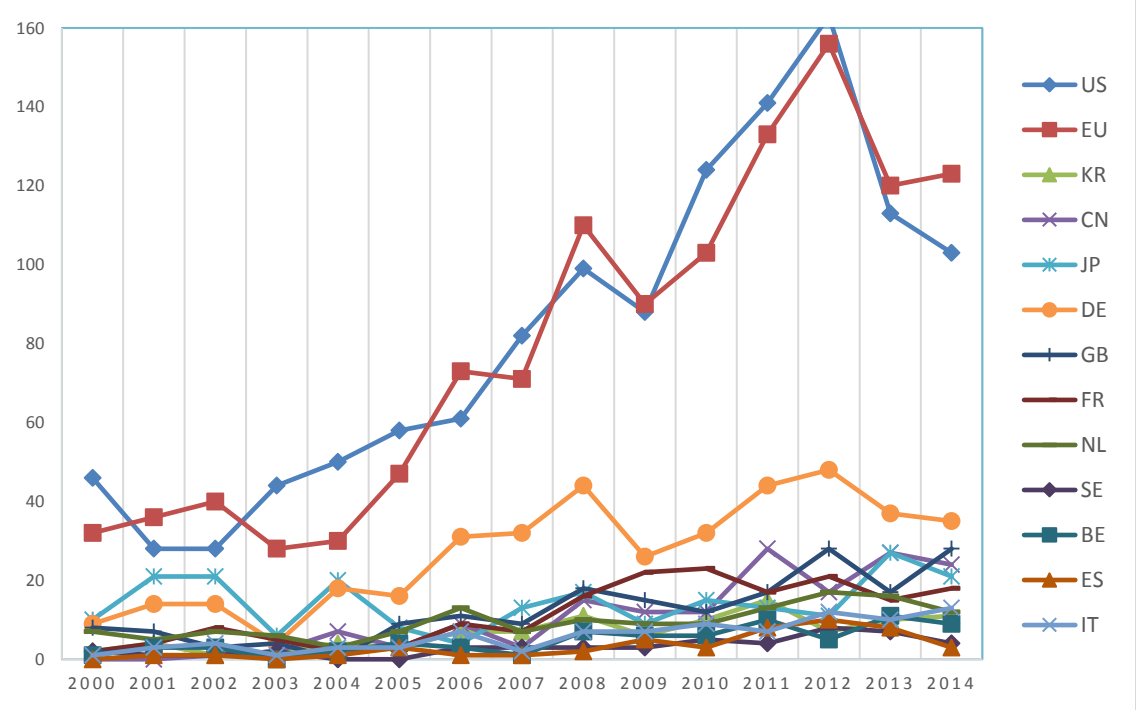
Bioplastics patenting[16] activities in most countries took off in 1990s, having the most dynamic development between 2000 and 2012. During this period, the number of patent filings for bioplastic-related technologies grew at double-digit rates in the most relevant countries. The overall number of the world patent applications in bioplastics has more than tripled between 2000 and 2014. The European Union (EU) as a whole ranks first in

[15] PEF = Polyethylene furanoate; PP = Propylene; PVC = Polyvinylchlorid

[16] For the analysis of the bio-plastic patent activities of different countries, the research of transnational patent applications, based on the WIPO patent database, was carried out. The bioplastic related patents were identified on the hand by using keyword searches “biopolymer”, or “bioplastic”, or “PE”, or “polyethylene”, or “PET”, or “polyethylene terephthalate”, or “PTT”, or “polytrimethylene terephthalate”, or “PA”, or polyamide”, or “PVC”, or “polyvinyl chloride”, or “PP”, or “PEF”, or “polypropylene” or “polyethylene furanoate”. Whenever necessary, the searches were specified by the supplement “bio”. On the other hand IPC classes with relation to plastics and terms relating to bioplastics were crossed. Some classes, e.g. medicine or semiconductor were excluded.

terms of the number of patent applications to the WIPO, followed by the US. Aside from the US, the world's main patenting countries in this technology field are Germany, Great Britain, China, Japan and France (Figure 13).

Figure 13: Transnational Patent Applications for bio-based plastics



Source: Fraunhofer ISI based on WIPO

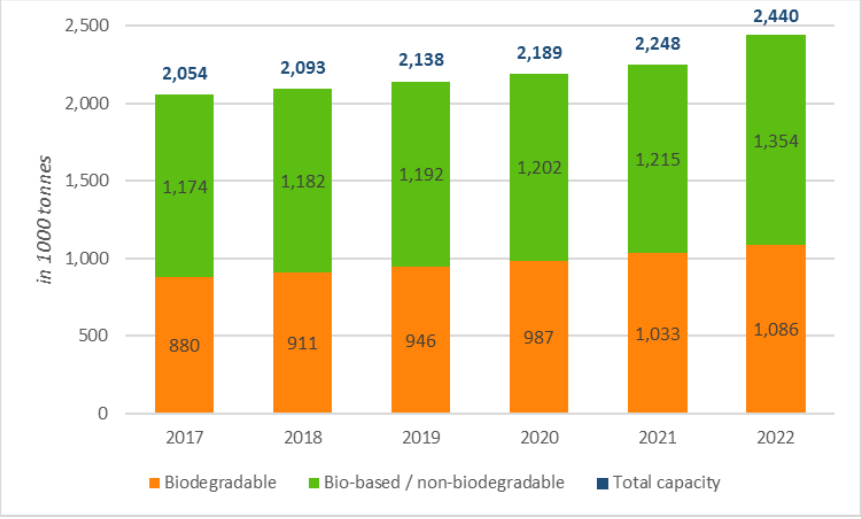
The EU as a whole exhibited between 2000 and 2012 an average yearly growth rate of 14%, which was slightly above both the average global and the average US growth rate. The number of patent filings in the entire EU increased almost fivefold between the years 2000 and 2012. Among all EU countries, Germany shows the highest level of performance, followed by the Great Britain, the Netherlands, Italy and Belgium. The most dynamic growth of patenting filings was registered in Germany, Great Britain, France and Italy, surpassing that of the EU area's average growth of 14% between 2000 and 2012. While demonstrating no patenting activities in 2000-2004, Poland, the Czech Republic and Slovenia registered some patents in bioplastics between 2010 and 2014. However, the number of WIPO patent application from Slovakia, Hungary, Lithuania, Latvia, Romania as well as of Portugal and Ireland have remained extremely low. According to the WIPO data, a group of the EU Member States involving Bulgaria, Greece, Croatia, Malta, Estonia and Cyprus have no single registered bioplastic related patent application in the last five years available.

In China, we observe a continually rising number of patents applications since 2002. Starting from a very low level, they were expanding between 2002 and 2014 with an annual average growth rate of around 37%. Although China achieved a breakthrough in patenting activities compared to the period 2000-2002, when hardly any patent applications in bioplastics were registered, its current level of patent filings amounts to only a fraction of that of the EU and the US.

3.2.3.2 Market trends

Currently, bio-based plastics [17] still represent a niche with a share of about roughly one per cent of the 300 million tonnes of plastics produced annually worldwide. However, the market has grown considerably in the last five to ten years at a rate of about 20 per cent per year (Bio-Tic 2015b; European Bioplastics 2016a). There have been several changes in market data regarding the inclusion of certain type of plastics. According to most current data, (European Bioplastics 2017) global bioplastics production capacity is estimated to be around 2,05 billion tonnes and expected to grow to around 2,44 million tonnes in 2021. Hence, despite the low-oil price bio-based plastics are expected to grow in the next years. However, earlier market expectations for 2020/2021 (see European Bioplastics) have been reduced significantly.

Figure 14: Global production capacities of bioplastics (in%)

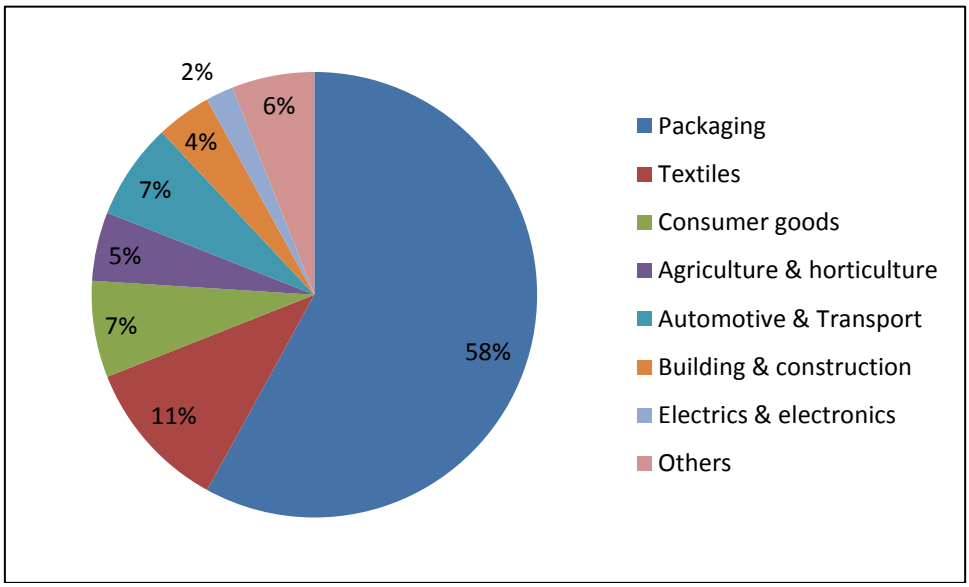


Source: European Bioplastics, Nova Institute (2017)

[17] An analysis of Aichinger et al. (2015) on the basis of IFBB (2015) on biomass-based plastics shows that in 2013 product groups which are produced via biotech processes have a market share of around 75-85%[17], with rising trend. Hence, the following analysis for bio-based plastics, for which most data exists, can be regarded as appropriate proxy for IB.

Bio-based plastics are used for a wide range of applications; with packaging capturing almost 60 percent (1.2 million tonnes) of the total bioplastics market (flexible and rigid packaging). In addition, a range of other markets has emerged in the past (consumer electronics, automotive), as can be proxied by the distribution of production capacities (Figure 15).

Figure 15: Global production capacities of bioplastics by segment in 2016 (in %)

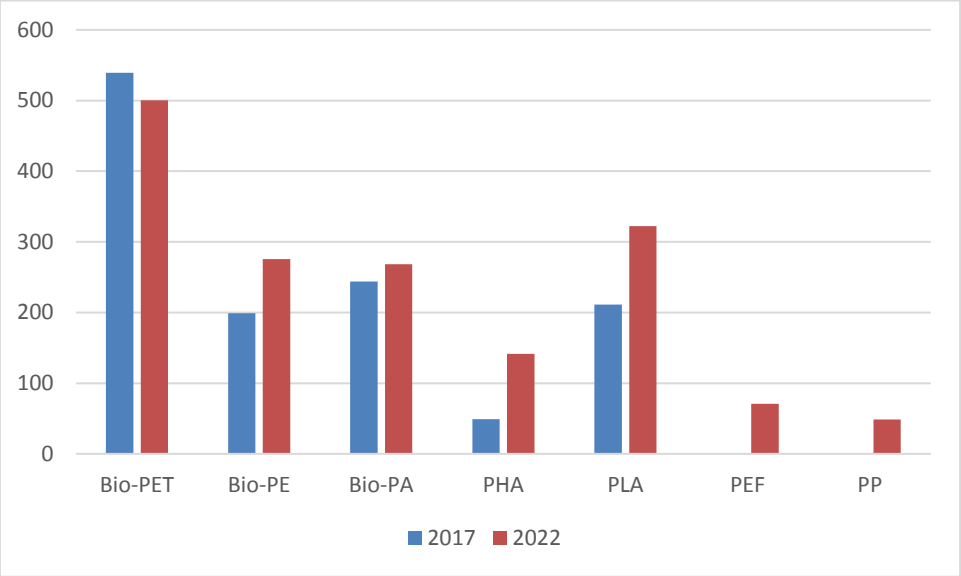


Source: European Bioplastics (2017)

Currently, the majority of bio-based plastics are drop-ins for existing mass markets (Aichinger et al. 2016). Drop-ins have identical or similar technical properties as their fossil counterparts. Drop-ins do not face high market uncertainties, can be partly built on existing infrastructure and existing technological knowledge for the conventional product and do not lead to switching costs for users. However, competition against the fossil based products with similar performance is mostly reduced to relative price. Current low oil prices significantly hamper the cost competitiveness of bio-based plastics.

Hence, market outlooks have been revised significantly, as earlier plans to execute the planned extension of Bio-PET 30 for the use of bioplastic bottles mainly by Coca-Cola Inc. have been set on hold. Instead, potential growth is now expected mainly for non-drop-ins such as PLA and PHA, two biotechnologically-produced compounds (see Figure 16).

Figure 16: Global production capacities for selected (IB produced) bioplastics



Source: IFBB (2017)

For 2030, the Bio-Tic study (Bio-Tic 2015b) projects growth rates of 12% annually (10% for the low scenario and 15% for the high scenario). The bio-based plastics market value in Europe is expected to reach approximately 5.2 billion Euros in 2030 in the reference scenario and 4.3 billion Euros and 6.7 billion Euros in the low and high scenarios, respectively. In these projections, Europe is expected to maintain its position as the main consumer of bio-based plastics.

Regarding key market drivers, there are some differences between the different bioplastics and different applications, but some overall trends can be observed.

Cost competitiveness is a key market factor for all applications (Bio-Tic 2015b). In particular, for the drop-ins a continuity of low oil prices would impede cost competitiveness in the future. Bio-based plastics are currently more expensive than fossil-based plastics on weight basis. A recent overview by Wageningen Research (van den Oever 2017) shows that prices vary quite significantly between different bio-based plastics. While some bio-based plastics are considerably more expensive than fossil based ones (e.g. PHA) there are some exceptions (e.g. PLA for some products). For the future, it can be expected that bio-based plastics become more cost competitive, if economy of scale of production and learning effects are realized and if the oil price increases considerably.

Today, the market is highly dependent on Consumer behaviour towards bio-based polymers and willingness to pay a bio-premium for the environment. The Bio-Tic (2015b) study points out that bio-premium can be justified in four cases: 1) bio-based origin is a

key buying criterion, 2) environmental sustainability is used as a marketing tool to build brand image, 3) bio-based plastics represent at least a certain minimal share of the final product value, and 4) there are regulatory requirements for the use of bio-based plastics.

A recent survey conducted in the H2020 project “Bioforever” reveals that almost 85% of the experts report Green Premium prices for bio-based plastics (Carus et al. 2017). 60% of the participants considered the Green Premium to be a range between 10-20% of the product price, almost 20% indicated a price premium of 20 up to 40%. About 6% of the respondents estimate the premium more than 50% for bio-based plastics. While these numbers show quite an optimistic picture of the willingness-to-pay, the differences between the current prices of bio-based and fossil based products are often higher.

While various studies show generally a positive attitude of consumers towards bio-based plastics, different challenges arise: The environmental advantage of many biopolymers is ambiguous, as the impact of bio-based plastics and fossil-based plastics are in different categories. E.g. the Federal Environment Agency in Germany states in a meta analysis shows that bioplastic lower CO_2 emissions, but farming and processing of the plants used in packaging cause more severe acidification of soil and eutrophication of water bodies than the production of common plastic packaging (Detzel et al. 2013; van den Oever 2017). Bio-plastics’ producers still struggle to signal the potential advantages and characteristics (e.g. bio-based content, saved CO_2 emissions) of their product sustainable production/processing from biomass (Hogan et al. 2015).

3.2.3.3 Industry Structure and actors

The actor landscape of bio-based plastics is diverse. There are few suppliers of bio-based plastics such as large chemical firms like BASF, NatureWorks (owned by PTT Global Chemical and Cargill), Corbion, Braskem and some specialized firms (NovamontNatureWorks, FkuR Kunststoff, Innovia Films, Biomer, or BIOTEC). Instead, there is a rather high number of converters of bioplastics to further/final products - various catalogues or databases show that there is considerable number of firms (>100), which supply products based on bioplastics[18]. These companies range between the different application fields and from small SMEs to large brand owners. The latter group is an important decision-maker in the bioplastics value chain because it usually demands rather high volume of bioplastics for its mass markets, has the channels to increase the awareness of bio-based plastics and takes considerable market risk (e.g. regarding acceptance, higher costs) of opting for bio-based plastics rather than conventional counterparts (Bio-TIC 2015a). The decisions of big brands to take up bioplastic solutions in

[18] See e.g. https://datenbank.fnr.de/produkte/biowerkstoffe/biokunststoffe/ or Molenveld et al. 2015

the past has had an important boost effect for bioplastics. E.g. LEGO, Procter & Gamble, Coca-Cola, Danone, Puma, Samsung, IKEA, Tetra Pak, Heinz, or Toyota have already introduced large scale products in Europe (European Bioplastics 2016a). Expectations toward big consumer brands to build up more sustainable value chains may create increasing market pull in the future. However, bio-based plastics here face the issue that brand owners must become aware of benefits and opportunities and compete against other options for increasing the sustainability of their value chain and building up their environment-conscious image.

The actors in this value chain are quite distributed across the globe. In 2013, Europe was the largest bio-based plastics consumer of the global bio-based plastics output (Bio-Tic 2015b). However, there is strong competition especially concerning the location of production sites with several countries having considerable policy incentives in place. According to the most recent estimates of European Bioplastics (European Bioplastics 2017), the share of production capacities of Europe in 2017 is around 17 %[19] with an optimistic outlook of a rise to 25% by 2022.

While in the past numerous value chains emerged in the bio-based plastics sector, some challenges remain. These include overcoming lack of cooperation and knowledge transfer between different actors along the value chain. It is also necessary to form novel actor configurations along the value chain, with a specific focus on industries, which wouldn't be in contact for their own core business, in order to stimulate exchange of information and knowledge between them and encourage the joint development of strategies and R&D&I priorities along the value chain.

[19] This share is considerably lower than in earlier publications of European bioplastics, e.g. in 2016 the share of Europe was estimated to around 27% (European Bioplastics 2016). Most probably, the large changes are connected to the abandonment to include PUR in the newest estimates.

3.2.4 Framework conditions and policies

There are currently still very few policies globally, dedicated directly to bio-plastics, especially compared to biofuels (OECD 2013/2017) and there is a general lack of a suitable framework conditions in the EU to promote and support the diffusion of bio-based plastics (BIO-Tic 2015b). A recent study from September 2017, for example recommends from a level playing field perspective that it might be useful to consider implementing a similar policy framework for bio-based plastics as for biofuels (Odegard et al. 2017).

Nevertheless, already for some years there are dedicated institutions in place in the EU that serve a purpose to create more supportive framework conditions for bio-plastics.

In the EU, initiation of bio-plastics related policies is a task of a specific 'Ad-Hoc Advisory Group for Bio-based Products'. This group works through the European Commission's Lead Market Initiative with a main goal: to promote bio-based products uptake and diffusion within the EU. One of the key policy instruments that would support further uptake and diffusion of bio-plastics is public procurement. The Green Public Procurement (GPP) programme was initiated in 2008, to (among other topics) encourage and guide the EU Member States to increase and promote the uptake of bio-plastics, meaning that products containing bio-based plastics would qualify for preferential selection by public authorities in the EU (BBIA-CEBR 2015). However, implementation of actions for public procurement are currently limited (European Commission 2017a).

Another emerging topic regarding bio-plastics in the EU is standardization, which has received a lot of attention over past years. Well developed and clear standards enable the verification of claims about bio-based plastics, such as biodegradability, bio-based content, recyclability and/or sustainability (Bastoli 2017). The EC issued an European Committee for Standardisation (CEN) Mandate (M491, 492) that was finalized in 2016, covering terminology, testing, and communication specifications for bio-based products such as bio-plastics (BBIA-CEBR 2015). Moreover, TC249 deals with the development of standards for biopolymers, specifying terminology of biopolymers and bioplastics (Ladu / Blind 2017).

In 2015, the "Carrier Bag Directive" (2015/720/EU) (European Union 2015) was implemented and called EU MS to introduce measures to reduce consumption of single use plastic bags. In 2011, Italy was the first EU Member State to forbid the distribution of traditional plastic bags, followed by France in 2015 (BBIA-CEBR 2015).

The other key EU policies on bio-based plastics include the EU Packaging and Packaging Waste Directive[20], the European Strategy for Plastics in a Circular Economy and the EU Bioeconomy Strategy.

The EU has prioritized a move towards a circular economy through its Circular Economy Action Plan (Publications Office European Union 2017), as bio-based plastics are believed to play an important role in the future circular economy. Their main potential and promise in this respect lies in decreasing the dependence from fossil based resources and emittance of CO_2 to the atmosphere and therefore reducing greenhouse gas footprint. Furthermore, bio-based plastics can facilitate to return valuable nutrients to the ground[21], (BIC 2015) and decrease microplastics and nanoplastics in soil and water (Odegard et al. 2017). The key feature of bio-plastics is that they would not create further waste, but re-enter the future circular economy as a useful biological nutrient. To fully benefit from bio-plastics, a supportive legislative framework is needed that would take into account and support all the positive characteristics that bio-plastics have to offer to circular-economy. Currently, the European Commission is in a process of adopting a new strategy on plastics (Publications Office European Union 2017). In the EU, also amendments in the Packaging and Packaging Waste Directive (PPWD)[22] are necessary that should include the clarification of the definition and terminology of bio-plastics and incentives supporting further uptake of bio-based plastics in the Member states (European Bioplastics 2016b).

20 http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:01994L0062-20150526

21 http://www.european-bioplastics.org/bio-based-plastics-play-an-essential-role-in-the-future-circular-plastics-economy/

22 http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex:31994L0062

3.3 Enzymes

3.3.1 Description of the value chain

Enzymes are proteins that act as macromolecular biocatalysts in living cells. They are used in different industries and applications where specific catalysis (i.e. reactions) are required to produce a variety of products. More than 3000 enzymes have been identified (Koeller 2001) and they are used in about 150 industrial processes as reaction catalysts (Adrio 2014).

Increasing demand for products made from renewable raw materials by using biotechnological processes is a key driver behind innovation activities in the enzyme sector. Enzymes have a potential to reduce manufacturing costs, contribute to sustainability and reduce environmental pollution. Additionally, they are critical for the development and production of many today's bio-based products. In the last decade, enzyme-based production processes have increasingly substituted chemical processes in a number of areas, especially in fine chemical and pharmaceutical industries, where specialty enzymes are applied.

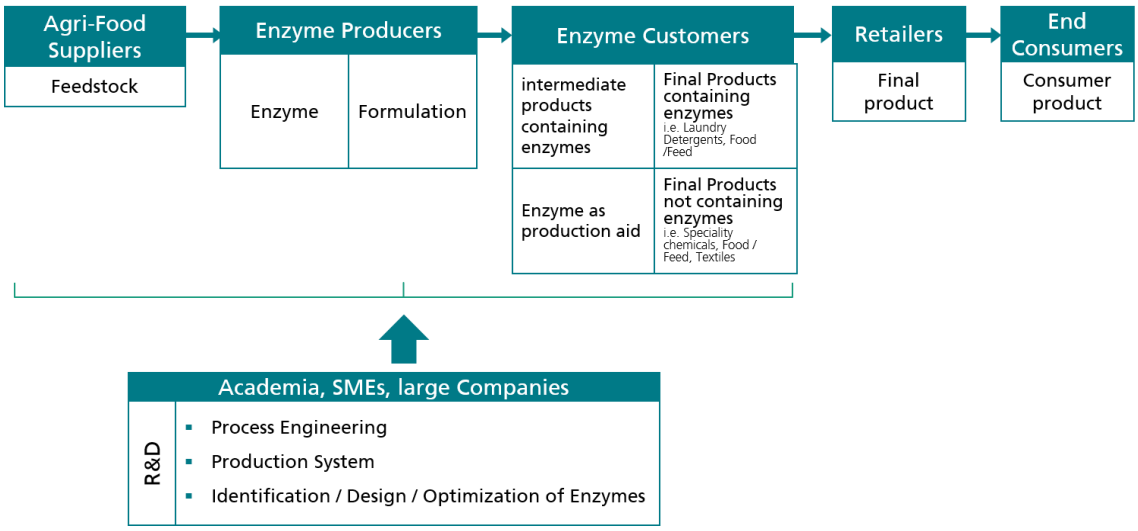
While enzymes are already established for many application areas, there is a demand for novel or improved enzymes to enable economically competitive and more sustainable solutions (van de Velde et al. 2013), as enzymes are key enablers for substituting fossil feedstocks by renewable ones.

Enzyme producers sell enzymes after purification and formulation as intermediate products to business customers (Figure 17). Here, enzymes are either used as production aid, e.g. for the production of fine chemicals, or are active ingredients in final products such as in laundry detergent. Depending on their specific application areas, they are divided between industrial enzymes and speciality enzymes (Aichinger et al. 2016).

Industrial enzymes are often produced by large multinational companies and include enzymes that remain in the product or are used to manufacture other materials, such as enzymes for food, animal feed and beverages production, starch processing, pulp and paper, textile, leather, detergents and biofuels production (Verma et al. 2017). SMEs play an important role either as manufacturer of speciality enzymes or as technology providers. Speciality enzymes are highly purified and used in a much smaller scale than industrial enzymes, hence, they are much more expensive (Freedonia 2016). Speciality enzymes are mostly used in biotechnology, pharmaceutical and diagnostics industry, biocatalysts markets and in research. Therefore, enzymes cover a broad spectrum of

products, ranging from low-value-high-volume products to high-value-low-volume products, delivered to other businesses or directly to consumers, with a significant contribution to the added value of final products.

Figure 17: Value chain for Enzymes



3.3.2 Technology and innovation potential

The main potential of enzymes lies in several distinct advantages over chemical catalysts that make them very attractive catalysts for biomanufacturing. These include for example: 1) high selectivity for the substrate, 2) increased catalytic power, 3) lower energy consumption, 4) milder reaction conditions (temperature, pH and atmospheric conditions), 5) fewer by-products and 6) a long half-life (Adrio 2014; van de Velde et al. 2013). However, there is a need to expand the number of enzymes for industrial use which catalytic properties e.g. the formation of C-C bonds, oxidations and reductions, catalyse co-factor dependent reactions and "dream reactions" (e.g. utilisation of CO_2 as feedstock in chemical synthesis). There is a general need to further optimize enzyme production processes with respect to biotechnological, economic, ecologic and safety parameters. This includes further automatization and integration of unit operations, process analytical technologies and digitalization of production. Additionally, there is a need for development of novel enzyme applications, optimization of enzyme applications and developing novel approaches of enzyme production, such as cell-free systems for different purposes and complex biocatalytic systems for cell-free metabolic engineering.

Recent advancements in different biology disciplines (i.e. biotechnology, genomics, metagenomics, proteomics, efficient expression systems and emerging DNA modification techniques) in conjunction with computational methods, have already facilitated the discovery of a number of new microbial enzymes with improved catalytic characteristics and opened up a number of new potential application areas, innovative products and process optimization and improvements (Scarlat et al. 2015). This is expected to accelerate even further the replacement of chemical processes by enzyme based production processes.

Currently, only very few of the enormous variety of naturally occurring enzymes are used in IB processes and a high potential lies in still non-discovered enzymes and their application in different IB application areas.

Main research avenues to broaden the spectrum of enzymes include:

1) Identification of potentially useful and novel naturally existing enzymes by screening natural sources (especially in “underinvestigated" sources/ecosystems with a higher likelihood of success: e.g. marine sources, or extreme environments), by using metagenomics, in silico screening, high throughput screening. Additional technological improvements of high-throughput screening methods are needed, which can be applied either for the screening of naturally occurring enzymes or in the process of enzyme engineering. These improvements include development of different screening concepts, such as cells as reaction compartments or in vitro compartmentalization via synthetic droplets and micro-chambers. Another approach would be screening of genomic libraries without a cloning step, using cell-free translation, thus overcoming limitations posed by the expression host *E. coli*; further miniaturization (e.g. microsystems, microfluidics) and lastly, development of novel detection methods, e.g. novel assays for the desired enzyme property, improved assays that mimic “real life” conditions suitable for high-throughput approaches, and novel detection systems for high throughput screening.

2) Next to identification of novel enzymes, there is a general innovation need to optimize enzymes for industrial purposes (i.e. enzyme engineering), as their application in industrial processes requires properties that do not exist in naturally occurring enzymes.

Generally speaking, properties of interest for engineering enzyme activity include: tolerance to harsh process conditions, altering the optimum range of enzyme activity, increasing or decreasing substrate and reaction specificity or selectivity, extension of substrate and reaction range to non-natural substrates and reactions, alteration of kinetic properties (e.g. Km-value, velocity of the reaction, reduced product inhibition, inducibility/conditional activity), stability under reaction conditions, and activity in organic solvents.

Enzyme engineering could be further improved if the general lack of structural and mechanistic knowledge about enzymes could be overcome. Enzyme engineering with the aim to establish more complex biocatalytic systems and processes could benefit from innovation activities to develop artificial multienzyme complexes, reactions cascades (e.g. by co-localising enzymes on scaffolds, enabling substrate channeling), etc.

3) Currently, *Bacillus subtilis* is the most widely used host organism in industrial enzyme production. New hosts for enzymes production have very high innovation potential, as there is a general need for secretory hosts to enable large–scale production. Therefore, there is a need to establish novel host organisms (e.g. fungi, yeast) with the ability to effectively secret proteins into the medium. This could be done by improving tools for engineering the host, e.g. in order to be able to introduce or delete genes and to improve the level of protein expression, and by applying systems biology, modelling and simulation. Furthermore, development of synthetic biology approaches (e.g. chassis and cassettes or genome reduction), and their application to construct minimal enzyme production hosts exists, as well as developing alternative concepts (e.g. cell-free enzyme production) to industrial scale maturity.

3.3.3 Economic analysis

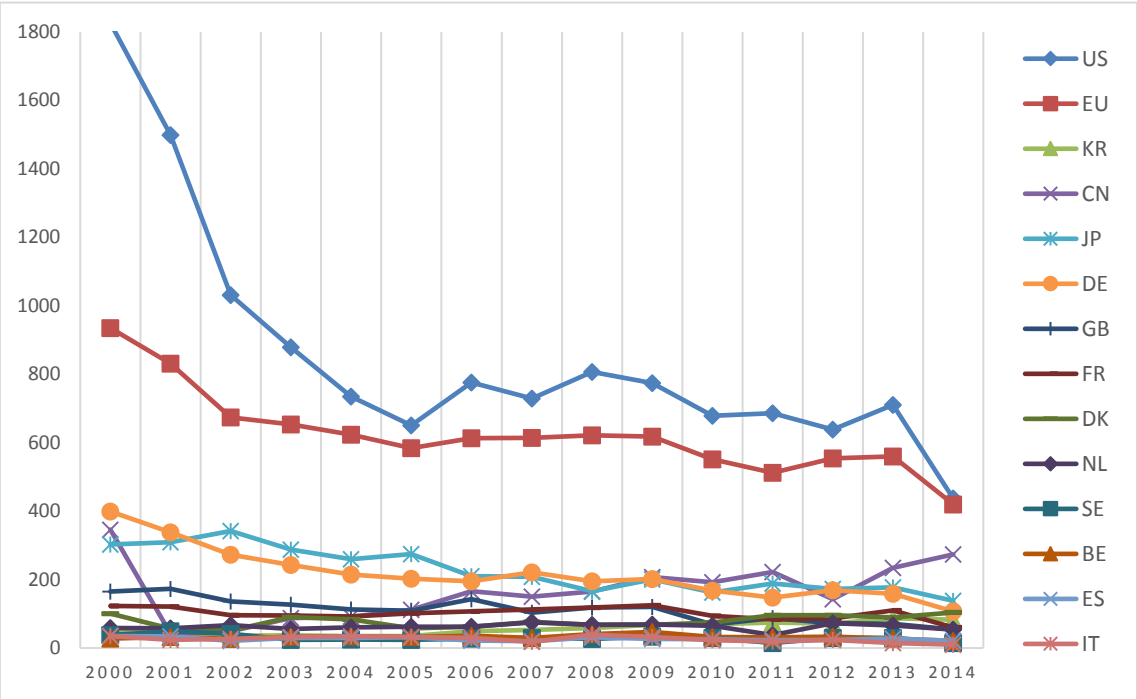
3.3.3.1 Patent analysis

Data on international patent applications in enzyme related technologies based on the WIPO patent database[23] provide evidence for a dynamic growth during the 1990s, followed by stagnant patent filings after 2000 for the most countries with enzyme invention activities. During the 1990s, most countries engaged in enzyme related innovation activities exhibit a double-digit average annual growth, ranging from 15% for Italy, Spain and Belgium, 13% for Germany and Denmark, to 11% for Great Britain over the period 1990-2000. Most enzyme patents originate from the US, contributing approximately 50% to the total worldwide patent applications in the early 2000s. To a great degree, this surge was due to quite liberal standards for IP practices in life sciences during 1990s in the United States, which also resulted in broad enzyme related patenting activities. In light of growing life science patent controversies, there has been a range of court decisions, which stressed concerns on broad patenting activities in life sciences. This induced decision makers to rethink the limits of patents (Arti et al. 2016), which is one of the reasons for a steep decline in US patent filings and patent grants since 2000 in this field of science. The growing importance of enzyme technologies in other countries, notably EU

[23] For the analysis, the IPC classes C12N9 and C12N11 were used to delineate patents for enzymes.

Member States and China, is another cause for the continuously decreasing share of the US in the global enzyme patent applications during the last decade.

Figure 18: Transnational Patent Applications in Enzymes



Data Source: Fraunhofer ISI based on WIPO

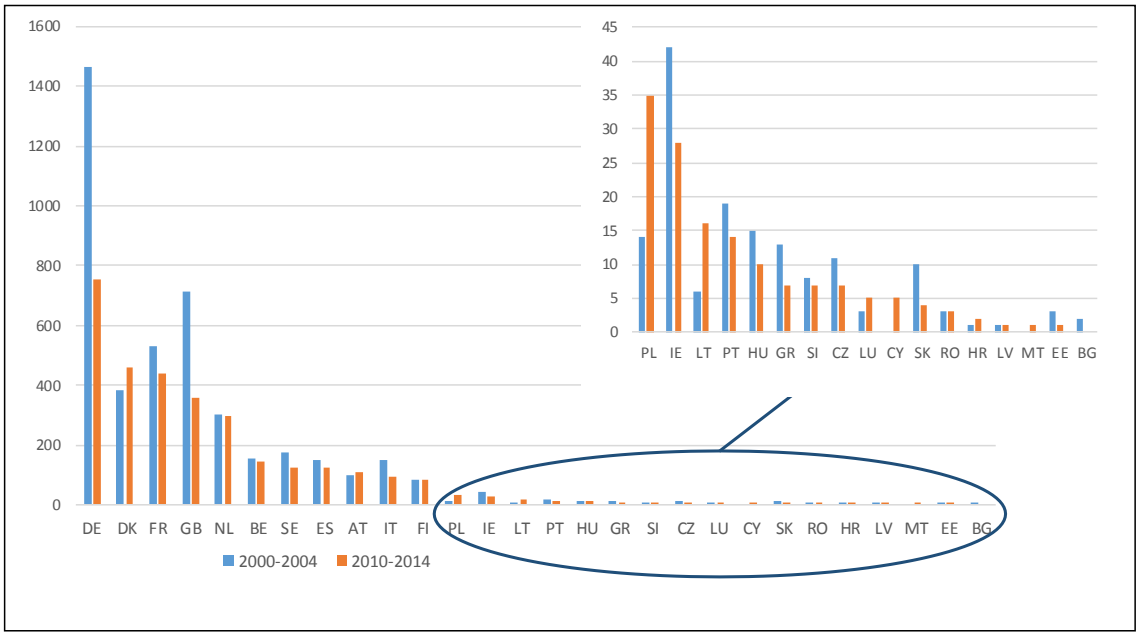
Along with the US, the main countries with intensive innovation activities in the field of enzymes are Japan, South Korea, Germany, Denmark, France and Netherlands (Figure 18). These countries recorded significant shares of total global enzyme related patent applications during the entire observation time span. However, Japan, Germany and Great Britain show a considerable and ongoing drop in registered patent filings since 2000. Most countries experienced a clear downward trend in enzyme patent filings over the period 2000-2013, having only a short intermezzo of a positive growth between 2005 and 2009, followed by further decline after 2009. Alongside China, South Korea is an exception to this overall global development in enzyme patenting activities. China achieved a remarkable breakthrough in the enzyme related patenting activities, with the number of patent filings increasing six-fold in 2013-2014 compared to 2001-2002. In South Korea, the number of patent applications in enzymes in 2013-2014 was double the level of total patent applications in 2000-2001.

Apart from Germany, Denmark, Great Britain, France and Netherlands, which are the main patenting countries in enzyme technologies within the EU, several other EU Mem-

ber States are engaged in enzyme related innovation activities. These are Sweden, Finland, Italy, Spain, Belgium and Austria. However, most EU countries display a continuously decreasing trend in enzyme related patent applications since 2000. The only EU countries with growing patenting activities in enzymes are Denmark, Austria, Poland, Lithuania, Luxembourg and Cyprus. It is noteworthy that Poland and Lithuania, which started from a very low level in 2000-2004, could achieve increases in patenting activities by a factor of about 2,5 and 2,6 respectively.

A relatively large group of EU countries including Ireland, Portugal, Hungary and Czech Republic, Slovakia, Slovenia and Greece, displays quite low levels of registered patent filings in this field of technology having filed even less enzyme patents between 2010 and 2014 than during 2000-2004. During 2010-2014, the patent filing activities were extremely weak in Romania, Estonia, Latvia, Malta and Croatia.

Figure 19: EU Countries: Transnational Patent Applications in Enzymes



Data Source: Fraunhofer ISI based on WIPO

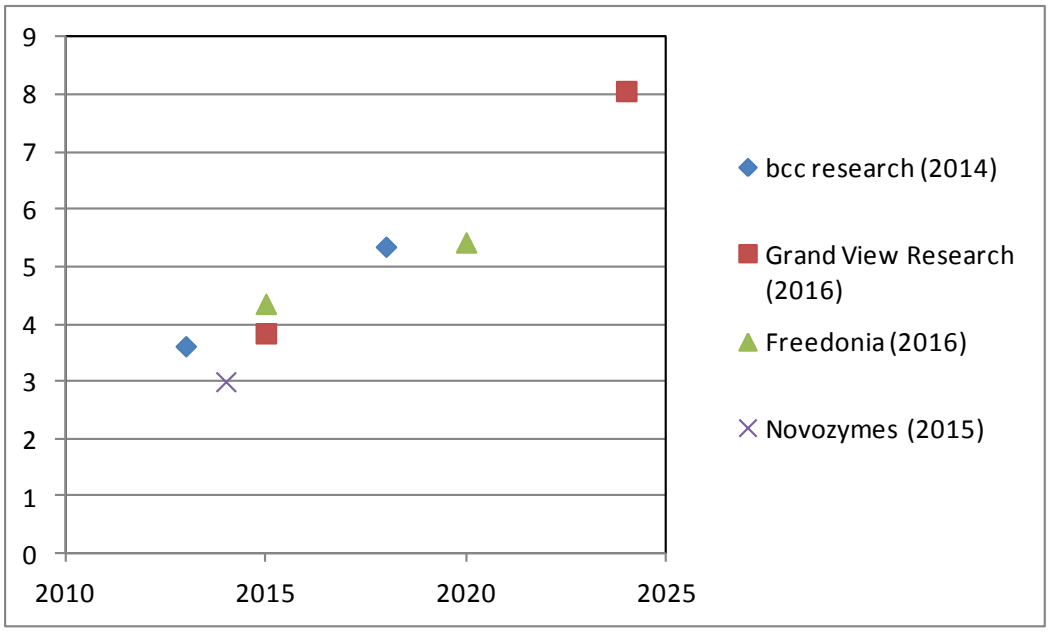
3.3.3.2 Market trends

Traditional enzymes industry is a very competitive, mature and settled market. There are more than 500 industrial products made by using enzymes as catalysts (Kumar 2013). Furthermore, recent scientific advancements in genetic engineering and biotechnology have accelerated a further uptake of enzymes in new application areas (e.g. biopharmaceuticals production), new products and process improvement (Scarlat et al. 2015). This includes introduction of new technologies and enzymes' increased efficiency at lower

temperatures or extreme pH conditions or decreasing costs by optimizing manufacturing processes by reducing energy and water consumption (Freedonia 2016). Also, chemical industry is increasingly opening up towards life sciences and increased use of enzymes in different production processes (Schmidt et al. 2002).

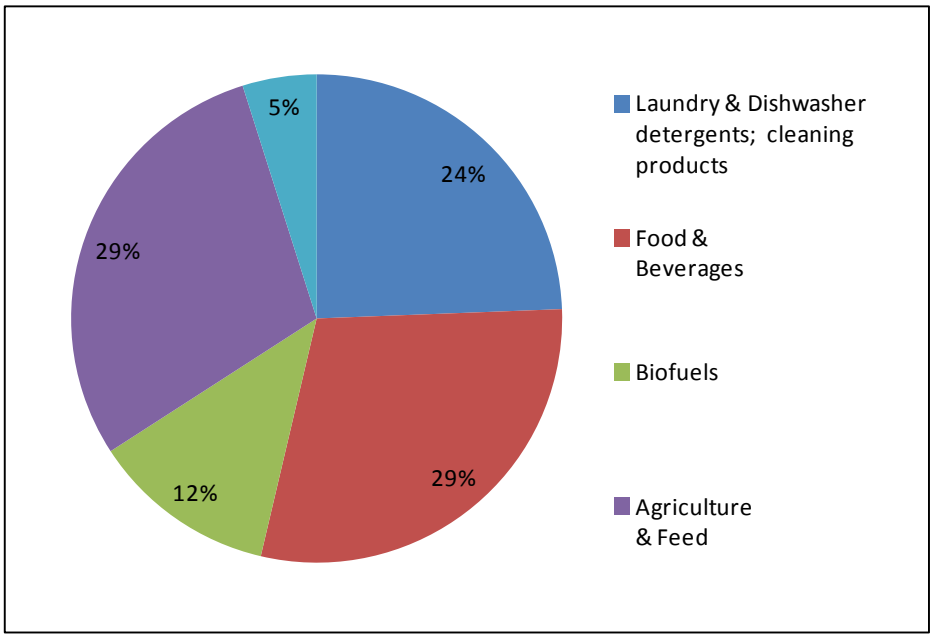
The global market for industrial enzymes was estimated to be around 4.2 billion US-Dollars in 2014 and was expected to reach 6.2 billion US-Dollars (Singh et al. 2016) to 7.2 billion US-Dollars (Freedonia 2016) by 2020 – at a compound annual growth rate (CAGR) of 7% (Singh et al. 2016). Other market studies' assessments of the enzymes market fall in with it and predict high growth for the next years (Figure 20). E.g. bcc research (2014) calculated 4.8 billion US-Dollars for 2013 and projected an increase to approximately 7.1 billion US-Dollars for the year 2018 (bcc research 2014). This would mean a CAGR of 8.2% from 2013 to 2018. Industrial enzymes are the largest market segment, at 72% (around 4.2 billion US-Dollars) in 2015 (Freedonia 2016).

Figure 20: Market estimations for enzymes (world market in billion Euros)



Source: Own calculations Fraunhofer ISI, data from sources mentioned in the figure

Figure 21: Share of segments for industrial enzymes (world market)



Source: Calculations based on Novozymes (2015)

Food and beverages are and will remain the largest market segment for enzymes, also other industrial enzymes markets are predicted to increase over the next years, except for biofuels (Freedonia 2016). The fastest growth of industrial enzymes market is expected to take place in developing countries along with per capita increase of incomes (Freedonia 2016). In Europe, Freedonia (2016) estimates that enzyme demand is likely to increase an average of 4% annually, whereas speciality enzymes will have higher increase compared to industrial enzymes (around 13% annually).

Specialty enzymes growth is above average, driven by increased interest of healthcare and pharmaceutical sectors in specialized enzymes. Out of specialized enzymes, the fastest growth will be for biocatalysts used in producing therapeutics (Freedonia 2016). This trend is partly driven by the rise of so called precision medicine practice, which would include an increased use of biopharmaceuticals and need for specific genetic testing, where specialized enzymes are largely used (Freedonia 2016).

North America and Europe are the two largest markets for industrial enzymes (Adrial 2014; Sarrouh et al. 2012). However, since 2005, Western Europe is losing its position to the Asia-Pacific Region. In general, enzyme markets in developed countries are near saturation whereas significant growth takes place in developing countries, where a growing middle class drives the demand for enzyme-related products. Western Europe has a strong position in enzyme R&D&I and production. It is the only net exporter of enzymes, distributing its products globally but also investing in production capacities in international growth markets. Nevertheless, there will be substantial competition from emerging enzyme producers, especially in the Asia-Pacific region.

Western Europe accounted for 20% of global enzymes market in 2015 (Freedonia 2016). The European market was estimated to be around 1.2 billion Euros 2012/2013 (Ambjerg 2012; Bio-Tic 2015b). The Bio-Tic (2015) study expects a market growth to around 1.8 billion Euros, which would imply a more moderate growth (< 3 p.a.) compared to the global market studies. The European market is dominated by Germany, France, the United Kingdom, Italy, the Netherlands and Spain, who account for around 80% of the enzymes market in Western Europe. Germany is the largest in Europe and fourth largest globally (Freedonia 2016).

3.3.3.3 Industry Structure and actors

Different players, ranging from small specialized biotechnology firms to major multinational chemical companies, are part of the European enzyme industry. A few large companies dominate the enzymes production market. However, a considerable number of SMEs are also active in R&D&I activities, especially as technology and service providers or in screening and designing novel enzymes. Overall, the required scientific-technological competencies are well present in private sector. The five biggest enzyme manufacturers are Novozymes, Dow-DuPont, Royal DSM, Roche and BASF that accounted for 61% of sales worldwide in 2015 (Freedonia 2016). However, only few of them are dedicated enzyme producers (i.e. Novozymes) next to large diversified multinational chemical and pharmaceutics companies (i.e. BASF, Dow-DuPont, Roche, Royal DSM).

Novozymes is the world's leading producer of industrial enzymes that operates in more than 40 different market segments. The company produced between 30% (Freedonia 2016) to 48% of the global enzymes in 2015 (Novozymes 2016). In 2014, the sales of Novozymes were around 4 billion US-Dollars (about 3 billion Euros) (Novozymes 2015).

Dow-DuPont has the second largest share of the market after Novozymes. The company is specialized on industrial enzymes production. Dow-DuPont is a chemicals company that is selling enzymes as secondary products (Freedonia 2016). Dow-DuPont gained a much stronger position on the enzymes market after acquisition of global enzymes company Danisco in 2011.[24]

Royal DSM is the third largest enzymes producer globally and focuses primary on industrial enzymes production as its primary product. Royal DSM is specialized in food and beverages market and is also active in biofules and feed enzymes market. Royal DSM is also active on the chemical market, like Dow-DuPont (Freedonia 2016).

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[24] http://investors.dupont.com/investor-relations/investor-news/investor-news-details/2011/Dow-DuPont-to-Acquire-Danisco-for-63-Billion/default.aspx

Roche held the fourth largest share of the global enzyme market in 2015. The company is specialized in speciality enzymes production and produces a major share of the world's polymerases, nucleases and other enzymes used in biotechnology and research markets.

BASF is the fifth biggest player in the global enzyme market (Freedonia 2016). In addition to a number of cooperative agreements, the company increased its presence by acquisition of a specialized enzymes company Verenium in 2013 to decrease the gap on market leaders Dow-DuPont and Novozymes in the enzyme industry (Bloomberg 2013).

All these companies play an important role in the global chemical industry and there is high competition between them to improve the quality and performance of their products. The companies mainly compete on product quality, performance, use of IP rights and innovativeness (Adrio 2014). The typical goals of companies on the enzymes market are to strengthen the current position and access new market segments.

For newcomers, high R&D&I investments present one of the main barriers for market entry in the enzymes industry. Capital spent on innovation will not create fast revenues in the short term. Therefore, it is especially critical for smaller players, who often lack resources to spend on R&D&I compared to large companies with a lot of resources. This situation can lead to collaborative agreements between small and large companies that are rather common in the enzymes industry. The main motivations for cooperative agreements are cost sharing, access to technologies and manufacturing capabilities. Different types of collaborative agreements in the enzymes industry include R&D&I agreements, licensing agreements, contract manufacturing (i.e. one party is responsible for manufacturing. Examples include New England Biolabs and Thermo Fischer Scientific; Novozymes and Royal DSM; Dow-DuPont and Quad County Corn Processors) and product agreements and joint ventures, but also to acquisitions. Acquisitions have been more dominant in the speciality enzymes market (rather than industrial enzymes market) over the past years by large companies that are motivated to increase their market share and access innovative enzymes related technologies. For example, Dow-DuPont acquired Danisco in 2011 and Dyadic's Industrial Technology in 2015, Merck acquired Sigma-Aldrich in 2015, and Thermo Fischer Scientific purchased Life Technologies in 2014 and finally Roche gained an ownership over Kapa Biosystems in 2015 (Freedonia 2016). Most of the other acquisitions have involved of a smaller enzyme business purchased by a larger company.

There are a number of different strategies that companies apply in enzymes industry in order to maintain or improve their competitive position. The choice of a strategy depends largely on whether the products differentiation is high and moderately cost-driven (i.e.

speciality enzymes), or commoditized and highly cost-driven (i.e. industrial enzymes) (Freedonia 2016). One of the dominant strategies, especially for resourceful large companies, is to increase product differentiation, by improving performance, product quality and process efficiency via costly R&D&I activities. As enzymes are extremely complex large molecules with hundreds of amino acids, there is a huge potential for different incremental advancements to improve their performance.

For more commoditized enzymes industry sub-markets, low-cost products present an alternative business strategy for producers especially in an industrial enzymes market with minimal innovation and established products portfolio (i.e. feed, cleaning products, food & beverages).

3.3.4 Policy and Framework Conditions

There are a number of EU regulations and policies in place that influence enzymes production and consumption.

Certain fields of applications are directly linked with specific policy targets. For example, a biofuel mandate in the EU, as the enzymatic production process of biofuels is often most favourable for such a conversion of biomass.

Furthermore, there are many regulations relevant for enzymes, used for food and beverages market, as they are intended for alimentary purposes. The regulations vary slightly between the Member States, but they all require that enzymes used for human consumption have to be safe, meet earlier unmet technological needs and must not mislead or confuse consumers (Freedonia 2016). Since 2003, the safety of food enzymes is assessed by the European Food Safety Authority. Furthermore, in the EU, a regulation is in place (Regulation (EC) No 1333/2008), which requires pre-approval of enzymes used for food and beverages production. This regulation on food enzymes, was fully applicable from January 2010 and harmonizes for the first time the rules for food enzymes in the EU.

According to Article 17(2) of Regulation (EC) No 1332/20081 interested parties may submit applications for the inclusion of a food enzyme in the European Union list. The deadline for submitting such applications started from 11 September 2011 and ended on 11 March 2015. The European Commission (2017b) received 301 applications for their inclusion in such list.

Also, enzyme applications in pharma and medicinal products depend heavily on regulation. Diagnostics is a growing field, where enzymes could be applied, development

greatly depends on framework conditions within the national health care systems, i.e. opening health care to more applications of telemedicine, decentralized health care etc. will lead to an increased demand for diagnostic enzymes. Market growth can be strongly hampered by the efforts to control health care costs in the Member States. This makes enzymes market strongly influenced by the EU political framework.

3.4 Production of Biopharmaceuticals

3.4.1 Description of the value chain

Biopharmaceuticals (or biologics) refer to large molecules from biological sources, which are a class of protein based drugs (e.g. hormones, antibodies) with a therapeutic effect on diseases, where usually no other alternative treatment options are available. They are often of human origin and manufactured in specifically engineered organisms. Compared to other bio-based industrial products, biopharmaceuticals are extremely high-value and very low-volume products. In the vast majority of published studies, the R&D&I process and market penetration of new molecules or biosimilars is in the focus of analysis. At the same time, the manufacturing stage (see Figure 22) (either for clinical trials for phase I-III of the R&D&I process or for the commercial production of biopharmaceuticals) is often neglected, even though a significant share of the added value of biopharmaceuticals comes from the manufacturing stage. Compared with the manufacturing of small molecule drugs, the manufacturing of larger biopharmaceutical molecules is much more important because it is inseparable from the safety and efficacy of the product, and also because of the higher unit cost. Production of biopharmaceuticals gives a competitive advantage to industrialized countries and regions (e.g. the EU) over developing countries, as the compliance with quality standards outweighs the importance of labour and production costs. Moreover, key decisions regarding the supply chain logistics, manufacturing technology development and use, quality assurance, costs, investment and outsourcing decisions are taken in the manufacturing part of the value chain, which makes it an important value chain segment to study.

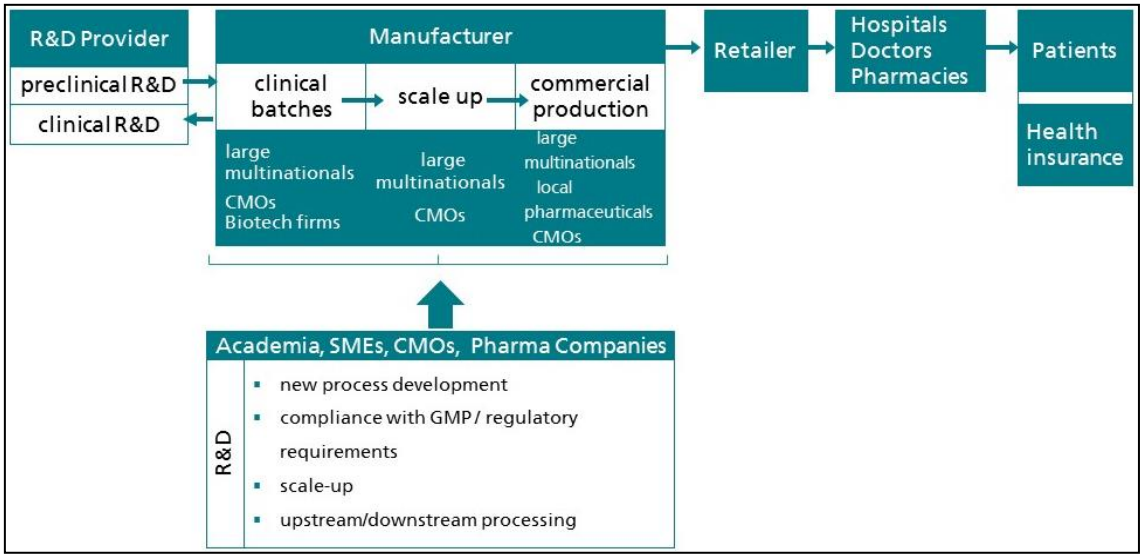
Production challenges can significantly impact the development process and its duration. Manufacturing of biopharmaceuticals is significantly more complex and costly than producing traditional chemical drugs or other bio-based products (Gennari et al. 2017; Behme 2015; Otto et al. 2015). The production of such a medicinal product has to be carried out in officially licensed, often tailor-made technically complex manufacturing facilities (Behme 2015).

While the R&D&I phase of biopharmaceuticals comes first, it stands in close relationship with the manufacturing process. The manufacturing process is fixed and has to be described in detail in the dossier that is submitted to regulatory authorities for gaining authorization of the product. Therefore, the details of the manufacturing processes have to be defined very early and will thereafter be changed only in exceptional cases. This means that in order to shorten the time to market, the manufacturing process has to be designed and planned in parallel to the drug development process (Behme 2015).

The actor landscape in production is divided into few groups and depends on the stage of production. Large multinational biopharmaceutical companies are active along the whole value chain, from development of new molecules to production and sales of biopharmaceuticals. However, high uncertainty, technological complexities and economic pressure lead to increasing cooperation between stakeholders along the value chain. For R&D&I they often collaborate with academia as well as partner with, or acquire multiple dedicated biotechnology firms (DBFs) where novel technologies can be drawn out of university laboratories and go through the initial tests of technical and commercial viability (Reynolds et al. 2016). While some of these firms possess production capacities for clinical batches, they usually do not have the necessary capabilities for scale-up. Instead, for manufacturing the large companies usually rely on contract manufacturing organizations (CMOs) at both early clinical stages and later scale up stages during the commercial phase.

Eventually, sales and marketing are commonly provided by large pharmaceutical companies, because of their access to markets and necessary resources to successfully introduce new products to the markets.

Figure 22: Value chain for biopharmaceutical production



3.4.2 Technology and innovation potential

The manufacturing of biopharmaceuticals requires highly complex and sophisticated production processes together with the necessary organisational procedures to ensure product quality, safety and compliance with regulatory standards. This implies high investments into production facilities: The standard in the past decades were often large

manufacturing facilities for a single product, equipped with large stainless-steel fermenters, with investment costs usually in the order of magnitude of 50 to 150 mio. Euros. As investment decisions already have to be made during the R&D&I phase of a novel biopharmaceutical in which the development to market approval may still fail, a large proportion of biopharmaceutical manufacturing is carried out in contract manufacturing organisations.

However, the concept of facilities for manufacturing of biopharmaceuticals is changing, due to the following factors:

The current processing paradigm of large scale cGMP manufacturing facilities dedicated to single product production is no longer needed for most biopharmaceuticals under present frame conditions. In order to stay competitive and to maintain the market share, innovations in manufacturing technologies are required.

There are high expectations around innovative technologies and processes that would support biopharmaceutical production. In particular, improvements in the following aspects are desirable: Continuous biomanufacturing is a manufacturing process where the products are automatically moved to the next step as each unit process is completed. It is currently dominated by small-scale perfusion and there are a number of issues around contamination risks and stability of production. There is a need and potential to develop equipment and instrumentation that would allow for integration of unit operations so that by using stable cell lines, continuous flow from raw material to finished product could be achieved on large scale production. Improvements in continuous manufacturing upstream processing (USP) are necessary for biomass concentration and control, oxygenation and ventilation. Further improvements in down-stream processing (DSP) would enable to implement a continuous purification process and non-chromatographic separation technologies.

Complementing or replacing the currently dominant “one line, one product” production mode by flexible multiple product operations, for example in the form of single-use bioreactors (SUS). SUS already exist in biomanufacturing and there is a trend towards higher use of SUS. Further developments would significantly improve SUS performance to scale up SUS production capacities and increase suitability for microbial processes. However, there is an additional need for the development of standards to increase compatibility of equipment solutions from different suppliers.

Over the last years, on-line process monitoring technologies have been developed, i.e. process analytical technologies (PATs). Further R&D&I in PATs is necessary in order to

enable non-invasive on-line and at-line monitoring of product quality in down-stream processes unit operations. It would enable process understanding to the extent that closed loop control feeding could be implemented.

New classes of biopharmaceuticals will be coming to the markets these years, especially bispecific monoclonal antibodies, and advanced therapy medicinal products (tissue engineered products, gene therapies, cell therapies). They have the potential to complement and even replace many biopharmaceuticals. Advanced medicinal products require the GMP manufacturing of DNA and cells rather than therapeutic proteins, so that manufacturing processes on industrial scale and in compliance with regulatory standards have to be implemented in order to be in a leading position to manufacture also this new class of therapeutics.

In 2014, the vast majority of biopharmaceuticals (104 of 240; 43 %) were produced with the help of bacteria and yeast, followed by mammalian cell cultures (35 %), chicken eggs (14 %), human cell cultures (8 %) and insect cell cultures (2 %) (Kaltwasser 2016). Only two (0.8 %) biopharmaceuticals were produced in transgenic animals. Against this background, innovation potential lies in the establishment of alternative production systems. However, comparative advantages over existing production systems must outweigh the additional efforts to bring novel production systems to the maturity level required for assuring quality of the product, compliance with Good Manufacturing Practice (GMP) and approval by the authorities. Of specific interest are production systems based on human cells and cell lines, transgenic crop plants, cell-free production systems (Ogonah et al. 2017) and systems which allow the tailored glycosylation of therapeutic proteins. These systems have specific strengths in non-immunogenicity, in reduced risk for human pathogen contamination, in scale-up, distributed manufacturing schemes, for therapeutic proteins which are difficult to express in established production systems (e.g. cytotoxic substances, membrane proteins).

3.4.3 Economic analysis

3.4.3.1 Market trends

The volume of biopharmaceuticals to be produced is mainly dependent on the development, approval and reimbursement of new biopharmaceuticals or biosimilars. Production costs represent only a minor share of costs compared to R&D&I related investments and market diffusion is very little cost-driven.

The biopharmaceutical industry can be characterized by full recovery from recent global economic crisis and has demonstrated a stable growth over the last years that will continue for the near future (McKinsey 2014). In comparison to small molecule drugs, biopharmaceuticals are occupying an increasingly larger market share, both in terms of numbers and percentage.

The value chain in the biopharmaceutical industry is highly globalized. While R&D&I for new products (new molecules, bisoimilars) and production for clinical batches are closely interwoven and co-localization offers clear advantages (Reynolds 2011), localization of commercial production is not necessarily geographically coupled to R&D. Currently, Europe possesses around 32 % of the biopharmaceuticals production capacity, while North America is leading with around 52 %, and Asia produces around 16 % (Seymour / Ecker 2017). Details on the capacities of those facilities are not publicly available. In Europe, Germany is the leading location. While many EU countries have at least one facility, there is a clear concentration towards western European countries.[25] For the future, experts do not expect a rise of new facilities in Europe, but an expansion of existing ones.

On average, investing in biotechnology R&D&I has generated higher profits than the pharmaceutical industry average returns (McKinsey 2014). The global market for biopharmaceuticals is exceeding 200 billion US-Dollars, out of which the recombinant protein market is more than 150 billion US-Dollars (BioPlan Associates. Inc. 2016). The expected annual growth rate for the biopharmaceutical market is between 8% and 15% (BioPlan Associates. Inc. 2016; McKinsey&Company 2014) and thus above the average economic growth. A large part of it is due to sales of a growing number of recombinant monoclonal antibodies, whose market is estimated to be about 50 billion US-Dollars (BioPlan Associates. Inc. 2016). Oncology and infectious diseases drugs are the most active areas in the biopharmaceuticals' R&D&I pipeline – with more than 5,000 and 3,000 products respectively in development (BioPlan Associates. Inc. 2016). The main driver for this development is that biopharmaceuticals offer often significantly higher treatment efficacy compared to small-molecule drugs and enable the treatment of previously incurable conditions, which creates a high demand for these type of new drugs.

Since most biopharmaceuticals are used for indications for which there are few, if any, alternatives, the overall market is rather protected from widespread cost-containment and controls (BioPlan Associates. Inc. 2016). However, due to increasing economic concerns, all pharmaceuticals, particularly biopharmaceuticals, which tend to be the most expensive, face increasing cost containment and control efforts worldwide. Moreover, national healthcare systems are often not able to afford these expensive drugs due to

[25] http://top1000bio.com/

their underfinanced and restricted budgets. Therefore, there is an urgent need on the market for alternative ways to fulfill demand for innovative products with affordable prices

Concerning manufacturing, the cost of goods of biopharmaceutical products are currently estimated to represent between 10 and 25% of the sales price of the drug. For monoclonal antibodies, rising productivities have seen this figure fall significantly such that the cost of production is now less than 5% of the selling price in some cases (Alldreach/ Robinson 2015). Hence, the manufacturing costs are limited compared to turnover. However, there are some indications (e.g. see below biosimilar market) that manufacturing costs and hurdles present a more important barrier for biopharmaceuticals than for small molecules. Potential cost reductions are mainly dependent on technological advantage as regulatory relaxations or offshore activities in low-cost country in large manner are not likely in the near future.

Biosimilars

Implications for manufacturing also occur from the growth of biosimilars. Biosimilars are biopharmaceutical products that are almost identical to original drugs, but manufactured by a different producer after the original drug's patent has expired. By 2021, 70-80 billion US-Dollars worth of highly priced best-selling biopharmaceuticals are scheduled to have their patents expired (Frost&Sullivan 2017). This has led to a rapid development of the biosimilars industry. The global biosimilars market is expected to reach 24 billion US-Dollars by 2019 at a compound annual growth rate (CAGR) of more than 60% (Frost&Sullivan 2014). In Europe, the first biosimilar was approved in 2006 and, by 2016, 20 biosimilars were available on the EU market (Rémusta et al. 2017). The European biosimilars market is the largest globally, with a share of 49% (in 2014), out of which Germany has the largest share (around 57%) (Frost&Sulivan 2017). But also emerging countries with extremely limited healthcare budgets show growing interest in biosimilars and new players from developing countries (e.g. China, India) have been recently entering the biosimilars R&D&I market (BioPlan Associates. Inc. 2016).

The development of biosimilars adds a new dimension to the pressures on biopharmaceutical manufacturing costs. Biosimilars are estimated to have only limited potential for cost reductions (compared to generics for small molecule drugs), but at the same time their market segment is rather price sensitive. Specific manufacturing challenges include lack of access to the biologic cell line of the reference product and lack of detailed information on the manufacturing process (e.g. fermentation, purification etc).

3.4.3.2 Industry Structure and Actors

Large established multinational pharmaceutical companies drive the biopharmaceutical industry. These includes world's leading pharmaceutical firms who have forcefully shifted their focus onto large molecule drugs (biologics) in the last decade. Table 4 shows that e.g. Sanofi-Aventis generates 53 % from its revenue from biopharma in 2012 (right column). The left column states that this share increased by 53 % from 2010-2012, meaning that the share of revenue from biopharma was close to zero in 2010.

Table 4: Change of revenues (%) between 2010-2012 to biopharmaceuticals

Company	Change in percentage of revenues from biopharma 2000-2012	Share of revenue (%) of biopharma in 2012
Sanofi-Aventis	53%	53%
F. Hoffmann-La Roche	53%	79%
AbbVie	52%	52%
Pfizer	29%	29%
Bristol-Myers Squibb	23%	23%

Source: adapted from Otto et al. 2014

Manufacturing of biopharmaceuticals is a much more complex process than producing traditional small-molecule pharmaceuticals (Gennari et al. 2017). Therefore, in parallel, these multinationals have become increasingly dependent on CMOs and dedicated biotechnology firms (DBFs) in order to acquire the necessary additional capabilities, as the internal capabilities of even the most powerful pharmaceutical firms are not sufficient to develop, manufacture and market these new and innovative technologies by themselves (Gennari et al. 2017).

The main reason for outsourcing is being able to balance risk in biopharmaceutical companies, e.g. only after the achievement of key milestones in clinical trials or market uptake are met they can justify investing in-house. High investments are required. The cost of constructing a traditional biopharmaceutical plant is in the order of tens of millions (US-Dollar) for medium sized (1000–5000 l) facilities to hundreds of millions for larger ones (10,000–200,000 l) (Allbread / Robinson 2015). Other key reasons for outsourcing are lack of own capabilities (e.g. in cell line development, process development and scale-up) and the higher flexibility (lower fixed costs, etc.) (Gennari et al. 2017).

The CMOs most often provide to pharmaceutical companies specific services (e.g. analytical testing, bioassays, fill/finish operations, clinical trials, validation services) that they are specialized in. The market share of biopharma CMOs has risen steadily in this market segment in the past decade, and it is expected to reach 7 billion US-Dollars in 2019 (Gennari et al. 2017).

Some large firms act as so-called 'Excess companies' (i.e. companies that are developing products, but also sell or make available any excess manufacturing capacity), as for example Böhringer-Ingelheim.

Currently, a majority of the production capacity is still owned by product companies (companies focused on product development). They hold approximately 73% of the installed mammalian cell culture capacity, while Excess companies and CMOs control significantly less capacity (13% and 14%, respectively). The forecasted distribution of capacity changes only slightly for 2021, with Product companies holding 68% of the installed capacity, while CMO companies will increase to 15% and Excess companies to 17% of the capacity (Seymour / Ecker 2017).

The market share of CMOs has been constantly increasing over the last years. Despite profit margins of more than 30 percent in the biopharma CMO sector versus up to 10 percent in the traditional pharma market (Gennari et al. 2017), there is still a shortage of CMOs.

A lack of production capacity exists in the biopharma industry in particular for large-volume biopharma drug substances. This is due to the fact that there are few CMOs with large reactor lines and that brand owners prioritise their own products (Otto et al. 2015).

There are a number of other reasons that inhibit CMOs from successfully entering the biopharma market. One of the main challenges is the lack of qualified staff and the high investments required to prepare high skilled biopharma experts with multidisciplinary background, necessary to manage the necessary start-up, biomanufacturing and product transfer capacities (Gennari et al. 2017).

For low-volume production the picture looks different, as market entry barriers are lower. Market forecasts indicate a strong trend towards low-volume manufacturing as productivity continues to increase, biopharmaceuticals become more effective (requiring lower doses), and treat more niche indications (Gennari et al. 2017).

Europe is the second largest biopharmaceutical contract manufacturing (CM) market trailing behind the US (Frost & Sullivan 2013). The European CM market is a highly concentrated market with two companies (Lonza and Boehringer-Ingelheim) controlling

nearly 70 per cent of the share, both in terms of sales revenue and manufacturing capacity (Frost & Sullivan 2013). Other production facilities are mostly controlled by mid-sized firms, while SMEs are hardly present as manufacturers. [26]

Outsourcing to emerging markets is relatively limited as most of the market is in the US and Europe (Gennari et al. 2017), and also because of IPR issues, ensuring a high-quality product and gaining relevant approvals . E.g., currently, no authorized production of biopharmaceuticals for the US and European market takes place in China and large multinationals have not built up any production capacities for biopharmaceuticals there. However, there are some signs that CMOs based in emerging markets will continue to capture market share, albeit slowly (Quing et al. 2016).

3.4.4 Policy and Framework Conditions

The Pharmaceutical sector is one of the most highly regulated sectors in the world. The main regulation instrument is the so-called Good Manufacturing Practice (GMP). The GMP describes the minimum standard that a medicines manufacturer must meet in their production processes. GMP requires that medicines 1) have consistent high quality, 2) are appropriate for their intended use and 3) meet the requirements of the marketing authorization or clinical trial authorization (European Commission 2017c). Across the world, many countries have legislated that pharmaceutical manufacturers follow GMP procedures. In Europe, various EC regulations, directives and guidelines lay down the principles of GMP in the EU. The EU GMP guidelines provide interpretation of these principles (EMA 2016). Any manufacturer of medicines intended for the EU market must comply with GMP, irrespective of the location of production. The inspections to verify compliance with the EU standards is coordinated by the European Medicines Agency (EMA) (EMA 2016). The two key legal instruments applying to GMP of active substances and medicines for human use are Regulation No. 1252/2014[27] and Directive 2003/94/EC[28].

However, the regulatory framework is currently, facing certain challenges regarding harmonization. Biopharmaceuticals is a worldwide business and globally there are around 20 different GMPs implemented. The lack of international harmonization of regulations causes uncertainty for globally operating manufacturers (GM 2017). As mentioned

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[26] http://top1000bio.com/

[27] http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32014R1252

[28] http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2003:262:0022:0026:en:PDF

above, currently no finished biopharmaceutical produced in China is allowed to be exported to the EU or the US because of lack of compliance with authorization requirements (Qing et al. 2016).

In addition, there is a trend towards “zero risk”, when it comes to biopharmaceuticals manufacturing – i.e. regulation for building manufacturing facilities and operating them without any contamination. This has made risk assessment, management and mitigation one of the top priorities for manufacturers (GMP 2017)

A review of price regulations and authorization procedures and their impact is out of the scope of this analysis. However, concerning the whole value chain of biopharmaceuticals, regulations that influence the authorization and reimbursement of biopharmaceuticals are of key importance. Generally it can be stated that currently, majority of biopharmaceuticals on the market are used for patients, for whom there are often no alternative treatment options available. Therefore, the biopharmaceuticals market is rather well protected from widespread cost-containment and controls in the EU (BioPlan Accociates 2014). However, it is very likely that cost will become a major obstacle regarding authorization and market access, because of constraints in public budget and rather high costs of biopharmaceuticals.

Regarding biosimilars, across the world, it is very challenging for regulatory authorities to guarantee the similarity of biosimilars to the original drugs. The approval process for biosimilars in Europe is very long and pricing varies across the EU according to the different drug policies in different EU Member States (Frost&Sullivan 2017). However, the European Commission has initiated a Project Group on Market Access and Uptake of Biosimilars, to facilitate and promote uptake of biosimilars within the EU (Rémusta et al. 2017).

3.5 Biotechnologically produced Flavors and Fragrances

3.5.1 Description of the Value Chain

Flavors and fragrances (F&F) are a very large group of substances of very different molecular structure and different chemical functional groups, e.g. polyketides, nonribosomal proteins, saccharides, alkaloids, terpenoids, and many more. These substances are characterized by their potential to sensitize the receptor cells of the human olfactory system which mediate the senses smell and taste. Many natural aromas are complex mixtures of hundreds of different compounds.

F&F are widely used in a broad range of industries and products, such as food and beverage, pharmaceuticals, perfumes and cosmetics, toiletries, tobacco, detergents and household products.

Often, only very small amounts of F&F (in the parts per billion range) are sufficient for triggering smell and taste. From an economic point of view, F&F are only minor components in a final product, but may represent a large share of the cost of the final product and may be the decisive factor for customers' purchasing decisions. The F&F value chain therefore represents a (very) low volume - high value product group.

There are three major routes for industrial production of F&F:

- Extraction from their natural source (e.g. plant material)
- Chemical synthesis or chemical transformation of precursors
- Biotechnological production methods. Biotechnological production routes are de novo biosynthesis, biotransformation and bioconversion of precursors, and synthetic biochemistry (for more details, see below).

Each route has specific strengths and weaknesses (see Table 5). In the PROGRESS project, the focus is on the biotechnological production methods that can be employed in industrial biotechnology. Biotechnological approaches which are targeted at the plant material as a source for extraction (e.g. breeding, agricultural cultivation) are outside the scope of this chapter. As will be described in more detail in the following section, a significant innovation potential lies in biotechnological production methods which could either complement or replace extraction or chemical synthesis or make novel aromas and products possible that cannot be produced by other routes.

Table 5: Overview of major routes of industrial F&F production, their characteristics, and their specific strengths and weaknesses

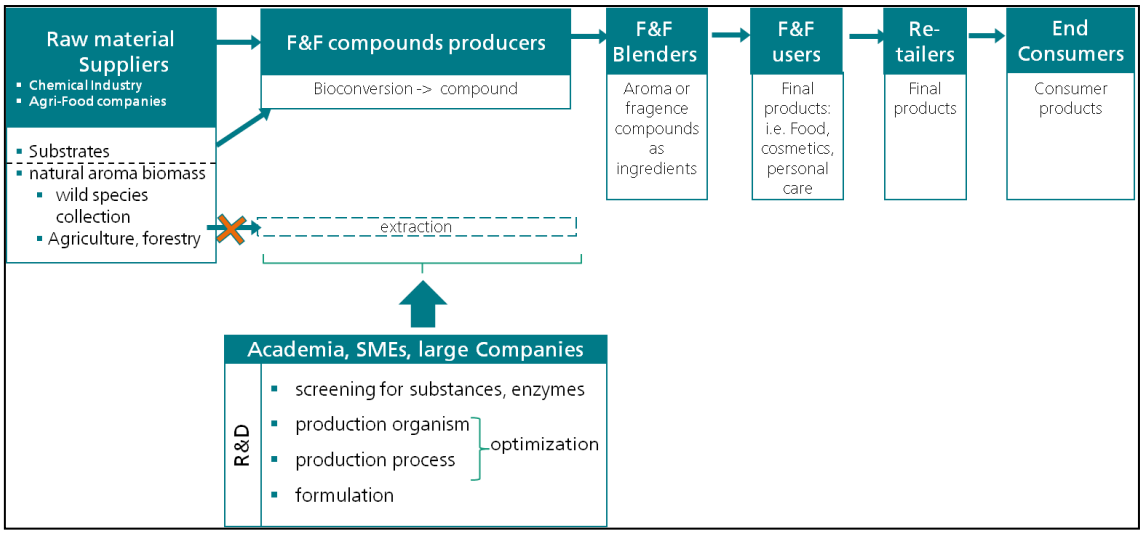
Extraction from natural sources	Chemical synthesis	Biotechnological production
aroma often a complex mixture	aroma made up of one or few major components	aroma may be a complex mixture or aroma made up of one or few major components
aroma produced under natural conditions by the source organism	F&F chemically synthetised de novo or from precursors	F&F biotechnologically synthetised de novo from substrates such as glucose or from precursors
good sensory quality	may produce racemic mixtures composed of enantiomers/regio-isomers with different sensory properties	sensory quality depends on the aroma composition
may be labelled as "natural"	must not be labelled as "natural"	may be labelled as "natural"
highly appreciated by consumers	trend to avoid "artificial" F&F	label "natural" highly appreciated by consumers, but they may have a different expectation/understanding of the production method
relatively high market prices	low market prices	medium market prices
limited or fluctuating availability of natural sources, depending on seasonal, environmental and (geo)political conditions	very good availability, meets demand	very good availability, meets demand
in case of wild collections or endangered species as sources: limited supply, negative impact on biodiversity		
low concentrations in the feedstock, leading to high extraction and purification costs	purification costs low; may be higher if racemic mixtures have to be separated	purification costs low, if high titers can be achieved
fluctuating quality, depending on seasonal and environmental conditions		
extraction may use environmentally unfavourable solvents		

Source: Own compilation of information from Bicas et al. 2016

The value chain is rather similar for all three major production routes, and mainly differs in the early stages of supply of raw materials. In the case of biotechnological production

methods, the starting material for many different products may be a fermentation substrate, such as glucose, or a precursor, which is then converted by biotechnological production routes to the F&F compounds. The biotechnologically produced compounds are usually blended and the formulations are sold to the various F&F user industries. Usually, considerable R&D&I activities are necessary. Large F&F firms usually cover many of the steps of the value chain (Figure 23). For a F&F supplier, it is of high importance to control the entire production chain, from raw materials to final products, and to know the customer trends and the flavors in fashion (Brenna und Parmeggiani 2017). Small firms may cover certain steps of the value chain.

Figure 23: Value chain for biotechnological Flavors & Fragrances



3.5.2 Technology and innovation potential

In this chapter, the innovation potential of biotechnological production of F&F will be outlined, followed by an overview of the technologies required.

3.5.2.1 Biotechnological methods for the industrial production of F&F

Biotechnological methods for the industrial production of F&F comprise:

- *De novo* biosynthesis. This means the synthesis of the target compound by production organisms from simple substrates, e.g. sugars. The substrates are metabolized via complex metabolic pathways to form different and complex structures. *De novo* biosynthesis is the method of choice in complex conversions, if mixtures of products are to be produced, or if transformations of simpler substrates involve a large number of reactions to obtain the final product or if biosynthesis requires the regeneration of cofactors. The titres that can be achieved are usually below 100 mg/L, unless the

production organisms are engineered for higher titres, yields and production rates (see below).

- Biotransformation. In biotransformation, a single biocatalysed reaction is performed. It converts a precursor to a structurally similar molecule. This reaction is usually a breakdown or an oxidation/reduction reaction. Biotransformations are often done *in vitro* with isolated enzymes. Due to the lower complexity, biotransformations have a higher potential for the production on a commercial scale than de novo biosynthesis. Several F&F with annual production volumes of one to several tons are produced by biotransformation, e.g. vanillin from ferulic acid, 4-decanolide from ricinoleic acid, 2-phenylethanol from phenylalanin.
- Bioconversion. Bioconversion is similar to biotransformation, but comprises several (not only one) biocatalysed reactions, to convert a precursor to a structurally similar molecule.
- Synthetic biochemistry. The term "synthetic biochemistry" (Korman 2017) means cell-free systems designed to perform complex chemical conversions. Usually, purified or crude preparations of enzymes are mixed in a reaction vessel. As the complex regulatory systems and replenishing systems for cofactors and energy of living cells are not functional in these approaches, the reaction can only be performed for limited periods of time. Synthetic biochemistry falls between *de novo* biosynthesis and bioconversions. Synthetic biochemistry is an alternative to the metabolic engineering of living cells for de novo biosynthesis for complex molecules that are difficult to produce *in vivo*, e.g. due to their toxicity.

Organisms usually employed in biotechnological production of F&F are bacteria and fungi and to a limited extent plant cell cultures, as callus, plant cell or tissue culture showed reduced or no ability to produce volatiles, as compared to the intact plant (Brenna und Parmeggiani 2017, p. 275). Emerging production organisms are algae and photosynthetic bacteria. In addition, isolated enzymes from a large variety of sources are used. Fungi are more often employed in biotransformations than bacteria (Bicas et al. 2016).

3.5.2.2 Innovation potential

In general, the plethora of flavors and fragrances which are naturally synthesized by living organisms has not yet been exploited by industry: more than 6,500 volatiles have been identified in natural flavours and fragrances, whereas only 300 aroma compounds are produced industrially. Approximately 200 of these 300 compounds are synthetised chemically (Bicas et al. 2016, p. 314). Currently, less than 10 % of the F&F supply is derived from bioprocesses (Bicas et al. 2016, p. 327).

Challenges and strategic goals in the F&F industry and their business customers are to provide products to consumers which satisfy the demand for natural products (especially

food and personal care) without additives, for healthy but tasty convenience food (food low in sugar/fat/salt requires more flavors), for more sustainable production, including no chemistry or green chemistry, and for corporate social responsibility, e.g. with respect to maintaining biodiversity. Biotechnological production of F&F is well positioned to significantly contribute to these strategic goals: By substituting F&F extraction from natural sources or chemical synthesis by biotechnological production, limitations and disadvantages of these production methods could be overcome, and the advantages of the biotechnological production route could be exploited (Vespermann et al. 2017; see also Table 5 and Table 6):

- Label "natural". According to EU legislation, biotechnologically produced F&F may be labelled as "natural": natural flavors are chemical compounds with aroma properties, obtained from the raw material of animal or vegetable origin or by physical, enzymatic or microbiological methods. This property is highly appreciated by consumers, and premium prices may be charged for natural F&F.
- Stable supply. Biotechnological production could provide a stable supply of F&F and meet the growing demand: in contrast to extraction of F&F from natural sources, it does not depend on the fluctuating availability and quality of (scarce) raw materials whose supply may be limited by climatic and geopolitical factors or may have negative effects on biodiversity.
- Green chemistry. Biotechnological production complies with the principles of Green Chemistry. In general, milder conditions than in chemical synthesis are employed, fewer residues are generated, and better regio- and enantioselectivity can be achieved, often leading to enantiopure products with better sensory properties and lower purification costs than the racemic mixtures often obtained by chemical synthesis.
- Circular economy, waste as substrate. Biotechnological production of F&F bears the potential to valorise lignocellulose and waste fractions, e.g. to use agro-industrial wastes for the production of aroma (e.g. terpenes in waste from fruit and vegetable processing).
- Broadening the spectrum of industrially relevant F&F compounds. Biotechnological methods bear the potential to generate IP by identifying and producing novel aroma compounds not yet known or available to the F&F industry, and by novel combinations of aroma compounds to generate new scents and tastes. A largely untapped innovation potential lies in accessing new chemical space in the form of F&F compounds not found in nature. They could be made available by combinations of enzymes or metabolic pathways which are not found in this form in nature (Zebec et al. 2016), and by chemically modifying biotechnologically produced compounds.
- Other applications than F&F. F&F substances fulfil a broad range of biological functions in their natural hosts. If these compounds could be produced biotechnologically in higher amounts and at reasonable cost, other applications than the use as F&F will

become economically attractive which go far beyond the F&F sector. Depending on the molecules of interest, the applications range from pharmaceutical substances and antibiotics to health-promoting food, to pesticides and crop-protecting agents, to fine and bulk chemicals and biofuels.

- Revitalization of natural product research. F&F research into biotechnological production uses a toolbox of approaches, methods and technologies which can be applied in natural product research in general, and is not restricted to F&F. As will be outlined in the following chapter, significant advances in this toolbox have been and are being achieved that are considered suitable for revitalizing natural product research (Breitling / Takano 2016; Smanski et al. 2017). Advancing the F&F toolbox could therefore also be fruitfully be applied in other fields of natural product research, and vice versa.

Table 6: Driving forces to use biotechnological methods in flavor production

Market pull	Technology push
Increasing consumer demand for "organic", "bio", "healthy" and "natural"	High chemo-, regio- and stereoselectivities of biocatalytic systems
Industrial dependence on distant (frequently overseas), undesired or limited raw materials	Sustainability of bioprocesses
Search for natural character impact compounds	Improved biocatalysts by evolutionary and rational enzyme and metabolic engineering
Search for natural flavour compounds with additional functionalities (e.g. antimicrobial properties)	Improved down-stream processing, especially in situ product recovery techniques

Source: Dubal et al. 2008

3.5.2.3 Technology potential

F&F, often products of secondary metabolism, are present in very low concentrations in the range of µg to mg/L in their natural sources. Moreover, the natural sources are most often organisms that cannot be used in industrial production. Therefore, the major challenge for realizing these innovation potentials of biotechnological production of F&F compounds is to achieve sufficiently high titers, yields and production rates of the respective compounds in heterologous production systems (Bicas et al. 2016, p. 317; Korman et al. 2017). Up to now, they have only been realized in exceptional cases. As a rule of thumb, a biotechnologically produced aroma in the (medium) price range of 100 to 500 US$/kg would, to be economically viable, require titers of 1 g/L or above in the production process. Without advanced engineering, however, only titers in the mg/L range can usually be achieved.

The following reasons for the usually low production levels for F&F have to be addressed in R&D:

- Technically challenging, intrinsical properties of F&F precursors or F&F compounds, such as volatility, chemical instability, low solubility, resulting in low bioavailability, and toxicity to microbial cells.
- Difficult biosynthetic pathway optimization due to the need
  - to engineer central metabolic pathways which provide precursors for the F&F of interest, and to reduce flux through competing endogenous pathways, and to increase flux through the relevant metabolic pathway
  - to establish a regulatory systems which maintains the flux through the engineered pathways
  - to balance the supply of ATP and NAD(P)H,
- Toxicity of F&F intermediates or F&F products, leading to cell death before higher titers of the target substance can be achieved
- Expensive product isolation from complex growth media
- *in vitro* approaches (biotransformation, bioconversion, and synthetic biochemistry) suffer from short biocatalyst lifetime, long incubation times, and resulting high production costs.

In the past, general R&D&I strategies have been developed for natural product research, including F&F. They comprise the following steps (Bian et al. 2017):

- direct isolation and characterization of the target compounds from their natural sources,
- construction of mutants and screening for overproducers, to evaluate the contributions of enzymes to the yield of the target compounds,
- characterization of the relevant biosynthetic route, including suitable biocatalysts
- cloning of corresponding genes, assembly into expression vectors,
- selecting the best production host strain
- assessing the heterologous expression of each part within an assembled pathway and optimize the concerted enzyme expression,
- optimizing genes (e.g. promotor strengths, codon usage) and enzymes (by protein engineering)
- understanding and decreasing of side reactions
- optimizing the cofactor availability

However, these "classical" strategies are often too time- and resource consuming and thus expensive to allow their application to the development of F&F with limited market sizes. In recent years, concepts and technologies have been developed and proven effective which significantly speed up the screening and optimization process, especially

by avoiding laborious and iterative rounds of construction of mutants and their screening and selection for overproducers.

Significant progress and technological potential lie in the combined and synergistic application of different strategies and approaches.

For the screening for novel compounds of interest and novel biosynthetic pathways and enzymes, the classical screening procedures can be complemented by high-throughput screening approaches and genome mining. The latter builds on the achievements of whole genome sequencing which have made large and comprehensive genomic data available for a large number of species. These databases can be searched for genes involved in the biosynthesis of F&F and identified using bioinformatic tools. However, there is an urgent need to narrow down the immense genomic diversity to a limited number of biosynthetic pathways which can be evaluated. This is expected from the synergistic combination of progress in synthetic biology, synthetic biochemistry, mass spectrometry and computational tools (Medema /Fischbach 2015).

For metabolic engineering of production organisms, the state of the art consists on applying the design - build - test - approach of systems metabolic engineering (Becker / Wittmann 2016; Chen et al. 2017; Hansen et al. 2017). However, the process of optimizing F&F production can additionally be significantly speeded up if much of the pathway optimizing work is not done *in vivo*, but *in vitro*: This approach can be applied to the optimization of individual enzyme-catalysed reactions, their combinations in newly designed pathways, or in enzyme engineering. Each of these optimization steps can be supported and guided by appropriate bioinformatic tools. The benefit of *in vitro* optimization is especially relevant if it can be coupled with high-throughput screening or characterizing of the resulting species, and with combinatorial approaches.

For the optimization of key enzymes of F&F biosynthetic pathways or for generating a greater diversity of key enzymes, rational design and site-directed mutagenesis, combinatorial approaches of (sub)domain swapping, and evolutionary strategies are expected to deliver a greater spectrum of improved enzymes with respect to their substrate specificity, long-term activity and stability and other production-relevant parameters (Winkler 2017).

For reducing the toxicity of F&F intermediates and target compounds, strategies have been developed which aim at keeping the concentration of the compound below toxic limits. In order to achieve higher tolerance of the production organism, the activity of uptake systems for the respective substance can be reduced, or the activity of efflux pumps be enhanced. Another strategy is the compartmentalization of the pathway, thus reducing the active concentration and intrinsic toxicity of the produced chemical or the

pathway intermediates. Suitable compartments that are being explored for this purpose include peroxisomes in yeast and proteinaceous micro-compartments in bacteria. These strategies targeted at the production organism can be complemented by process design and engineering strategies: solutions to overcome product inhibition comprise biphasic systems, to facilitate the diffusion of the product to the extracellular medium, and *in situ* product recovery.

With optimized production hosts and state of the art process design and equipment, the environmental performance of production processes for F&F could be significantly enhanced by minimizing energy demand, use of solvents, water demand and waste water production, use of hazardous substances and production of side products.

The greater the available diversity of enzymes and pathways for F&F, the easier it will be to expand the chemical space of F&F, also to substances not found in nature. This can be achieved by developing promiscuous key enzymes which convert different precursors, by applying enzymes which introduce different modifications into the "standard" F&F molecule, by combining different metabolic pathways, or by mixing different F&F substances to novel aromas.

Taken together, the technological potentials lie in

- significantly speeding up the R&D&I process for biotechnologically produced F&F and to establish toolboxes and strategies that can be applied in natural product research,
- achieving industrially relevant titers, yields and production rates,
- making a greater diversity of F&F available to industry, also novel ones not found in nature, and
- establishing universal platforms of substances, production organisms and enzymes, that can readily applied in F&F and natural substances research.

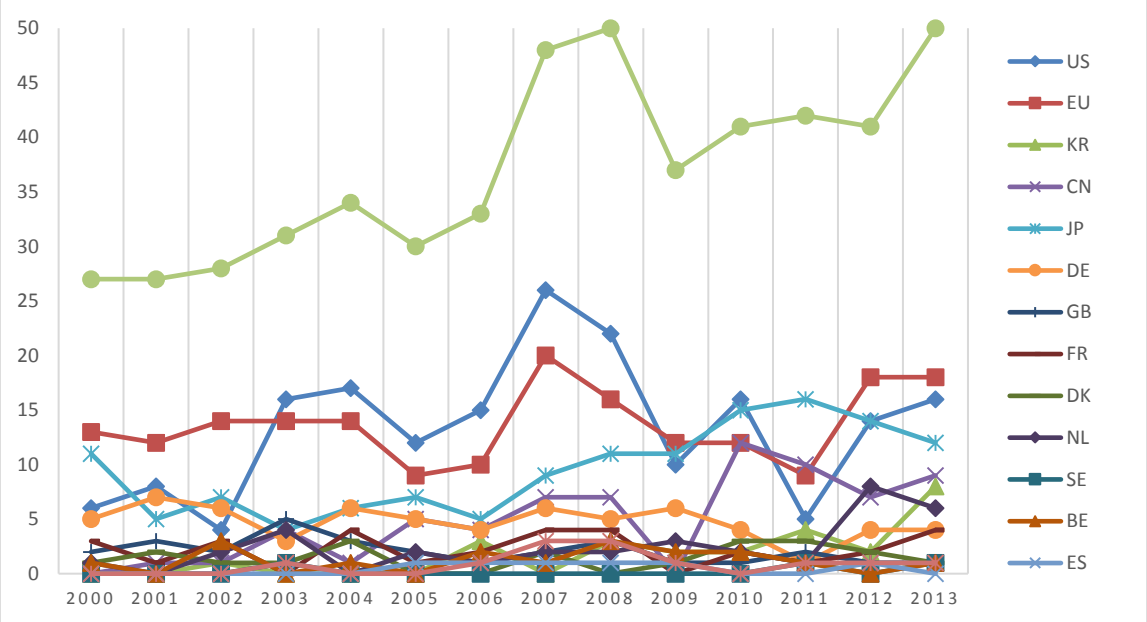
3.5.3 Economic analysis

3.5.3.1 Patent Analysis

The worldwide patenting activities in F&F are concentrated in a few regions, indicating that only a few countries are specialized in this field of technology. Between 2000 and 2014, the highest number of patent applications in F&F to the WIPO was recorded for the US, followed by the EU, Japan and China (see Figure 24). The most substantial growth achieved China by increasing the overall number of patent filings in F&F from 1 in 2001 to 12 in 2013.

Over the period 2000-2013, there was a steady growth of patenting activities in the most countries with recorded inventing activities in F&F. The number of patent applications worldwide rose at the rate of nearly 5% per year between 2000 and 2013. The highest increases were achieved in the US, China, the Netherlands, and the EU as a whole. After the patenting intensity across countries reached its peak in 2007, it dropped dramatically in 2009, but has been gaining momentum since then. Between 2010 and 2013, the highest average annual growth in patenting activities was registered in South Korea, Netherlands and France. In contrast to this situation, Denmark, Belgium, China and Japan show a somewhat negative development in terms of the number of patent applications in F&F since 2011.

Figure 24: Transnational patent applications in Flavors & Fragrances

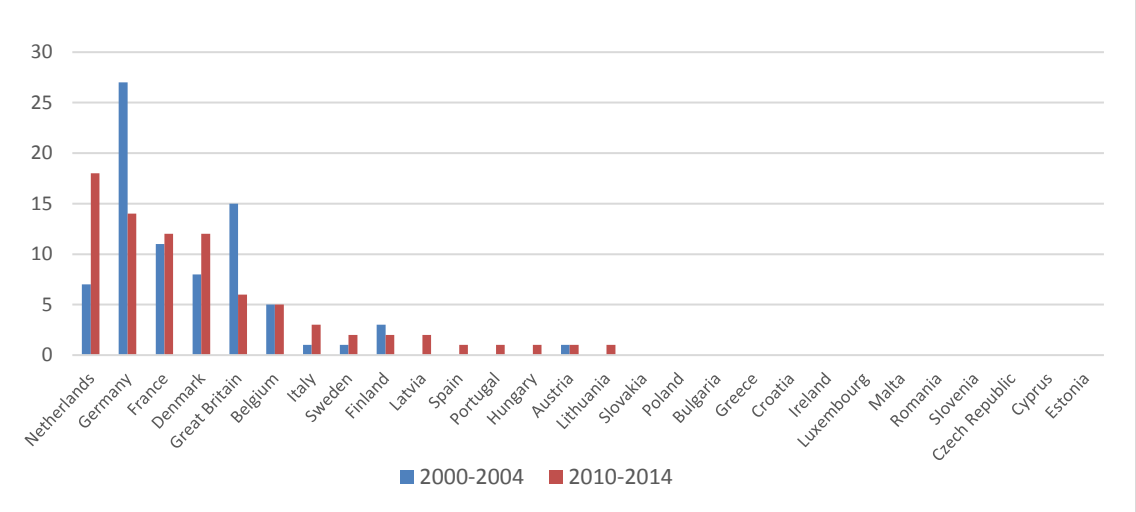


Source: Fraunhofer ISI based on WIPO

Among the EU Member States, the highest patenting activities in this technology field is found in the Netherlands, Germany, Denmark and France (Figure 25). Collectively, this group of countries filed about 80% of overall F&F patent applications within the EU. At the beginning of the observation period, Great Britain also belonged to the EU countries with the highest patenting intensity in F&F. However, the number of patenting activities in Great Britain dropped dramatically after 2004. Although Germany continues to be a leading EU country in terms of patent filings in F&F, it also experienced a significant reduction of patenting activities in F&F over time.

A small group of EU countries including Italy, Sweden, Finland and Latvia shows moderate levels of patent application activities in 2010-2014, while some EU countries have registered only one patent each and other EU Member States display no patent filings during this period of time.

Figure 25: EU Countries: Transnational Patent Applications in Flavours & Fragrances



Source: Fraunhofer ISI based on WIPO

3.5.3.2 Market trends

Flavours and Fragrances (F&F) is a 25 billion US-Dollars industry globally, growing at a compounded annual growth rate of around 4.5% since 2006 (Tully & Holland 2014). The market is almost equally split between flavours and fragrances. It is expected that middle single-digit growth rates will be also reached in the next years, because of the expected increasing demand for processed food (Tully & Holland 2014). The increasing demand of consumer towards natural products in the food industry will affect flavouring substances where consumers are increasingly demanding the replacement of synthetic for

natural ingredients. Experts state a faster market growth for natural flavours than industrial Natural Identicals.

There are no estimations of the current share of biotech flavours & fragrances publicly available. According to older estimates, less than 10% of the market value for F&F (Berger 2009) is derived from bioprocesses. This is still valid (TMR 2017; expert opinions). In particular, according to experts, the share of biotechnologically produced fragrances is estimated to be very low.

The existing product portfolio of biotechnologically produced F&F is diverse. However, the role of biotech F&F has been increasing steadily in the last decades (Brenna / Parmeggiani 2016) and this trend is expected to continue in the future. According to market forecasts, the global biotech flavour market is assumed to reach a yearly growth of almost 10% in the next five years (TMR 2017). The share of the European market is slightly smaller than one third and presents the second biggest market behind North America (TMR 2017). The European market is concentrated in few countries (DE, UK, FR, IT, ESP) as five countries represent more than 70% of the market. No major changes in the geographical distribution of markets are expected for the next years. Asia-Pacific markets are expected to grow at double growth rates compared to other regions, but from a rather small initial market. Concerning applications, the biotech flavour market is highly diversified into different product fields such as dairy products, beverages, confectionary products, bakery products and nutraceuticals.

Concerning market trends and drivers, major differences between the flavour and fragrance market have to be noted.

As indicated above, a very strong market trend for the absolute majority of biotech flavours is the demand for natural products and the "…fact that flavour compounds produced from natural raw materials by microbial or enzymatic methods in accordance with European and US legislation are labelled as ''natural''. This type of labelling is to the benefit of the manufacturer, considering the current consumer trends whereby products used in the food and flavour sector labelled ''natural'' are preferred and thus gain a higher sales price" (Gallage / Moller 2015, p.53). Hence, user companies are willing to pay a premium for ingredients that allow them to market their products with a "natural" claim.

Moreover, also flavours produced through metabolically engineered microorganisms can legally be defined as natural, as current regulation does not explicitly consider processes with genetically engineered microorganisms (see section 4), which are usually used by synthetic biology firms. Currently several flavour producers entered the market with products enabled by synthetic biology. E.g., valencene and nootkatone, which provide the

aroma of oranges and grapefruits in perfumes and cosmetics are produced by engineered yeast (Hayden 2014). In 2015, Evolva and IFF began to commercialize biotech-derived vanillin.

However, the label ‘‘natural’’ may be misleading for consumers. It can be supposed that a majority of consumers attribute the flavour compound to the plant species known as the common original source (Gallage / Moller 2015). There have been some movements that put into question whether GMO produced flavours should claim to be “natural” or what is the socio-economic impact of flavours produced by synthetic biology (Waltz 2015). E.g. the NGO ETC Group has published several case studies criticising flavour products produced by new genetic engineering techniques (ETC Group 2013; ETC Group 2014). Also, the NGO Friends of the Earth pushed an online petition calling for food companies not to use synthetic-biology-derived vanillin in ice cream (Hayden 2015). Moreover, consumer trends towards "organic products" challenge the use of synthetic biology for flavours. E.g., in the US the so called National Organic Standards Board exclude ingredients derived from next generation genetic engineering and gene editing in the production or final product of foods and beverages that are certified organic.[29]

Yet, market reaction for synthetic biology products is not clear, and according to experts, the development in either way will have a significant impact on future synthetic biology activities in the F&F sector.

For biotech fragrances the picture looks different, as natural claims are much less important than other issues. E.g., there are reports about allergenic reactions to synthetic as well as to natural fragrances. Instead, the main drivers for the biotechnological production of fragrances are potential price or sustainability advantages, and to a much lesser extent the "natural" claim.

Regarding sustainability, two advantages, which apply as well to flavours, arise:

- The availability of feedstock for plant-derived ingredients is quite often limited. One approach for biotech firms is to concentrate on fragrances and flavours, which are scarce in nature.
- The environmental footprint of biotech F&F is potentially lower than for chemically synthesized products or plant-derived natural ingredients.

In cases the biotech flavours provide such advantages, higher prices are paid in the markets.

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[29] http://www.centerforfoodsafety.org/issues/304/pollinators-and-pesticides/press-releases/4579/organic-standards-will-exclude-next-generation-of-gmos#

On the down side, different market hurdles arise:

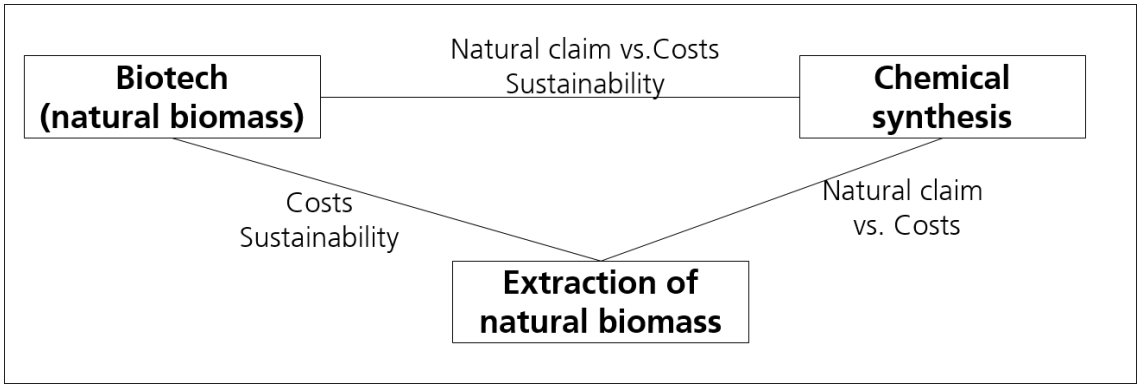
A main hurdle is the high fragmentation of the market. While most of the F&F user industries are dominated by multinational firms, these firms have to serve different geographical markets, which differ in consumer preferences and regulation. Hence, products and market strategies are highly diversified. Many F&F user markets are vulnerable regarding certain fashions. This may lead to a mismatch of current demand and required development for biotech products. This may lead to a lower uptake of these products and/or hurdle to start new R&D&I activities.

In addition, markets are often fragmented in many small volume products, in particular for fragrances. In a significant amount of cases it is not economically viable to engage in costly activities for a substitution of existing synthesized or plant-derived natural products by biotechnologically produced products. Here, one of the main challenges comes into play, the cost competitiveness. According to experts, while comprehensive information for a range of different products is missing, biotechnologically produced products are not cost competitive compared to chemically synthesized products and seldom compared to natural-derived ingredients.

E.g. Waltz (2015) states that prices for vanillin from 15 US-Dollars for a kilogram of vanillin from guaiacol and lignin (chemically synthesized), to 800 US-Dollars per kilogram for vanillin from ferulic acid and about 1,000 US-Dollars for a kilogram of vanillin from vanilla. “The reason a food company might pay 50 times more for the same ingredient can be attributed almost exclusively to the legal right to use the word "natural" on food labels in their target country” (Waltz 2015, p.331). Similar data is also known for other aroma compounds, e.g. γ-decalactone (synthetic = 150 US-Dollars per kg; natural = 6000 US-Dollars per kg; “biotech” = 300 US-Dollars / kg) and ethyl butyrate (synthetic = 4 US-Dollars / kg; natural = 5000 US-Dollars / kg; “biotech” = 180 US-Dollars / kg) (Bicas et al. 2015).

The resulting competition triangle between these different alternative pathways is summarized in Figure 26.

Figure 26: Competition situation for biotech flavours



Source: Fraunhofer ISI

For new technological developments and related R&D&I costs it has to be considered that the market for single products is usually relatively small. For fragrances experts state that it would be very valuable to have a biotech building block, from which different fragrances could be developed, as that would reduce cost. However, for the supplier of those building-blocks that would not be attractive, as they would have to offer large volume at low prices. Moreover, this is hardly an option for flavours, which are usually produced case-by-case.

However, there are two potential developments, which may raise competitiveness at least compared to natural-derived ingredients:

1. The high volatility of prices for plant-derived ingredients because of scarcity or unfavourable weather conditions may provide cost advantages for biotech flavours and incentives to invest.

2. Synthetic Biology may decrease costs if production organisms are designed for hyperproduction

3.5.3.3 Industry structure and actors

The F&F industry is a long established sector, which has become increasingly concentrated in the last decades. Companies aim to increase scale and to establish a global delivery model. The top 10 companies together account for nearly 77% of the industry sales today as compared to 64% in 2000 (Tully &Holland 2014). While medium-size companies (Sales 75 –100 Mio US-Dollars/yr) are mostly absent in the F&F industry, a

high number of specialized SME exist (sales 10-20 Mio US-Dollars/y). The number is estimated to around 500.[30]

The Top 10 F&F firms are all active in the field of biotechnology. They either possess in-house development competencies in biotechnology, have acquired biotechnology companies, and/or cooperate with biotech firms, in particular with synthetic biology (SB) firms. The later cooperations are not seldom transcontinental with either US F&F firms working with Europe SB firms or the other way around. Table 1 summarizes the top 10 F&F firms and their activities in biotechnology, while table 2 summarizes leading SB firms that are active in the F&F field.

Table 7: Top 10 of F&F firms regarding market share

Rank	**Company (country)**	**Market share 2016**	**Biotech Activities**	**Cooperations with Synthetic Biology Firms**
1	Givaudan (CH)	18.7%	In-house development, acquisitions, cooperations	Amyris (US), Evolva (CH)
2	Firmenich (CH)	13.5%	In-house development, acquisitions, cooperations	Amyris (US)
3	IFF (US)	12.3%	In-house development, acquisitions, cooperations	Amyris (US), Evolva (CH)
4	Symrise (DE)	9.2%	In-house development, acquisitions, cooperations	
5	Takasago (JP)	5.1%	In-house development, acquisitions, cooperations	Amyris (US), Evolva (CH)
6	Mane (FR)	4.6%	In-house development	
7	Frutarom (ISR)	4.2%	In-house development, acquisitions, cooperations	
8	Sensient Flavours (US)	2.6%	cooperations	
9	Robertet (FR)	2.1%	cooperations	Gingko Bioworks (US)

[30] http://sitn.hms.harvard.edu/flash/2015/the-flavor-rundown-natural-vs-artificial-flavors/

10	T. Hasegawa (JP)	1.7%	cooperations	

Source: Leffingwell & Associates 2016, desk research

Table 8: Leading synthetic biology companies active in the F&F field

Company	Product areas	Partners
Allylix (US)	Valencene	Acquired by Evolva (CH) in December 2014
Amyris (US)	Artemisinin, undisclosed F&Fingredients	Firmenich (CH), IFF (US), Givaudan (CH)
Evolva (CH)	Vanillin, resveratrol, stevia, nookatone, sandalwood oil	IFF (US), Cargill (US), Roquette (FR), Ajinomoto (JP)
Ginkgo BioWorks (US)	Rose	Robertet (FR)
Isobionics Geleen, (NL)	Valencene	DSM (NL)
Oxford Biotrans (UK)	nookatone, valencene	

Source: Waltz (2015), modified and updated

Table 8 indicates that the emergence of synthetic biology leads to increasing cooperations between F&F suppliers and biotech firms.

However, it appears unlikely that the industry structure will change enormously and the top F&F will loose significant importance, as their competencies regarding controlling the suply chain and knowing customer trends are still highly relevant (Brenna / Parmeggiani 2016).

Concerning geographical distribution of activity, Table 7 shows that half of the Top 10 firms possess their headquarters in Europe. However, European actors are faced with strong global competition. In the US several leading synthetic biology firms (Amyris, Gingko Bioworks) have reshaped their focus from bulk applications to high-value products such as F&F. In Europe, smaller synthetic biology firms that mostly dedicate their activities to the F&F industry have emerged such as Evolva changing their focus from

pharma to food ingredients or specialized firm such as the DSM spin-off Isobionics or the start-up Oxford Biotrans.

Overall, experts consider that there are strong F&F biotech activities in the US and in China. Accordingly, US firms are successful in selecting proper development projects, and strong networks have been established. These activities are backed-up by significant public funding. E.g. Amyris announced a multi-year technology investment agreement with DARPA, worth up to 35 million US-Dollars.[31] Amyris intends to expand its portfolio by adding hundreds of molecules across multiple development platforms.

In the EU, "organic" product-based growth prevails. Experts assess a high fragmentation of activities in the EU-28, many cooperations are on a national level or with actors from neighbouring countries. While numbers are missing, there are indications that focal point is mainly mid-western countries of Europe, with strong activities in Switzerland, Germany, France and the Netherlands. On the fragrance user side, European countries are among the global leaders. According to IFRA (2015), the European fragrances user industry is the largest in the world with innovations triggered by new fragrance ideas playing a critical role for them.

3.5.4 Policy and Framework Conditions

As outlined above, the biotech F&F market is heavily dependent on regulation for claiming "natural" on food labels. There are global differences regarding the regulatory frameworks to define an ingredient as natural, although many global bodies follow the regulations of the US or the European Union (EU) (Cataldo et al. 2016). In the EU, the Regulation (EC) No. 1334/2008 on flavours or certain food ingredients with flavouring properties for food applications came into force in January 2009.[32] This regulation has similarities to the US regulation, but the Food and Drug Administration (FDA, US) focuses preferentially on the raw material rather than the process. Instead, the European regulation refers to the process. It accepts a limited list of procedures, but with a vaguer definition for the raw material. As a result, both regulations allow enzymatic catalysis and fermentation to produce the flavour with a natural claim, if natural raw materials are used (Cataldo et al. 2016).

However, differences in practice still exist between global regions. E.g. Waltz states in the case for vanillin (Waltz 2015, S.331): "Vanillin from clove, for example, is considered a natural flavour in the US but not in the EU. Vanillin from turmeric is seen as natural in

31 http://investors.amyris.com/releasedetail.cfm?releaseid=932787

32 However experts states that despite this common regulation still differences in practice between European countries exist.

parts of Asia Pacific, but not in the EU. Vanillin from ferulic acid can typically be called a natural flavour in both the EU and the US. Making things more complicated, in the US, vanilla flavourings, including vanilla extract, have a special designation known as a federal standard of identity, and the rules for labeling vanilla differ from the rules for labeling other flavours."

Moreover, the regulatory definitions have not been updated since decades and do not explicitly consider processes via genetically engineered microorganisms (Cataldo et al. 2016; Waltz 2015). In 2014, the FDA declined the request of judges in different US districts to clarify its position regarding natural labels on foods made with genetic engineering with the argument of other priorities (Waltz 2015). However, considering public pressure this may probably be still a topic in future.

Hence, the future development of product labeling regulations and acceptance by the consumer will be of key importance for the value of biotechnological methods.

As pointed out above, the market and relevant regulation for fragrances is different. There is no official regulation regarding the “natural” claim and even if it would exist, it would be a less important market driver than for flavours.[33] Some labelling initiatives for natural cosmetics exist that may have relevance for fragrances. E.g. the Natural Cosmetics Standard explicitly considers non-GMO enzymatic and microbiological methods for the label claim “natural raw material “(NCS 2016).

[33] According to experts mineral water and flavors are the only existing product segments at all, were an official regulation for natural claims exist.

3.6 Microbiomes for food and healthy nutrition

3.6.1 Description of the value chain

Microbiomes is the term given to the collective genomes of mixed microorganism populations. In recent years, scientific-technological progress in metagenome sequencing and other -omics technologies as well as in the bioinformatic analysis and interpretation of the data has opened up the opportunity to better understand the composition of (often unculturable) microbial communities, the functions and interaction of their members, and their interaction with their hosts (humans, animals, plants) and the environment (e.g. food, soil).

In the PROGRESS project, the focus is on human microbiota (e.g. microorganisms that normally inhabit the skin, mouth, nose, digestive tract, and vagina of the human body). Microbiota of animals, plants and their environment (e.g. soil) are not covered here34. Within human microbiota, the focus is on microbiota-host-interactions for maintaining health and preventing disease, and on human microbiome engineering in nutrition, via food and food ingredients and in products that are available without medical prescription, e.g. over-the-counter pills, supplements. Consequently, the microbiota-host-interactions in disease and therapeutic interventions are not the focus of this value chain analysis.

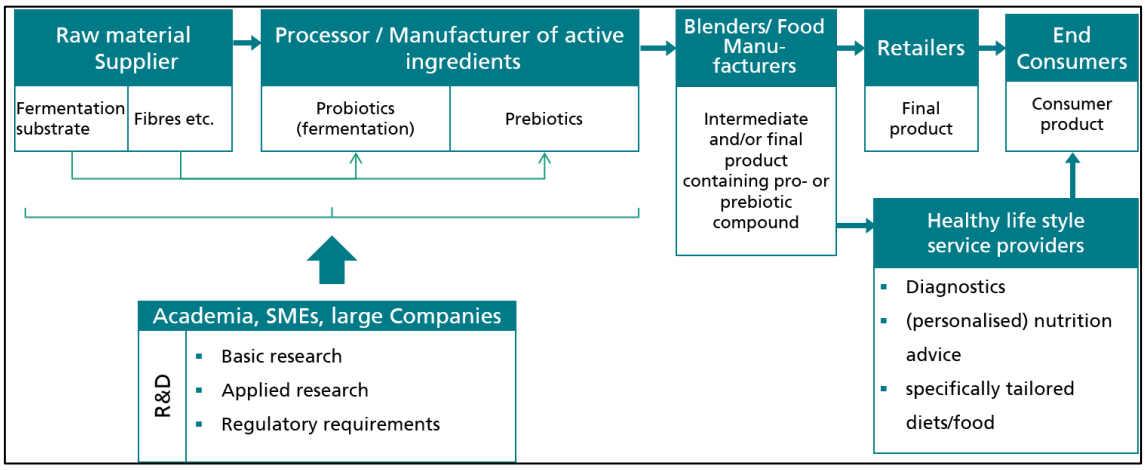
This value chain has the focus on healthy nutrition, lifestyle and prevention. However, the borderline to medicine, disease, and treatment is blurred. This field offers opportunities not only for companies firmly established in the food sector, but also for new entrants, such as diagnostic companies, pharmaceutical companies, bioinformatic companies, big data handlers, and technology providers such as developers of apps or wearables (Figure 30). It bears the potential of novel products, which can only be produced by biotechnology or novel services, which are enabled by biotechnology. They are likely to be positioned as products or services in the medium to high-value-low-volume range, delivered to B2B and B2C customers. Many microbiome-related products and services are closely related to personalized nutrition or personalized nutritional advice, respectively.

As this value chain represents an emerging, science- and technology driven field, major activities take place in R&D. On the EU level, until the end of 2017, a total of 160 microbiome research projects with an overall budget of 420 M € have been funded under the 7th Framework Programme (91 projects for 243 M €) and within Horizon2020 (69 actions for 177 M €). These EU funded activities covered microbiomes from several body sites

34 The approaches and technologies of human food-related microbiome research can also be applied in other fields of microbiome research, dealing with livestock health, crop plants, or soil microorganisms. This research also bears large potentials for the bioeconomy, but is outside the scope of the PROGRESS project.

(i.e. gut, skin, respiratory tract, mouth, vagina), established the relationship between microbiomes and a large number of diverse pathological states, and also covered microbiomes in agro-food and nutrition, plants, animals, marine environments, soil, and included R&D on data and knowledge management as well as on evolution and biodiversity generation (Hadrich 2017). EU-funded projects with specific relevance for human nutrition were META-BIOME35, MetaHIT36, and MyNewGut37.

Figure 27: Value chain for microbiomes for food and healthy nutrition



3.6.2 Technology and Innovation potential

Societal need and public health potentials

Due to efficiency gains in agriculture and food production, changes in life style and dietary habits, the incidence and prevalence of nutrition-related diseases have increased dramatically in the EU. Although the components of a healthy diet are known and educational efforts on healthy dietary practices are taken, dietary interventions often show a low efficacy over a longer period of time. One factor contributing to this low efficacy is the individualized response to food, and the lack of knowledge of the mechanisms which underlie these responses (Bashiardes et al. 2017), with the consequence that "one-size-fits-all" dietary recommendations do not seem appropriate.

35 https://cordis.europa.eu/project/rcn/185584_en.html

36 https://cordis.europa.eu/project/rcn/87834_en.html

37 https://cordis.europa.eu/project/rcn/111044_en.html

Against this background, recent technological advances in powerful genome sequencing technologies, bioinformatic tools for data analysis and interpretation and machine learning allow the comprehensive analysis of the microbial communities which inhabit the human. As evidence is accumulating that microbes make a vital contribution to human health and wellbeing, the microbiota can be seen as a causal element or mechanistic link between nutrition and health status (Yadav et al. 2017).

This raises the expectation that by targeting the microbiota, the interindividual variation in response to diet can be explained or predicted to a larger extent than today, and that the one-fit-for-all diet approaches can be complemented by more personalized nutrition approaches, including specifically designed or engineered functional food. It is hoped that personalized diets will show a higher long term efficacy than customary population based dietary recommendations, that compliance will be improved, and in the end better results with respect to prevention, amelioration and treatment of nutrition-related diseases will be achieved. However, whether the prerequisites for realizing these public health potentials can be created, depends to a large extent on progress in the areas of microbiology, nutritional sciences, and novel products and services. These scientific, technological and innovation potentials are outlined below. Moreover, the integration of microbiome-targeting approaches into holistic concepts for preventing nutrition-related diseases will be required. It then remains to be shown by the generation of clinical and epidemiological evidence whether the postulated public health effects can really be achieved.

In the following paragraphs the scientific, technological and innovation potentials will be outlined in the areas of microbiology, nutritional sciences, and novel products and services.

Microbiology

Studying microbiota with powerful -omics technologies means a paradigm shift in microbiology: the previously dominating culture-dependent approaches, mainly focussed on isolated, pure bacterial strains, can now be complemented by culture-independent methods which can also be applied to mixed cultures of many different bacterial strains, and of undefined or unknown bacteria. Thus, whole biocenoses become amenable to investigation which could not be analysed before because many of the constituents of these biocenoses could not be cultured in the laboratory. However, the shift from pure cultures of single strains to mixed cultures adds a level of complexity which has hardly been addressed before in microbiology.

This capability opens novel routes of research: an expansion of knowledge can be expected because novel research questions can now be addressed which could not be investigated before. R&D issues comprise

- description of the (changes of) composition of microbiota under different conditions
- elucidation of functions of components (= organism groups) within the microbiota
- elucidation of mechanisms of functions of the microbiota
- studying interactions of organism groups (e.g. synergistic/symbiotic, parasitic) within the microbiota
- studying communication and interaction within the microbiota, between microbiota and host, between microbiota and environment.

Moreover, microbiomes could be mined *in silico* for novel probiotic strains (based on knowledge of the relevant probiotic traits which exert a health benefit (Sanders et al. 2018)), for novel enzymes, or for novel small molecules (e.g. antibiotics, regulators, effector molecules) (Medema and Fischbach 2015; Medema 2018). They could form the basis for novel products and services (see below).

Nutritional sciences

It is well established in nutritional sciences that the individual response to diet depends on life style factors, environmental exposures, the human genome and epigenome, and the microbiome. The interplay of the human genome and nutrition has been studied since the completion of the Human Genome Project in the novel disciplines of nutrigenetics (effect of genetic variations on the response to diet) and nutrigenomics (interactions between dietary components and the genome). However, only recently has it become possible to also address the microbiome. Microbes in the gut are known to perform a range of essential tasks, e. g. release of energy from food, production and release of vitamins, metabolising drugs, assisting in the maturation of the immune system and influencing the host's immune system both at a local and systemic level, so that it is plausible to assume that microbes make a vital contribution to human health and wellbeing (Yadav et al. 2017). Moreover, there is accumulating evidence that microbiota are a causal link between nutrition and health status, as dysbiosis (i.e. a deviation of the microbiome from "normal" state) is often closely associated with many acute and chronic diseases.

With the aim of achieving a higher level of understanding of the links between diet, lifestyle, genetics, and the microbiome, novel research questions arise and novel routes of research open up, from which an expansion of knowledge can be expected. R&D issues comprise

- understanding the interaction of host and microbiota: how does the host influence the microbiota, and how do the microbiota influence the host? What is the underlying mechanism?
- establishing associations of microbiome status with health status: which microbiome composition and functions can be linked to specific health conditions or diseases? Can a "healthy" microbiome be described? How does it differ from dysbiosis? What are the underlying mechanisms?

Novel products and services, interventions

Establishing a causal link between nutrition, microbiota and health status bears the potential for novel applications, products and services in the nutrition and food field, such as

- Analytics and diagnostics: Microbiome profiling, biomarker-based screening and health monitoring
- Novel active ingredients for functional food or dietary supplements: probiotics, prebiotics, bacteriophages, small molecules to alter the microbiota (e.g. metabolites, signalling molecules) or the host response
- Food: Functional food and optimized diets without or with health claims, food and diets for special target groups or specific health conditions
- Dietary supplements: over-the-counter supplements and medicines with active ingredients targeting the microbiota
- (Personalised) services: microbiome analysis and interpretation, dietary advice and education, personalized nutrition plans, personalized food and diet solutions as intervention, intervention monitoring (Bashiardes et al. 2017)
- R&D services: microbiome mining as screening service in order to identify novel small molecule medicines and functional ingredients (e.g. effector molecules, regulatory molecules, antibiotics, ...), novel enzymes, novel probiotic strains (Brown und Hazen 2017; Medema 2018)
- Devices: point-of-care testing of microbiota or relevant biomarkers, monitoring of health status, microbiota or relevant biomarkers (Srinivasan et al. 2017)
- Microbiome-based surveillance systems for authentication, safety, and process management along the whole food process chain: Underlying rationale is that the baseline microbiome of food should shift if the food is e.g. contaminated with a pathogen, a toxin or raw materials from other sources (Beans 2017; Doyle et al. 2017).

Moreover, for most products and services listed above, additional applications beyond the food sector are possible, e.g. as medical food, as medicinal products, cosmetics, or cosmeceuticals.

To sum up, microbiota for healthy nutrition is an emerging, science and technology driven field for which novel products and services have been outlined, but are still in an infant stage of development. Progress in this field requires competencies in microbiology, molecular biology, omics technologies, bioinformatics, machine learning, manufacturing in industrial biotechnology and food technology, health apps and point of care testing, nutrition and medical sciences. Therefore, players from microbiology, food, pharma and ICT and data industries will have to work synergistically together. Moreover, there is a need for dedicated R&D resources, such as biobanks, data bases, reference catalogues, standard operating procedures and standards, cohort studies etc. (Winickoff 2016). Although there is still a need for basic research, especially with respect to elucidate the functions of microbiota in health and disease and the underlying mechanisms, in the nearer future additional efforts should be devoted to translational research in order to establish evidence-based interventions which target human gut microbiota (Hadrich 2017).

3.6.3 Economic analysis

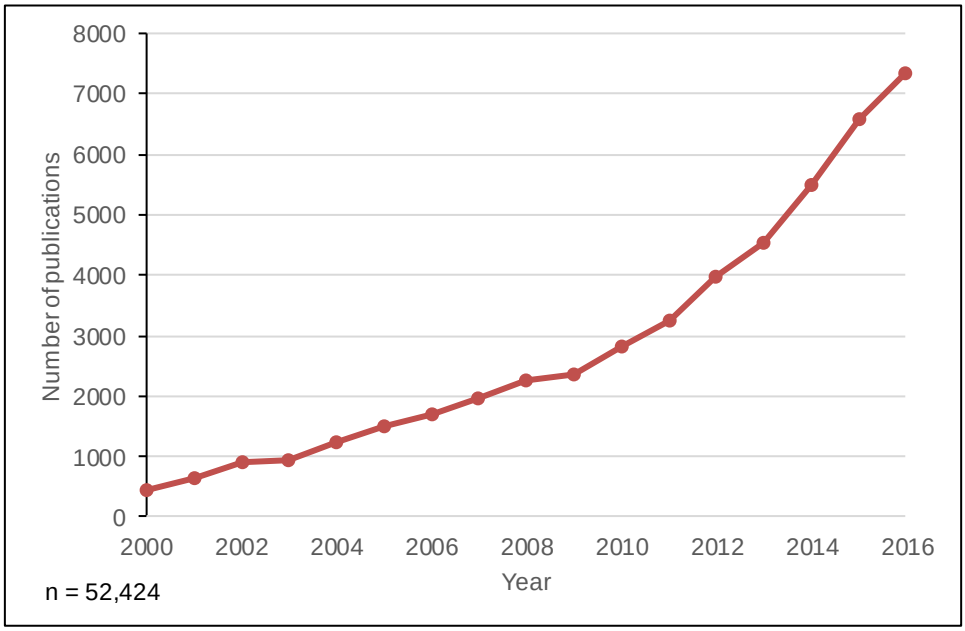
While the focus of activities regarding microbiomes is still on (academic) research in order to build the required knowledge base, various industrial players (e.g. biotechnology companies, technology service providers, food ingredient producers, consumer goods companies, medical device and pharmaceutical companies) engage in the field with the aim to commercialize services and products. Hence, in contrast to the other value chains investigated in the PROGRESS project, the following analyses sets a higher focus on the R&D stage and therefore includes a publication analysis next to patent analysis.

3.6.3.1 Publication and Patent analysis

The scientific publication activities in microbiome research have grown dynamically in the last years (see Figure 28), especially since 2007/2008, the year in which the first large scale collaborative programmes on microbiome research started: these are the NIH funded programme "Human Microbiome Project" (2007-2012; 170 M $)38, and the EU FP7-funded programme "MetaHIT: Metagenomics of the Human Intestinal Tract" (2008-2011; 21 M €). The EU is the leading world region regarding scientific publication activities and patent applications, which are most active in microbiome research, together with the U.S. and Asian countries, especially China.

Figure 28: Scientific microbiome publications worldwide, 2000-2016

38 https://hmpdacc.org



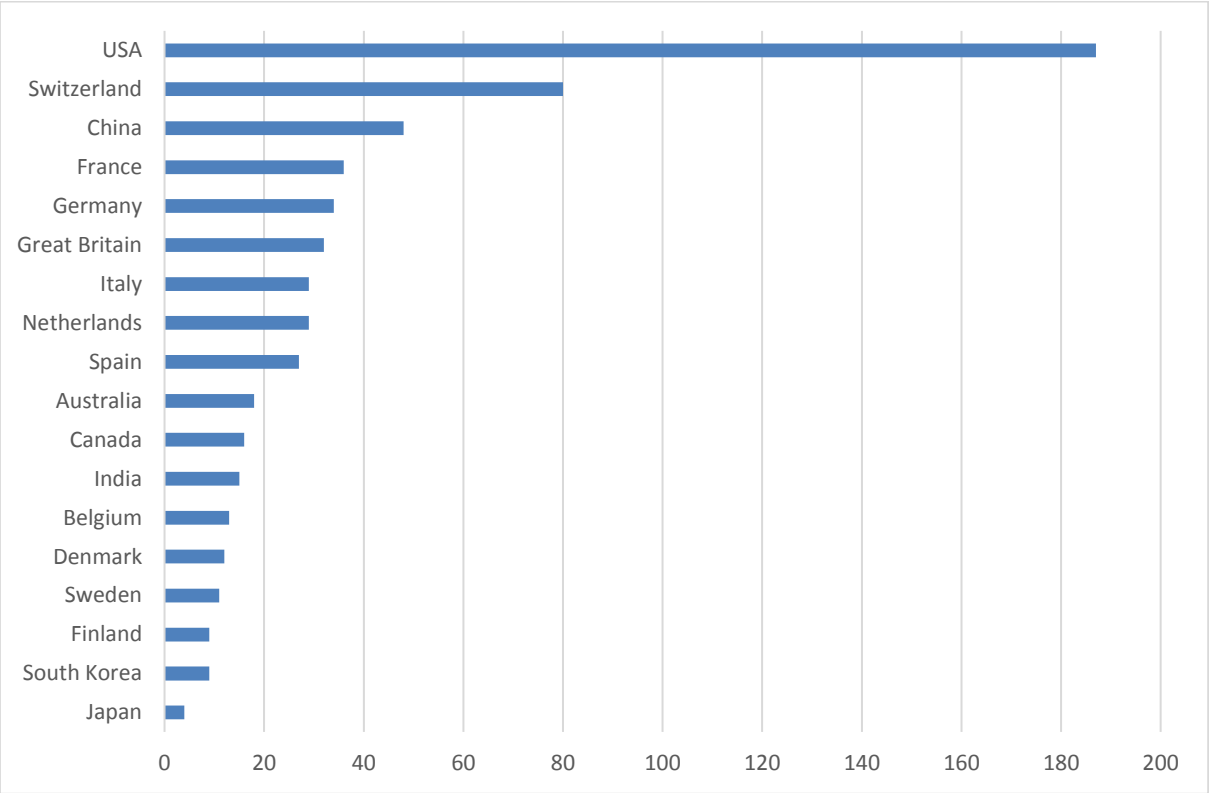
Source: SCOPUS database, search terms in title, article, keywords: microbiome* OR prebiotic* OR probiotic*

With a broad recognition of the significance of microbiomes for human health, microbiome research is becoming increasingly important all over the world, leading to a considerable competition between countries and companies in terms of research output. The data on patenting activities in microbiomes provide an evidence that along with industrially advanced countries, emerging economies, like China and India, also have a vested interest in this field and devote much research efforts to it.

Figure 3 demonstrates which countries currently have the highest patenting intensity in microbiomes.39 Among these, USA ranks first in terms of patent applications, while Switzerland and China possess second and third rank, respectively. It is noteworthy that six EU member states - France, Germany, Great Britain, Italy, the Netherlands and Spain - rank among the top ten in this field of technology.

Figure 29: Transnational Patent Applications in Microbiomes (2010 – 2014)

39 In difference to the other value chains only the most recent years are analyzed. As mentioned above, most research output before 2007/2008 refers only in few cases to the microbiomes. Hence, the patents that are captured by the analysis moist probably refer to research for prebiotics or probiotics without linked to microbiomes research.



3.6.3.2 Market trends

While the potential for novel applications, products and services has been outlined and recognized, the realization is still in an infant stage. The potential portfolio ranges from analytics and diagnostics (e.g. microbiome profiling, biomarker-based screening and health monitoring) to novel active food ingredients (e.g. probiotics, prebiotics, phages, metabolites, signaling molecules) or microbiota-addressing functional food with or without health claims to dietary supplements. It is complemented by services, such as dietary advice and education, personalized nutrition plans, personalized food and diet solutions and related devices (e.g. for point-of-care testing and monitoring), as well as microbiome-based surveillance systems for authentication, safety, and process management along the whole food process chain.

Market analyses that include the whole range of these products plus therapies expect the market to grow considerably, e.g.

- Markets and Markets expect the market to reach USD 899.1 Million by 2025 from USD 506.5 Million in 2022 growing at a CAGR of 21.1% during this period.40

40 https://www.marketsandmarkets.com/PressReleases/human-microbiome.asp

- Research and Market expects the Human Microbiome market to grow at a CAGR of 17.05% over the forecast period to grow to US$635.829 million by 2022, growing from US$289.411 million in 2017.41
- According to Stratistics MRC, the Global Human *Microbiome Market* is expected to grow from $235.8 million in 2018 to $521.23 million by 2022 growing at a CAGR of 21.9% during the forecast period. 42

It has to be noticed that the focus of this value chain analysis is on the food and nutrition market. However, no information is publicly available about the share of these food and nutrition products of the whole market. It can be assumed that the market forecasts listed above are to a large extent determined by medical applications of microbiome research and related therapies (e.g. fecal transplants, pharmaceuticals), as the majority of R&D activities of the private sector are directed to medical applications.

One of the major (and already established) product groups of microbiome-addressing food are probiotics, mainly included in dairy products. Frost & Sullivan give the following market estimations (Global Visionary Science Research Team at Frost & Sullivan 2017):

The total probiotics ingredient market was valued at €1.31 billion in 2016 and is expected to reach €1.82 billion by the end of 2021, based on a CAGR of 6.8%. Probiotic ingredients are incorporated primarily into food, beverages and supplements.

The total probiotics retail market was valued at €44.97 billion in 2016 and is expected to reach €59.61 billion by the end of 2021, based on a CAGR of 5.8%. Major market segments are food, beverages and infant formulas.

As indicated microbiomes are mainly in research phase, with few products commercially available yet. Experts estimate that it will take at least one to two decades until novel first microbiome food products such as pre- or probiotics with supporting health claims will reach the commercialization stage (Titoria and Groves 2017). This does not exclude the possibility that novel products without health claims will be successfully commercialized earlier. As will be outlined in more detail in the following section, several companies already offer microbiome-related services to healthcare professionals and consumers, which comprise microbiome profiling by metagenome sequencing, data analysis, and nutritional advice.

From the point of view of industry, there is a need to communicate the health-promoting properties of their respective probiotic or prebiotic food to the consumer, not least to be

41 https://www.researchandmarkets.com/research/kq38n8/human_microbiome

42 http://www.strategymrc.com/report/human-microbiome-market

able to charge premium prices. However, the communication has to be evidence-based and should not mislead consumers. The Commission authorises different health claims provided they are based on scientific evidence and can be easily understood by consumers. Health claims only receive approval from the European Commission following an EFSA opinion upon a submission of the scientifically substantiated dossier.

Despite intensive research efforts, health claims that modulate gut function so far have had very little success in obtaining approval in Europe. Until 2015 not any probiotic or prebiotic product received an authorized health claim.[43] The OECD reports only one such product on the market today: In March 2017, the firm Winclove Probiotics announced to have the first probiotic with an EU health claim.[44]

3.6.4 Industry Structure and actors

Potential products address the microbiome can be placed in the continuum between food and pharmaceuticals. Figure 30 shows that this research field offers opportunities for various industrial sectors (OECD 2017):

- the food ingredients and food industry, especially those companies with a strategic focus on development and production of healthy nutrition
- Activities of pharmaceutical companies aim at mining the microbiome for small molecules which could be used as therapeutics, search for microbiome functions which could enhance the intended effects of medication or reduce unintended side effects, search for novel biomarkers and targets, and even develop live bacteria as theraputic interventions.
- A growing number of companies is offering nutritional advice based on full genome analysis and information on biomarkers and biochemical testing (D'Hondt 2017; Shankar 2017).
- Moreover, diagnostic companies and technology providers such as app developers, the wearables developers and big data handlers may become active in this field (D'Hondt 2017).

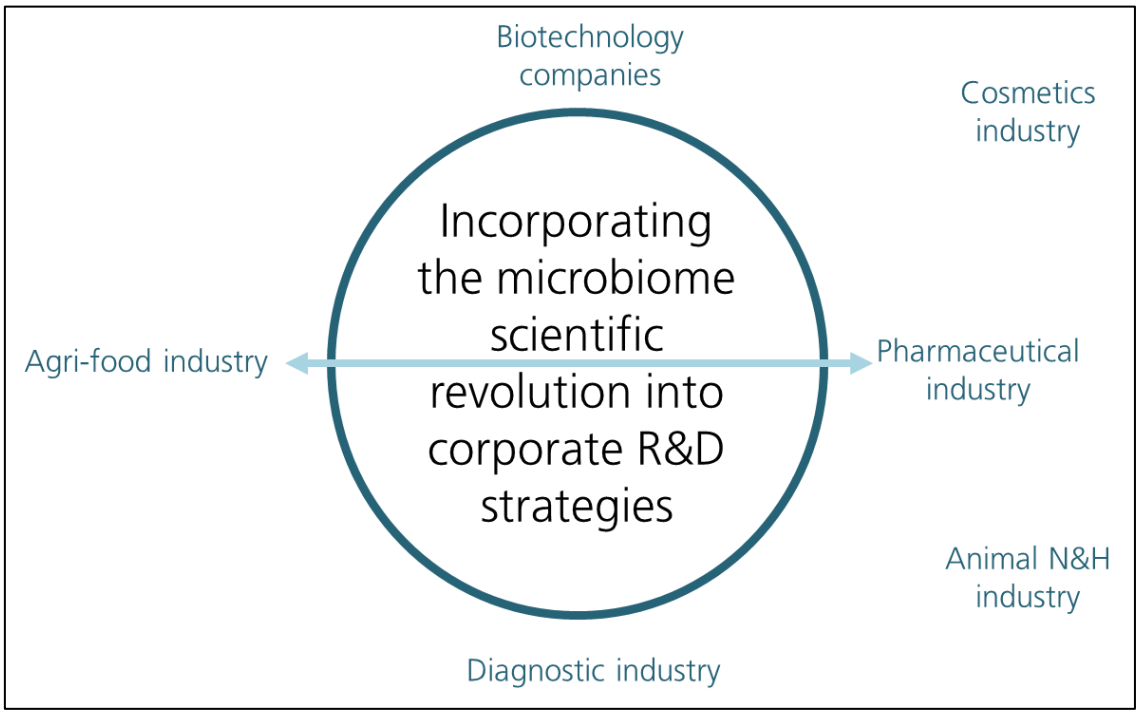
Presently, spin-off and start-up SMEs play an important role as innovators, technology and service providers in this high-risk field in addition to (a few) large multinational companies, which are also active in R&D, but could also acquire successful start-ups or invest venture capital into promising SMEs. However, these innovative SMEs differ in many respects from the SMEs that represent the majority of players in the European

43 https://www.nutraingredients.com/Article/2016/08/26/EU-rejects-more-than-90-of-all-health-claims-Study;

44 https://www.wincloveprobiotics.com/sites/default/files/headerpics/winclove_press_release_first_eu_probiotic_health_claim_0.pdf

food sector: the latter are usually not research-intensive and focus on process and incremental product innovation. This points to the challenge how commercialization of microbiome research results can be made usable to the food industry at large.

Figure 30: Industry sectors involved in microbiome R&D and commercialization



Source: Shortt (2016)

The future economic development will depend highly on whether academia-industry and cross-industry collaborations (e.g. biotech – food – pharma / medical devices) and knowledge transfer can successfully be established. The food industry may have to collaborate more closely with the pharmaceutical industry should it need clinical testing on large populations to demonstrate the health benefits of novel foods or food products with health claims assigned to them, since this specific expertise lies with the pharmaceutical industry (OECD 2017). However, business models differ highly. Companies seem to cope differently with the upcoming challenge of competence gaps at the interface of the food and pharmaceutical sectors (Bornkessel et al. 2016). Hence, the challange lies in implementing adequate innovation strategies and collaboration models, especially for food SMEs.

The innovation strategy of Nestlé Health Science (Epalinges, Switzerland)[45] will be described here as an example of the innovation strategies presently pursued by multinational, research-intensive food companies in the microbiome field:

Nestlé Health Science has a strategic focus on the development of nutritional therapies and an intent to take a leadership position in the developing microbiome therapy field. The company's microbiome portfolio interests range from diagnosis, to therapeutics and nutritional therapies. In order to achieve these goals, Nestlé Health Science has built up a wider innovation network of universities, start-ups and suppliers and acquires technologies, businesses, as well as key individuals and skills. Part of it is financed by Nestlé's venture funds, and via the strategic partnership with Flagship Ventures (Cambridge, Mass., USA), a venture capital and venture creation firm by investing in entrepreneurial companies developing breakthrough technologies for novel nutritional therapies, including brain, gastrointestinal and metabolic health. Major recent investments by Nestlé Health Science with specific relevance for microbiome-targeting therapies are listed in Table 9.

The case of Nestlé Health Science is a representative example how multinational companies strategically invest in microbiome research and companies: venture capital companies such as Seventure Partners (Paris, France), and Arix Bioscience (London, UK) have set up dedicated funds to invest in microbiome-related businesses, especially in UK-based and European innovative companies with a strong academic research record (Sansom 2018). DuPont Nutrition & Health, Copenhagen, Denmark has set up Microbiome Venture with the aim to invest into strategic partnerships with microbiome science leaders in academia and industry to accelerate product development in the field of pro- and prebiotics and human milk oligosaccharides[46]. DuPont's first partnership through the venture is with the APC Microbiome Institute in Cork, Ireland. Table 10 gives a - non-comprehensive - overview of small companies with a focus on microbiome research with relevance for food. As can be seen from the table, diagnostic companies predominate. Presently, there are several test kits on the market which promise health advise based on microbiome analysis, offered by DayTwo, uBiome, Viome, and MapMyGut. However, the borderline between clinical tests and medical interventions on the one hand and lifestyle tests and dietary recommendations on the other hand is blurred.

Several small companies aim at altering the gut microbiome towards health benefits with interventions other than nutrition. Among them are Caelus Health, Whole Biome,

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45 https://www.nestlehealthscience.com/about-us/key-investments; last accessed 18.4.2018

46 http://www.dupont.com/industries/food-and-beverage/press-releases/microbiome-venture.html (Press release 29/11/2017; last accessed 6/4/2018)

Symflor, which work on applying cocktails of microorganisms; TargEDys, working on GMO as probiotics; and LNC Therapeutics, GnuBiotics and Microbiome Therapeutics working on prebiotics (Gevers 2017).

Table 9: Major recent investments of Nestlé Health Science with relevance for the microbiome field

Company	Focus of activities	Remarks	Source
Enterome Bioscience SA (Paris, France)	development of pharmaceuticals and diagnostics for personalized therapies in microbiome-related diseases (e.g. Inflammatory Bowel Disease (IBD), cancer, metabolic diseases)	Strategic investment	
Enterome Biosciences (Paris, France)	Development of the small molecule FimH antagonist (EB 8018) that targets adherent invasive *Escherichia coli* proliferation in the gut, one of the main causes of IBD	Venture capital investment of 14.5 M $ (series C round) by Nestlé in 2016	Anonymus 2017
Microbiome Diagnostics Partners (MDP)	Development of microbiome profiling tests for inflammatory bowel disease (IBD) and non-alcoholic fatty liver disease (NAFLD)	50:50 joint venture with Enterome Biosciences (Paris, France); Nestlè investment of 20 M € in 2017	Anonymus 2017
Seres Therapeutics	Preclinical and clinical development of four programs to treat C. difficile infection and inflammatory bowel disease, which includes ulcerative colitis and Crohn's disease, with microbiota-containing therapeutics (Ecobiotics®)	Investment of 120 M $	https://www.xconomy.com/boston/2016/01/11/seres-inks-nestle-as-potential-2b-partner-key-microbiome-data-soon/; last access 9/4/2018
Imperial College London (London, UK)	Pre-clinical and clinical studies; gut-brain-axis; role of microbiome in diabetes and obesity	Investment of 10 M CHF into collaboration	http://www.imperial.ac.uk/news/172598/imperial-nestle-research-create-research-partnership/
Prometheus Laboratories Inc. (San Diego, California, USA)	Detection, diagnosis and treatment of disorders within the fields of gastroenterology and oncology by complementing pharmaceutical products with proprietary diagnostic testing services	Acquisition	https://www.nestle-healthscience.com/about-us/key-investments, last access 17/4/2018

Atrium Innovations	development, manufacturing, and commercialization of science-based nutritional and supplement health products, e.g. probiotics	Acquisition	https://www.nestle-healthscience.com/about-us/key-investments, last accessed 17/4/2018

Table 10: Small companies with a focus on microbiome research with relevance for food

Company	Profile	Source
Viome Inc., Mountain View, CA, USA	Viome, Inc. is a company that collects and analyzes physiological, physical, and molecular data for the purpose of understanding and optimizing the wellness of individuals. VIOME offers a direct-to-consumer wellness service: a microbiome profile is produced from an at-home test kit. Artificial intelligence is applied to the complex biological data to provide consumers with personalized diet, nutrition and lifestyle recommendations.	https://www.viome.com
Day Two Ltd. Rehovot, Israel	Day Two provides direct-to-consumer services, comprising microbiome analysis and online personalized nutrition recommendations based on this analysis with respect to blood glucose levels	https://www.daytwo.com
MapMyGut	MapMyGut provides direct-to-consumer services, comprising microbiome analysis and online personalized nutrition recommendations based on this analysis	https://mapmygut.com/
EvolveBiosystems, Davis, CA, USA	Evolve BioSystems' product is Evivo (activated *B.infantis* EVC001-ActiBif™), a probiotic powder which is mixed with breast milk and fed to babies in order to restore the infant gut microbiome to its original, natural state. Evolve BioSystems is a spin-out from the Foods For Health Institute (FFHI) at the University of California, Davis	https://www.evolvebiosystems.com/
Kallyope, New York, NY, USA	Kallyope is a technology platform and drug discovery company. Its platform integrates technologies in sequencing, computational biology, neural imaging, cellular and molecular biology, and human genetics to provide an understanding of gut-brain biology and to identify therapeutic targets that can be modulated with gut-restricted molecules	https://www.kallyope.com
uBiome	Ubiome offers two sequencing-based microbiome tests for gut microbiota linked with irritable bowel syndrome, and inflammatory bowel disease, including ulcerative colitis and Crohn's Disease (SmartGut) and vaginal microbiota (SmartJane). The tests are ordered by doctors.	https://ubiome.com

ISOThrive LLC	ISOThrive LLC produces ingredients for the dietary supplement market to improve the health of the gut microbiome. The company offers ISOThrive Prebiotic Nectar, a prebiotic soluble fiber.	https://isothrive.com/
Genova Diagnostics Asheville, NorthCarolina, USA	Genova Diagnostics is a global clinical laboratory, offering a wide range of laboratory tests, among them PCR-based stool tests for commensal bacteria profiles.	https://www.gdx.net

3.6.5 Framework conditions

Concerning framework conditions, several issues are relevant for innovation and commercialization of research in microbiome for food and healthy nutrition.

It is important to note that food on the one hand and medicinal products on the other hand are placed on the market under fundamentally different regulatory regimes. At the same time, the present R&D activities and possibly resulting products are often difficult to locate unambigiously in the continuum between food and medicinal products, between maintaining health and treating disease. Against this background, it is a constant challenge for companies which are active at this borderline to define a regulatory strategy for their potential products already early in the innovation process, and to keep in close contact with regulatory authorities.

Regarding market access, regulations for health claims for foods are of key importance.

Globally, regulations differ in terminology and procedures. Different regulations also use different terms referring to food, food additives and ingredients, food with associated health claims, food for dietary management and food for special medical purposes (OECD 2017). E.g. in the EU “probiotics” refers to a health claim and hence it cannot be used without prior approval. Instead, the terminology is more vague in other regions and not connected to regulatory approval.

The European Union is one of the most extensively regulated areas in this matter (OECD 2017). Health claims for food, including food supplements, are covered by the Nutrition and Health Claim Regulation (NHCR) (Regulation EC No. 1924/2006). Nutrition and health claims for food products are only allowed when listed on a so-called positive list. The European Commission bases its approvals on European Food Safety Authority (EFSA) positive opinions as conclusions from scientifically substantiated dossiers submitted.

In many cases, health claim applications were evaluated with a negative outcome by the EFSA – often because they were not supported by sufficient scientific evidence (Verhagen & van Loveren, 2016). Often the causal effects on health of these products were not sufficiently measurable. The poor success rate presents a main challenge for the food sector, and some analyses suggest that innovation activities in the food sector are slowing down (e.g. in terms of R&D, product differentiation), because of these challenging requests (Bröring et al. 2017; Khedkar et al. 2016).

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