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. For that purpose, we will first provide a comprehensive and dependable information base (including modelling and simulation approaches) which allows for plausible estimations on the future of IB in the EU in the short and medium-term. Second, in collaboration with stakeholders we will elaborate a future scenario and a common vision for IB in Europe containing the most promising value chains, related R&D&I needs and necessitated policies for IB in Europe. Based on these steps, we will 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 will be to identify opportunities for collaboration between EU Member States and proposed actions to increase awareness and incentives for those collaborations. For more information see www.progress-bio.eu

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Executive Summary

Industrial Biotechnology (IB) is a key enabling technology (KET). It facilitates new products and processes and poses disruptive qualities to markets, due to numerous technological and economic advantages. Among them are superior quality, novel functions, higher resource-efficient and climate-friendly production processes, substitution of harmful by benign substances, and using renewable, non-fossil raw materials. Hence, IB has high innovation potential to contribute highly to quality of life via new or more sustainable products and services, to foster the rejuvenation of industry, to the transition to a bioeconomy and a circular economy, and to tackle environmental and climate challenges.

The project "PROGRESS" – Priorities for Addressing Opportunities and Gaps of Industrial Biotechnology for an Efficient Use of Funding Resources, funded under the Horizon 2020-LEIT Work Programme of the European Commission, had the objective to support and accelerate the deployment of Industrial Biotechnology (IB) in the EU by identifying high-value opportunities for IB and to propose actions how to address them successfully.

In order to maintain a strong and leading position of the EU in Industrial Biotechnology and to realize its socio-economic potential, a broad portfolio of IB technologies, products, processes and applications should be supported by a comprehensive and coherent policy framework and a set of well-balanced, targeted policy actions. R&D&I policy and corresponding actions are an integral part of this framework. In PROGRESS a broad set of recommendations and related actions has been identified. The priority fields of action – based on the whole project analysis as well as key discussions in the Final Conference – can be summarized as follows:

- Secure strong **science and technology base** by continuing R&D&I support for a broad set of IB innovations on all TRL stages. Here, integration with other technologies is of key importance (e.g. "green chemistry", digital technologies and bioinformatics). Moreover, demand- and market driven R&D&I, also for application in not yet addressed industrial sectors and applications, should be fostered.
- **Foster the economic viability and impact of IB**. Specific focus of actions have to address present bottlenecks in scale-up of processes, relevant workforce skills shortages (e.g. experts for scale up, market intelligence, etc.) as well as implementing comprehensive and coherent demand-side policies (e.g. public procurement of products with a superior environmental profile, standards and labels, mandates or bans of certain chemical/fossil-based products).
- **Address public perception and consumers** by supporting dialogues, target-group specific communication of benefits and adapting the regulatory framework in various value chains: Regulations have to be considered as instruments for

establishing trust and credibility in IB by balancing incentives for R&D&I and industry with - potentially differing - interests of the public and consumers.

- **Increase impact on sustainability** by ensuring sustainable feedstock supply, preferably from non-food biomass, integration of IB into circular economy concepts and setting IB standards for sustainability assessment and certification schemes.
- **Support stronger network and development across EU countries** by integrating actors from EU countries with presently low activities into existing IB networks and value chains. This would include supporting their competency and visibility as well as providing incentives for collaboration between countries at different IB maturity stages.

1 Introduction

The CSA "PROGRESS" – Priorities for Addressing Opportunities and Gaps of Industrial Biotechnology for an Efficient Use of Funding Resources, a 15-month project (2016–2017) has the objective to support and accelerate the deployment of Industrial Biotechnology (IB) in the EU by identifying high-value opportunities for IB and to propose actions on how to address them successfully.

Therefore, a range of activities were carried out, with series of workshops, quantitative and qualitative analyses on different aggregation levels (i.e. specific value chains, and also IB in general), a Final Conference and other dissemination activities (e.g. various presentations at OECD events). This report[1] aims to present key results from the whole CSA and covers the following issues:

- Impact and Potential of IB in Europe (section 2)
- Analysis of developments and drivers for IB, in particular assessment of current status of IB and future scenarios for six selected value chains (section 3)
- Role and potential of EU Member States in IB (section 4)
- Recommendations (section 5)

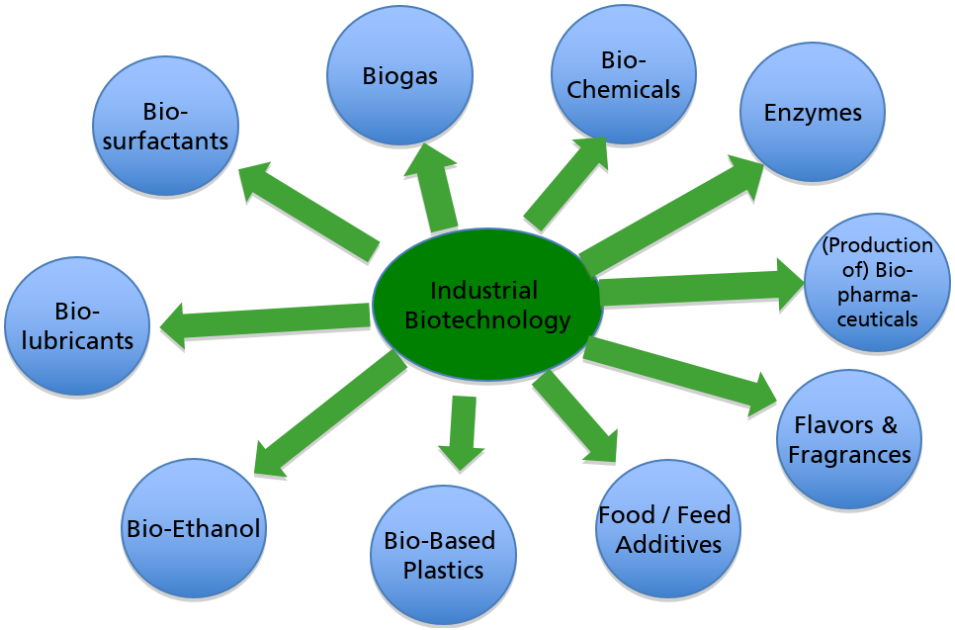
These issues were in the focus of the Final Conference of the CSA on the 27th September 2017 in Brussels (see ANNEX III). Where appropriate, the feedback from the Final Conference has been included in this report as well.

[1] This report is complementary to the Brochure, which has been prepared before the Final Conference. The Brochure contains short summarizations of the various topics of the PROGRESS CSA and is more relying on the quantitative analysis from the European Manufacturing Survey and the system dynamic modelling approach. As these analyses are necessarily limited in coverage of value chains and geographical coverage (only EU) they are not included in this report.

2 Impact and Potential of Industrial Biotechnology in Europe

Industrial biotechnology (IB) employs organisms or parts thereof such as tissues, cells, cell extracts or isolated enzymes in order to develop/produce a wide range of products or provide services. As Figure 1 shows, IB is applied in many different applications and sectors.

Figure 1: Selection of current applications for Industrial Biotechnology



Source: Fraunhofer ISI

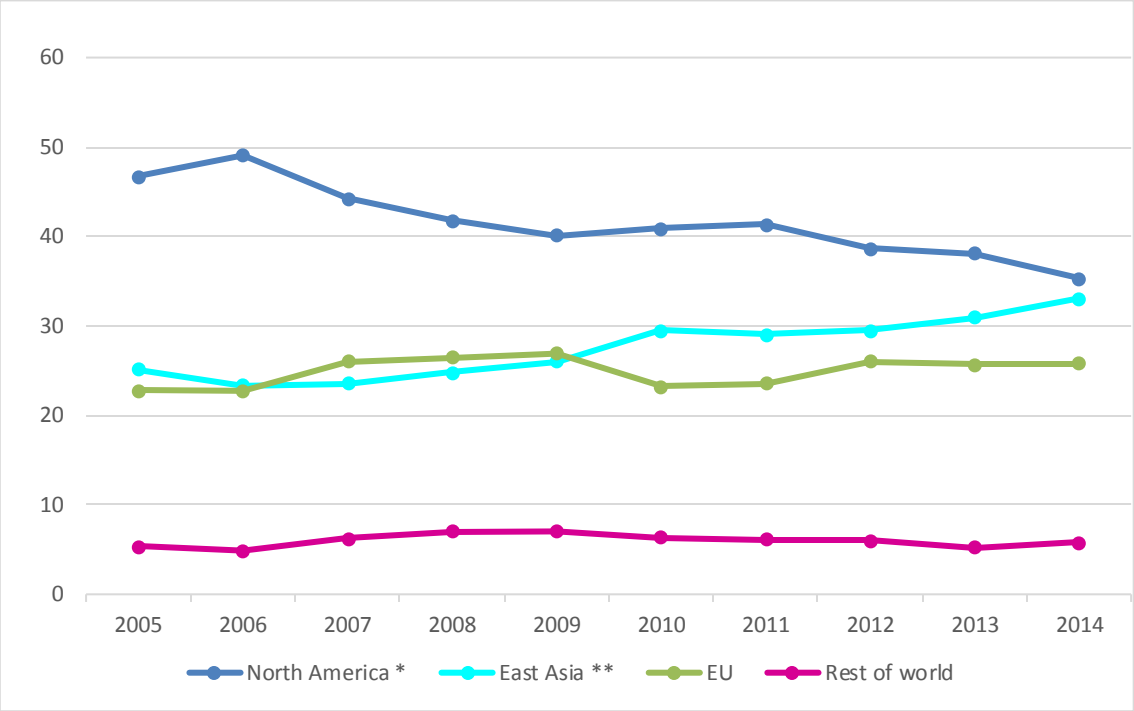
Biotechnological production processes offer numerous technological and economic advantages compared to classical chemical synthesis, for example products of superior quality or with novel functions, higher resource-efficient production processes and substitute environmentally harmful substances. Moreover, biotechnological production processes typically use renewable, non-fossil raw materials. In addition, IB enables the elaboration of products that are biodegradable or amenable to be reused or recycled. Therefore, IB products can contribute to repeated use and hence to circular economic concepts. Hence, IB is a key source of innovation in the concept of the bioeconomy, the gradual replacement of fossil resources by biological resources in order to contribute to societal goals such as mitigating climate change, lowering resource use, increasing food security, generating economic growth and securing jobs.

The low oil price leads to missing cost competitiveness of bio-based mass products, in particular for drop-ins[2]. Hence, there is stronger industry focus on products with high value added and novel functionalities. Moreover, the goal of pure substitution has lost in importance, while the contribution of the bioeconomy to sustainability has become critical and is the key for legitimacy of support. Technological challenges such as the use of non-food feedstocks (e.g. lignocellulose, side-streams in industrial production or waste) have become more urgent. Under these conditions the role of IB becomes even more prominent due to its characteristics as a key enabling technology (KET), with a strong potential to facilitate new products and processes and to disrupt existing markets. IB can generate new growth, spur innovation, increase productivity, tackle environmental and climate challenges, and give rise to new applications, which contribute to opening up entirely new markets, or at least to shift product quality in existing markets to higher levels (EC 2009). This potential is not only connected to the concept of the bioeconomy, as IB also enables innovations that do not rely on biomass (e.g. use of CO_2 for industrial purposes).

To realize the described potential, the EU has to aim for a strong position against global competition. Currently, Europe has a rather strong technology base in IB and holds around 23 % of triadic patents and ranks third behind North America and Asia (see Figure 2). Europe could at least maintain its share in recent times, while the US has been constantly loosing share towards East Asia.

[2] Drop-ins are bio-based products have the exact same chemical structure as the fossil-based equivalent)

Figure 2: Share in IB patents for world regions (in %)

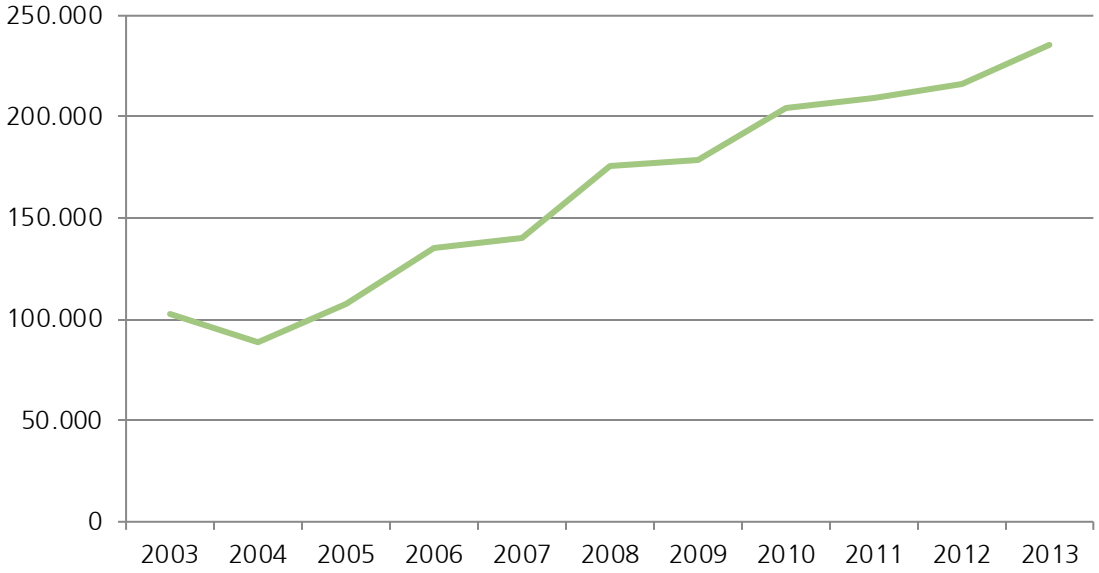


Source: Fraunhofer ISI calculations based on based on World Patent Index; * North America includes the US and Canada ** East Asia includes China, Japan, and Korea

It has to be remarked that this results for IB as a whole differs significantly between specific segments, e.g. in the selected value chains in section 3 the EU share is considerably higher than the overall one.

Information on commercialization of IB is still scattered, but there are strong indications that it has a significant impact on the European economy. According to the KETs Observatory, IB-enabled employment in Europe has been growing significantly in the last ten years and exceeded 200.000 jobs in 2013 (van de Velde et al. 2015). This time trend analysis reflects nicely the steadily rising importance of IB for commercial production & services; and shows the potential for significant increase in the future, as confirmed by EuropaBio (2016).

Figure 3: IB employment in the EU-28



Source: KETs Observatory(https://ec.europa.eu/growth/tools-databases/ketsobservatory/sites/default/files/newsletter/kets_observatory_newsletter_issue_04.pdf)

3 Innovation and Commercialization in IB: State of play and drivers for future development

3.1 Value Chain Analysis: Selection, Goals and Concept

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

For each value chain, the current status was characterized and several scenarios of possible future developments of the respective value chain until 2025-2030 were elaborated as part of dedicated workshops. On that basis value chain specific recommendations were drawn. Please note that the recommendations only capture those that cannot be generalized for broader fields of IB, for which the recommendations are presented in section 5. The value chain specific recommendations in this section mostly refer to specific R&D&I needs or regulations.

The analyses are structured in a similar manner for all value chains and contain the following sections:

- 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
- Scenarios
- Conclusion and value chain specific recommendations

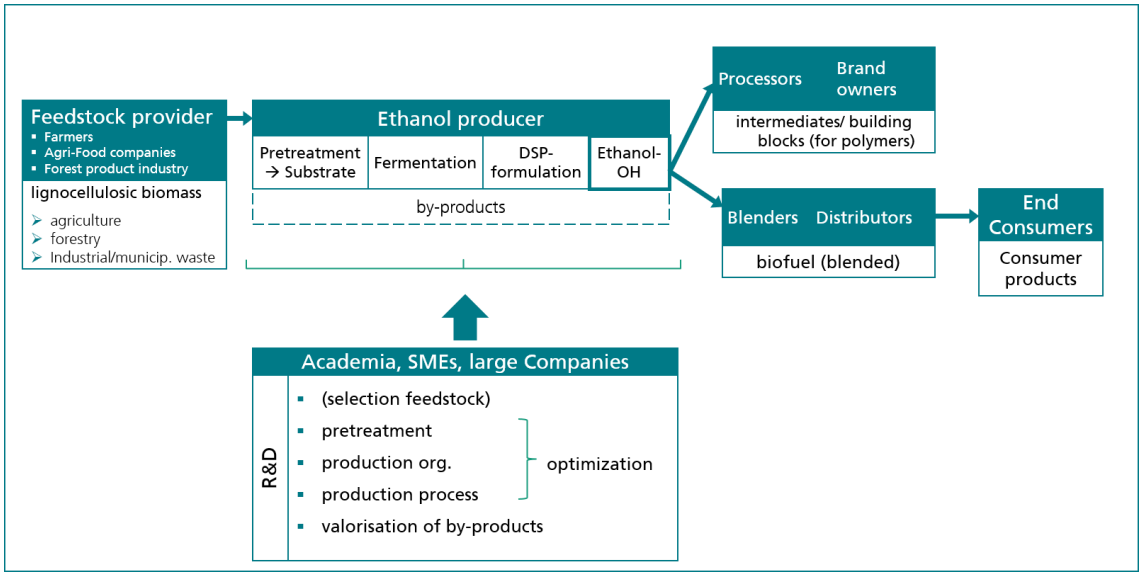
3.2 Lignocellulosic ethanol

3.2.1 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 4 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.

Figure 4: Value chain of lignocellulosic ethanol



3.2.2 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 a production of lignocellulosic ethanol poses 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.

3.2.3 R&D&I needs

As outlined above, technologies for the production of 2nd generation/lignocellulosic bioethanol are approaching maturity and have been developed for demonstration at commercial scale. However, production volumes are still low, as besides policy issues, the production at commercial scale is not economically feasible or profitable at the currently low oil prices. There is also competition from US and Brazilian bioethanol. As a consequence, R&D&I must primarily be focussed on improving cost-competitiveness of production concepts, giving economic considerations and assessments a key role. A techno-economic roadmap should be elaborated which covers the whole supply chain from feedstock price, transport, storage, conversion to ethanol and by-products, downstream-processing and formulation, to product commercialisation. In this roadmap, the costs and the cost-reduction potential of different options should be assessed and R&D&I performed on those approaches which will be required to achieve cost-competitiveness at realistic market prices. It should also take the interdependence of various steps in the process into account, which means that solutions chosen in early process steps may create or avoid problems in later steps.

From the point of view of consulted experts, addressing the following R&D&I issues should be prioritized:

- achieving complete conversion of sugars in the fermentation stage
- achieving higher ethanol production rates and concentrations in the fermentation stage
- cost optimisation of downstream processing (i.e. separation and concentration of ethanol)
- converting by-products (e.g. lignin, xylose) to higher-value products

Table 1 lists options and approaches for these issues. These options and approaches, however, must be assessed and prioritized with respect to their expected contribution to improving cost-competitiveness, as outlined above.

Table 1: R&D&I needs for lignocellulosic ethanol

Topic	*State-of-Art*	*R&D&I needs*
2nd generation/advanced cellulosic bioethanol: pre-treatment	A number of pre-treatment strategies have been developed to enhance the reactivity of cellulose and to increase the yield of fermentable sugars.	• In addition to improving the cost-effectiveness of the pretreatment steps themselves, the quality of the pretreatment also influences the yield and bioavailability of fermentable sugars and the presence of inhibitory substances which impact the following fermentation and downstream processing steps. – Identification of cost-efficient combinations of different pre-treatment methods (e.g. alkaline pre-treatment followed by steam pretreatment or organosolvent pre-treatment coupled with steam explosion), to improve the biomass digestibility. – achieve higher degrees of hydrolysis of lignocellulosic biopolymers components into sugars, especially higher yields of hemicellulose separation, of cellulose from lignin, and of glucose from cellulose – achieve low concentrations substances which act as inhibitors in the fermentation step • Addressing the following issues may improve the knowledge base for optimisation of pretreatment – Development of tools to investigate the cell wall deconstruction and understand the recalcitrance during the pre-treatment process, expansion of knowledge on cell wall structure and ultrastructure, and the physicochemical changes occurring within the cell wall at the molecular level and the cellular/tissue scale during various pre-treatment technologies – Breeding (with the help of marker-assisted breeding, genetic engineering and genome editing) of genetically modified lignocellulosic plants with altered lignocellulosic structures, rendering lignocellulose less recalcitrant to pre-treatment

Topic	*State-of-Art*	*R&D&I needs*
2nd generation/advanced cellulosic bioethanol: hydrolysis	Enzyme mixtures are applied for the conversion of pretreated lignocellulose to produce fermentable sugars. Yields of fermentable sugars are not yet high enough, and the enzymes are still too expensive.	• Yields of fermentable sugars need to be improved, the formation of inhibitory substances reduced, and costs for enzyme production and use reduced. Biotechnology and process engineering approaches are needed to develop new highly active enzyme mixtures which can be produced at lower cost: – Identification and optimisation of enzymes that can break down different types of polysaccharides to fermentable sugars, have superior activity and can be produced at lower costs. Lytic Polysaccharide Monooxygenases (LPMOs) are examples of recent progress in enzymes which act differently from known hydrolases (i.e. by oxidising on side of the glucosidic bond instead of hydrolysing it). – Optimisation of cost and performance by process engineering.
2nd generation/advanced cellulosic bioethanol: microbial fermentation	*S. cerevisae, E. coli, Zymomonas mobilis and some Clostridia spp* are currently most commonly used for bioethanol production. They have specific strengths and weaknesses with respect to the ability to metabolize pentoses and their tolerance towards high ethanol concentrations and inhibitory substances.	• R&D&I is needed to bring pentose (primarily xylose) fermentation up to the same speed as glucose fermentation for cases where xylose-rich feedstocks, such as agricultural residues or hardwood are to be used, and no alternative use for the pentoses can be found. • As ethanol is toxic, it is essential to improve the tolerance of the production organisms to ethanol, e.g. by systems metabolic engineering and release from end-product inhibition. This is particularly important in case other production organisms than S. cerevisiae with a lower ethanol tolerance are used. • Another option is the improvement of in situ bioethanol separation in order to keep the ethanol concentration in the fermentation broth below inhibitory levels. R&D&I needs are: – reduce the cost of pervaporation, reduce the costs of gas stripping equipment, improve energy efficiency, control foam formation • Inhibiting compounds are most likely present in the hydrolysate medium, e.g. carboxylic acids and various sugar degradation products. This can be addressed by the following options: – avoiding the formation of inhibitory substances by engineering the pretreatment steps – removal of inhibitory substances by engineering cost-efficient separation steps prior to fermentation – Improving the tolerance of the production organism to these compounds.

Topic	*State-of-Art*	*R&D&I needs*
	Saccharomyces cerevisiae is often chosen for ethanol production due to its high ethanol productivity, high ethanol tolerance and ability of fermenting a wide range of hexose sugars.	• In order to address the above mentioned issues, data-driven and synthetic biology as well as systems metabolic engineering approaches could be followed for different host organisms by introducing pathways for broadening the substrate spectrum (e.g. metabolise xylose), increasing tolerance towards higher temperatures, ethanol and other inhibitors, and for maximizing metabolic flux so that sufficient production rates and complete conversion of substrates can be achieved.
Lignin as co-product	Lignin as a major by-product is currently mainly used as fuel, providing process heat and/or electricity. Cost-competitiveness of the overall process could be improved if higher-value applications for lignin and other by-products could be developed to commercial maturity.	• Improvements in the lignin extraction procedure: lower costs, (higher) lignin quality, depending of its targeted use • R&D&I into various lignin uses, both higher-volume lower-value applications, as well as high-value, low-volume applications; e.g. aromatic building blocks for polymers, composites, coatings, adhesives

3.2.4 Economic Analysis

3.2.4.1 Patent Analysis

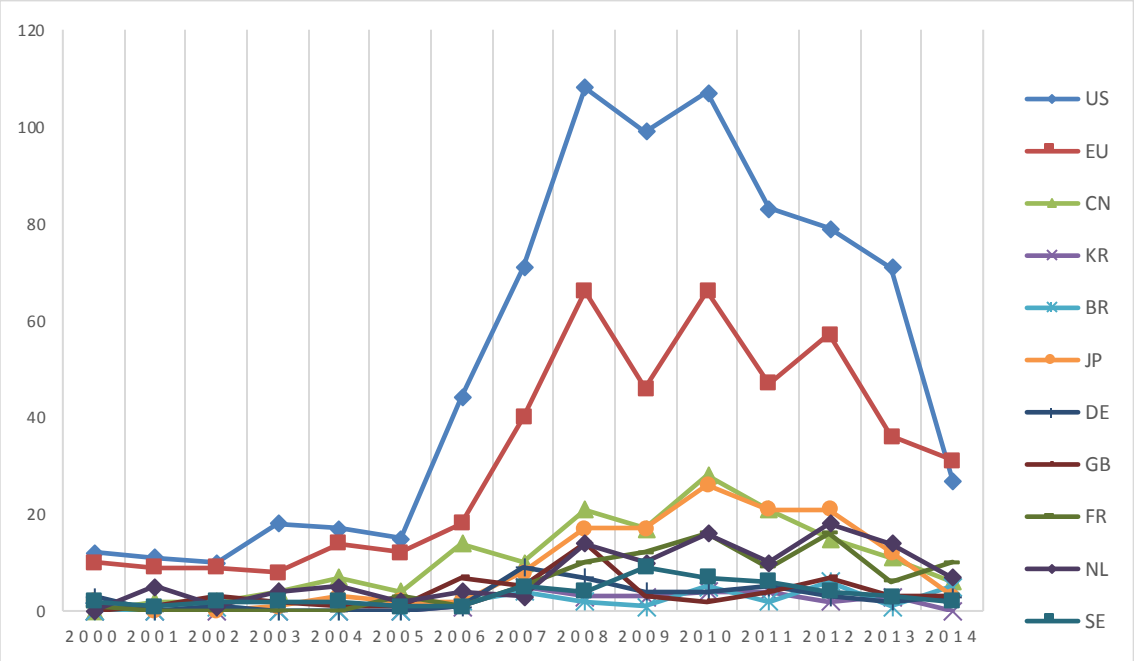
The sustainable production and uptake of biofuels largely depend on the technological breakthroughs, enabled by significant public and private investments in R&D. The US, Canada and many European countries as well as emerging economies such as China, Brazil and India are increasingly involved in the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

[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.

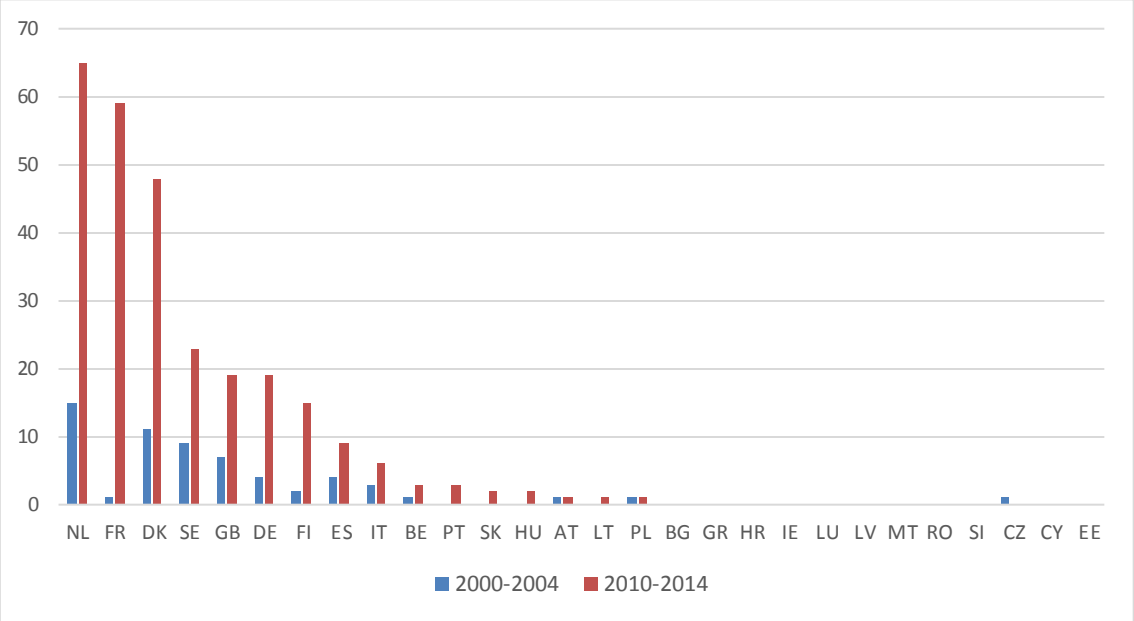
Figure 5: Transnational patent applications for cellulosic ethanol



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 6). 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 6: Transnational patent applications for cellulosic ethanol in the EU countries



Source: Fraunhofer ISI based on WIPO

3.2.4.2 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 3.2.5). 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%
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

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

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.

3.2.4.3 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 their activities (e.g. Enerkema, Raizen, POET-DSM).[7] Moreover, it has to be noted that

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

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

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).

3.2.5 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.

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

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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).

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, gradually decreasing to maximal 3,8 % by 2030. To facilitate the development and commercialization of more advanced biofuels, the contribution of conventional low-carbon

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

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.

3.2.6 Scenarios

Based on the value chain-workshop, the following scenarios for lingo-cellulosic ethanol were elaborated. In the following, a short narrative describing a selection of potential alternative scenarios referring to the respective supporting tables in the Annex. The tables contain the current situation for the critical factors that were identified and prioritized as well as the different future assumptions attributed to different scenarios. The narratives or story lines for the selected scenarios include links to the respective assumptions for the corresponding scenario as shown on the tables (the links T,B and P stand for Technology, Business, and Policy, respectively; the following number corresponds to the line in the table; and, A,B,C,D to the specific assumption). In each scenario, first the starting point is explained, which captures the starting idea of each scenario.

Scenario 1: Policy driven uptake

Starting point: This scenario is characterized by demand-side policy measures (P4B), namely a modification of the current proposal of a new Renewable Energy Directive (RED II). The modifications provide strong incentives for advanced biofuels, but do not contain the currently planned significant reduction in first generation biofuels. As a consequence, existing producers or investors in bioethanol as well as potential new investors commit to advanced biofuels. The measure is integrated in a broader policy mix that comprises coordinated policy funding or tax incentives for private funders for high TRL-stages or commercial production (P6B). Different demand-side measures that aim to realize RED goals are introduced (e.g. Price guarantees via local tenders or exemptions for the use of lignocellulosic ethanol) (P5B).

On the technology side, significant progress is enhanced by specific R&D&I funding for lignocellulosic bioethanol projects throughout different technological-readiness-scales (TRLs). The leading production concept for lignocellulosic bioethanol will be few large-scale versatile biorefineries (T1B). They will use different types of feedstocks, which include among other tailored biomass crops. Significant advances will be reached for pre-treatment and hydrolysis (T2A). Optimized pre-treatment techniques are leading to higher yields and are limiting adverse effects of inhibitors.. More efficient enzymes through optimization or better re-use of enzyme combinations lead to lower production costs. Economic performance will be enhanced by favourable valorisation of lignin and by-products (T3A). The integration of cellulosic bioethanol into biorefineries leads to highest value through broad spectrum of products as well as high value applications for lignin are broadly established. Here an important role of SMEs emerges in creating markets for by-products of ethanol; e.g. firms that are (independent from ethanol) active in

lignin markets (B3B). They create new value products and settle the path for others to use the lignin coming out from lignocellulosic ethanol production to produce those goods.

On the user and investors side commitment for the use of second generation ethanol and to finance new facilities arises (B2A). The build-up of new facilities will lead to scale and learning effects that lead to a convergence of lignocellulosic costs to those of 1 generation bioethanol and fossil fuels (B1B).

In this scenario, prices of oil and biomass have no decisive impact on the total development of the market. The biomass prices will probably increase because of the increasing demand.

Scenario 2: Partial established production

Starting point: This scenario presents a partial uptake of lignocellulosic ethanol. Rather favourable framework conditions with a rising oil price (P1A) and modest biomass price increases (P2B) go a along with only partial established demand-side policies that may foster the uptake of lignocellulosic ethanol. More concretely the current RED II proposal with binding mandates for lignocellulosic ethanol, but a significant cut in first generation biofuels come into place (P4C). Other demand-side policies or public/private financing of commercial activities are only fragmented (P5A, P6A).

Regarding feedstock, agricultural/forest residues, organic (industrial/household) waste as biomass are increasingly used (T1A), often in nearby small scale production sites. Significant advances will be reached for pre-treatment and hydrolysis (T2A). Optimized pretreatment techniques are leading to higher yields and are limiting adverse effects of inhibitors. More efficient enzymes through optimization or better re-use of enzyme combinations lead to lower production costs. Economic performance will be enhanced by favorable valorization of lignin and by-products (T3A). The integration of celullosic bioethanol into biorefineries leads to highest value through broad spectrum of products as well as high value applications for lignin are broadly established. Here an important role of SMEs emerges in creating markets for by-products of ethanol; e.g. firms that are (independent from ethanol) active in lignin markets (B3B). They create new value products and settle the path for other to use the lignin coming out from lignocellulosic ethanol production to produce those goods.

However, due to reluctance on the use and investor side (T2B) and modest policy support, costs competitiveness is only achieved for very few pathways of lignocellulosic ethanol and in certain regions, with favourable feedstock or political conditions. No major changes in industrial structure takes place, with large firms remain dominating.

Scenario 3: Stagnant development

Starting point: This scenario presents a stagnant development of lignocellulosic ethanol. There is neither a development of an external framework, which may drive activities, nor significant policy commitment to bridge the phase and overcome missing cost competitiveness. More concretely, oil price remains low and comparable to current price levels (P1D), public financial support for R&D&I is falling (P3D), there are no binding mandates for lignocellulosic ethanol (P4A) or other demand-side policy (P5A) or strong financing of (near) commercial activities (P6A).

On the technology side, only incremental advances in the provision of sustainable lignocellulosic bioethanol occurs (T1D). Concepts based on straw and wood are further developed, but no major advances in cost reduction achieved. Regarding pre-treatment and hydrolysis, biotechnological conversion does not emerge as favourable option, but gasification of biomass to syngas becomes the predominant process (T2B). Regarding the use of lignin and by-products, energy production remains the most economic advantageous option (T3B).

On the business side, large companies and SME will remain reluctant (B3A), as neither user industry nor financiers provide long-term commitment to build up new plants (B2B). In consequence, rather few scale and learning effects will be realized and cost competitiveness to first generation bioethanol and fossil fuels not be achieved (B1A).

3.2.7 Conclusions & Recommendations

Lignocelluosic ethanol represents a potential mass-market of IB based on non-food biomass and IB will be an important contribution to make biofuels more sustainable. There have been strong expectations in the past concerning the uptake and impact of lignocellulosic ethanol. However, so far development stayed significantly behind those hopes. Because of technological and logistical challenges, it is still not cost competitive against first generation bioethanol or fossil fuels. Hence, market development is mainly dependent on policy impulses. So far, current legislation for bioethanol has not led to a significant uptake of lignocellulosic ethanol, and there are no binding mandates for 2nd generation ethanol on EU-level. While a few plants are operating or are currently being built, there is a reorganization in the industry with some actors stepping out and others coming in. Future development will depend heavily on the specific regulation for 2nd generation biofuels, which has not been finally decided in the EU yet. Policy decisions are highly dependent on how public acceptance and the potential contribution to economic and ecologic goals are perceived. Other factors are of course important as well (e.g. demand needs vs. supply, industry structure, collaboration), but not the main bottleneck.

To foster the development of the value chain in the EU in such a way that it contributes to economic and societal goals the following actions should be taken:

- R&D&I support should be primarily focused on improving cost-competitiveness of production concepts, giving economic considerations and assessments a key role.
- A techno-economic roadmap should be elaborated which covers the whole supply chain from feedstock to product commercialisation. In this roadmap, the costs and the cost-reduction potential of different options should be assessed and R&D&I performed on those approaches which will be required to achieve cost-competitiveness at realistic market prices. It should also take the interdependence of various steps in the process into account, which means that solutions chosen in early process steps may create or avoid problems in later steps.
- The following issues should be the focus of R&D&I support:
  - achieving complete conversion of sugars in the fermentation stage
  - achieving higher ethanol production rates and concentrations in the fermentation stage
  - cost optimisation of downstream processing (i.e. separation and concentration of ethanol)
  - converting by-products (e.g. lignin, xylose) to higher-value products
- Consideration of revision of current mandate plans in a new Directive, which should include setting ambitious mandates for lignocellulosic ethanol, but slower decrease of first generation ethanol, to ensure smooth transition from first to second generation ethanol
- Consideration of increasing penalties, if mandates are not fulfilled, as these are of key importance for the functioning of the instrument

3.3 Bio-based plastics

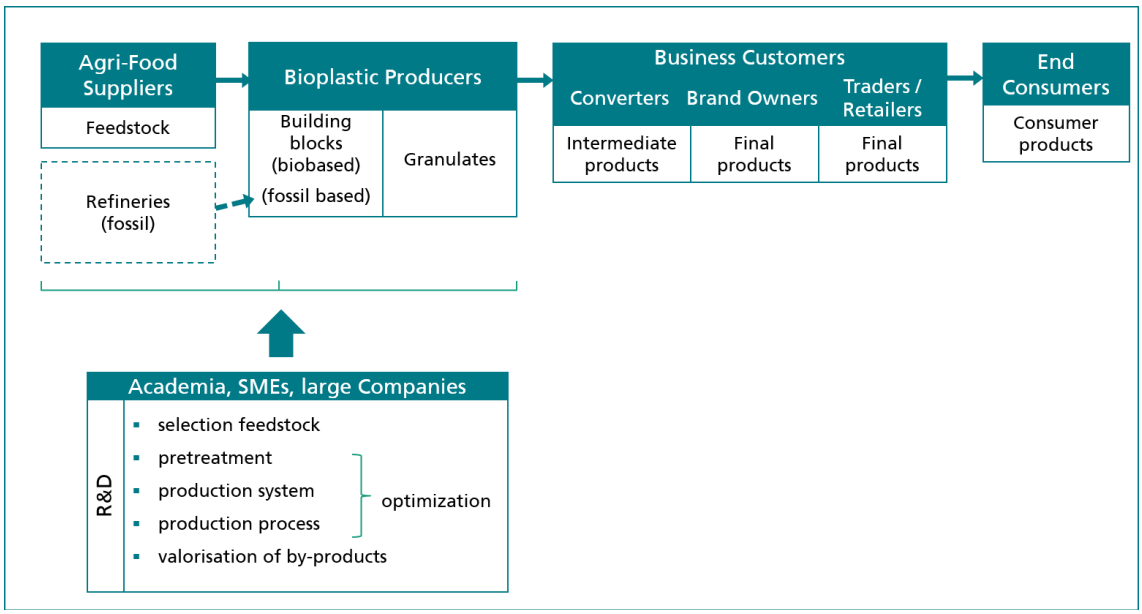
3.3.1 Description of the value chain

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 7) 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 7: Value chain for bio-based plastics



3.3.2 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]

3.3.3 R&D&I needs

Table 4 summarizes R&D&I needs for bio-based plastics which result from their technological and innovation potentials.

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

Table 4: R&D&I needs for bio-based plastics

Topic	*State-of-Art*	*R&D&I needs*
Novel bioplastics	Only few novel bioplastics have been developed to commercial scale. They are not suitable for all desired applications. Presently, bioplastics (partly) made building blocks which are not fermentatively produced are economically more important than most fermentatively produced bio-based plastics.	• R&D&I of innovative, novel bio-based plastics with novel properties and respective production processes is needed in order to satisfy the need for novel bio-based plastics with desired properties for novel applications and uses. However, the search for novel bio-based plastics should be market- and application-driven. These bioplastics comprise both biotechnologically manufactured building blocks followed by polymerization, as well as other bio-based plastics, e.g. based on lignin etc. – Market- and application-driven search for promising bio-based plastics, tailor-made bio-based plastics, including the design of novel bioplastics so as to ensure their recyclability. – Identification and characterisation of promising sources (besides corn, wheat, soy) of biomass feedstock to produce bio-based plastics (e.g. waste streams, lignocellulose, plant-based proteins; see also below). – Exploration of a broad spectrum of novel bio-based plastics in order to identify candidates with promising properties and functionalities for the identified market opportunities. This requires intensified cooperation between microbiologists, chemists, (bio-)process engineers, and material scientists. – For novel candidates of bio-based plastics with promising properties and functionalities, 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 see below). This requires intensified cooperation between chemists and/or microbiologists, (bio-) process engineers and material scientists. – Engineering the properties and performance of bio-based plastics, e.g. by blending, functionalisation, nano-particles, additives. – Scale-up of production processes for novel bio-based plastics in order to reach a critical mass for a given bio-based plastic (e.g. in order to achieve economies of scale, address different market segments and applications, etc.)

Topic	*State-of-Art*	*R&D&I needs*
		• Development of new value chains, establishing novel arrangements and collaboration of relevant actors along the value chain in order to bring the novel bio-based plastics to the market and address novel applications.
Novel bio-based plastics: example plant proteins as feedstock	Plant proteins 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.	• New promising sources (besides corn, wheat, soy) of plant based proteins to produce bio-based plastics need to be identified and characterised. • Protein-based bioplastics require R&D&I to improve mechanical and water absorption properties in order to make these materials applicable in various applications, e.g. packaging.
Novel bio-based plastics: example optimisation of PLA production	PLA production is done on commercial scale. However, further optimisation of the process is required in order to reduce production costs and improve yields and product quality (i.e. optical purity). Moreover, commercial processes for PLA from non-food feedstocks (lignocellulose) need to be developed	Different approaches should be followed for optimisation: • Development of large-scale PLA production processes from lignocellulosic feedstocks, specifically addressing scale-up of steam explosion and improving the yields of process steps of lignocellulose conversion to glucose (see below) • If the fermentation process to produce lactic acid is run at the pH optimum of the strain, precise control of the pH level is required and a certain amount of lactate salt is being produced, being both a cost factor and making downstream processing more difficult. In order to reduce the consumption of pH correcting agent, efficient acidophilic production strains with a pH optimum or tolerance near the pKs value of lactic acid (ca. 3.85) should be developed. • Downstream processing needs to be optimised with the aims to reduce production costs, improve yields and product quality (i.e. optical purity). • R&D&I on adding functionality to bio-based plastics (e.g. engineered PLA grades).

Topic	*State-of-Art*	*R&D&I needs*
Biomass: non-food feedstocks	The majority of bio-based plastics is produced industrially from food crops. Due to the food-first principle, there is a need to additionally exploit non-food feedstocks for bio-based mass products. Bio-based plastics based on non-food feedstocks are still mostly in various R&D&I stages. These processes are still technologically complex (and non-profitable)	There is a need for further R&D&I that would expand the technological biomass potential for IB, especially by utilizing non-food crops, both for production of established (e.g. drop-in) or novel bio-based plastics. • Screening for and assessment of novel, still underused non-food feedstocks: e.g. lignocellulose, whole plants or crop plant residues of 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 or from the textile industry), CO_2, municipal waste fractions. • Characterisation of quality of these feedstocks, followed by three complementary approaches: – achieving a constant level of quality independent of growth conditions in biomass production etc. – development of "feedstock-tolerant" green chemistry processes or fermentation processes and the respective downstream processes which can deal with fluctuating quality of input materials with a fluctuating content of (partly unknown) impurities • Concepts for collection, storage and logistics of the relevant feedstock supply • Development of processes for the fractionation of feedstocks into major components, hydrolysis, if needed cost-effective purification or conditioning processes routes to yield substrates without inhibiting or contaminating substances • Development of processes for valorisation of side streams and fractions of the feedstock which are not converted to bio-based plastics building blocks.

Topic	*State-of-Art*	*R&D&I needs*
Biomass example: lignocellulose	Lignocellulose is being investigated as an abundant non-food feedstock for the manufacturing of bio-based plastics. Cost-competitiveness can only be achieved, if all fractions of the biomass feedstock are valorised, preferably following the cascading principle. A major fraction of lignocellulose is lignin which is presently used mainly energetically. Research is underway to valorise lignin as a source of aromatic chemicals. Potential lignin-derived products could be hydrocarbons, phenols, macromolecules and oxidized products.	For wood as the most dense lignocellulosic material, the following challenges have to be addressed: • Safeguarding the supply of sufficient wood feedstock but at the same time protecting forest ecosystems, avoid contributions to climate change (by deforestation) and maintain soil fertility (by avoiding desertification) by implementation of (certified) sustainable forestry practices and making new plantations. • Addressing the following bottlenecks: – Upscaling of current steam explosion installations to the sizes required for large industrial scales – Improving the yields of hemicellulose separation at steam explosion – Improving the yields of separation of cellulose from lignin – Improving the yields of glucose production from cellulose – overcome hurdles posed by the structural heterogeneity of lignin and the presence of impurities • Market- and application-driven search for promising lignin-derived products • Develop processes for lignin-derived products in order to valorise the lignin fraction, e.g. by integration of biotechnology and green chemistry
Biomass example: Cashew nut shell liquid (CNSL)	CNSL, a relatively underused by-product/waste stream of cashew nut production, 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.	• Market- and application-driven search for promising CNSL-derived products, e.g. use in paints and surface coatings • Optimise cost-efficient extraction processes of CNSL and its subsequent processing • Improvement of CNSL-derived products for use in paints and surface coatings: improvement of colour range, minimize oxidation, improve adhesion to surfaces. • Synergistic combination of biotechnological and green chemistry process steps.

Topic	*State-of-Art*	*R&D&I needs*
Bioplastics Value Chain: Cooperation	There is a lack of cooperation and knowledge transfer between different actors along the value chain.	• Initiatives to support – the formation of novel actor configurations along the value chain, with a specific focus on sectors/industries, which wouldn't be in contact for their "own/core" business – the exchange of information and knowledge between different actors along the value chain, – the joint development of strategies and R&D&I priorities, shared by different actors along the value chain – R&D&I projects with industry-defined topics and goals.
Bioplastics Value Chain: Sustainability	Bio-based plastics (already in use or under development) have several drawbacks regarding sustainability. Recycling and reuse in the after-use phase have hardly been addressed yet.	• Taking economic, ecologic and social sustainability seriously into consideration already in the concept and design phase of R&D&I projects/processes • Improving the environmental footprint of bio-based plastics and their production process, e.g. by using low-input biomass, use of renewable energy in production of bio-based plastics, increasing yields, valorisation of by-products and side streams, improving the energy and resource efficiency of process steps, improving the water use efficiency by water recycling or reuse, waste reduction, replacing process chemicals by less hazardous ones • Water recycling/reuse for saving process steps, costs and improving downstream processing: a major challenge is to connect mostly water-free chemical reactions with biotechnological process steps in aqueous media. • Improving occupational safety of the production process • R&D&I into safety concerns of (bio-based) plastic products, e.g. additives, nanoparticles. • Development of a holistic system to recycle all plastics, including bio-based plastics after use, ideally to high-value products: Logistic concepts for the collection of used plastic products, separation of plastic waste from other waste fractions, recycling process or biodegradation process, processing of recyclate to high-value products.

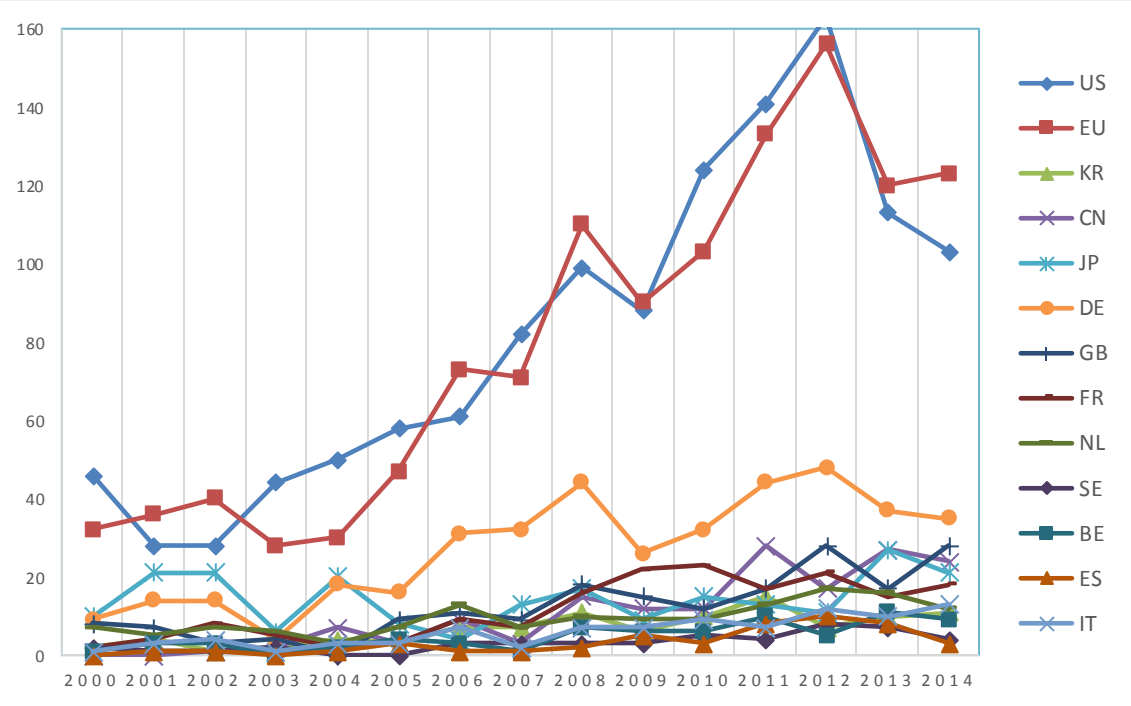
Topic	*State-of-Art*	*R&D&I needs*
Bioplastics Value Chain: Logistics	Logistic issues are crucial on all stages of the value chain, especially in the feedstock processing and in the after-use phase	• Logistic concepts and bio-based plastics manufacturing sites must be designed in a way that technical, environmental and economic requirements are simultaneously addressed: Challenges in collection of feedstock lie in the relatively large (agricultural) area for producing the feedstock, its low energy density and high water content and the resulting limited storability of many feedstocks, having implications for the size, number and location of biomass processing plants (on-farm-site small processing plants vs. large integrated biorefineries) • Logistic concepts in the after-use phase of bio-based plastics still need to be developed, aiming at either biodegradation or recycling, and being compatible with existing concepts for fossil-based plastics.

3.3.4 Economic analysis

3.3.4.1 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 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 8).

Figure 8: Transnational Patent Applications for bio-based plastics



Source: Fraunhofer ISI based on WIPO

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.

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.

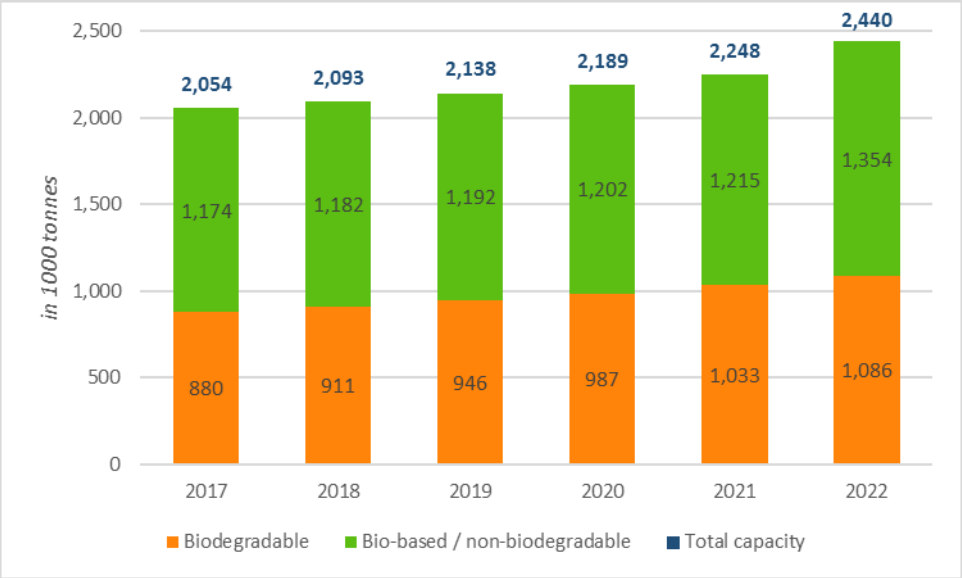
In China, we observe a continually rising number of patents applications since 2002. Starting from a very low level, they were expanding between 2002 and 2014 with an annual average growth rate of around 37%. Although China achieved a breakthrough in patenting activities compared to the period 2000-2002, 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.

3.3.4.2 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 2022. 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.

[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.

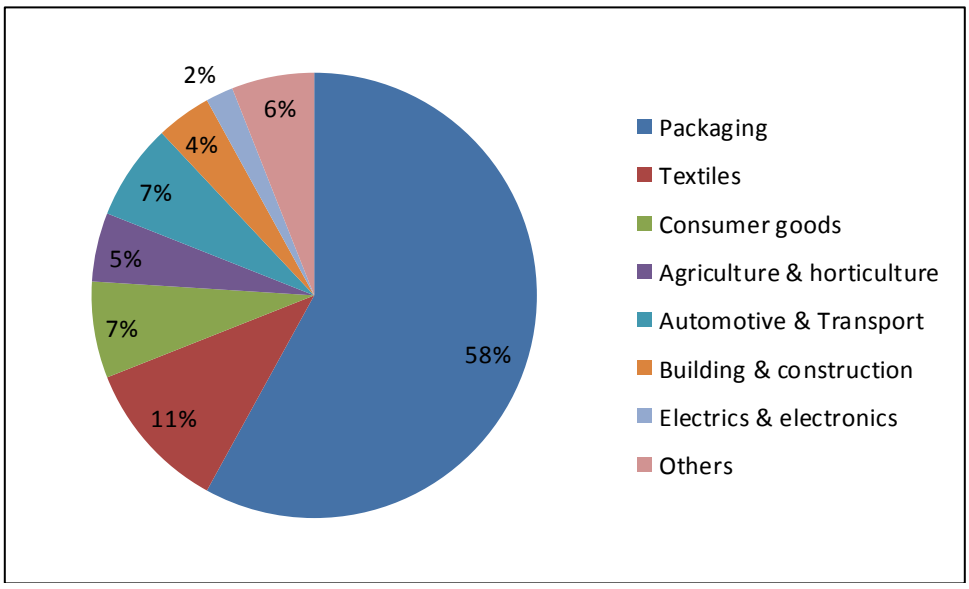
Figure 9: Global production capacities of bioplastics



Source: European Bioplastics, Nova Institute (2017)

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 10).

Figure 10: Global production capacities of bioplastics by segment in 2016 (in %)

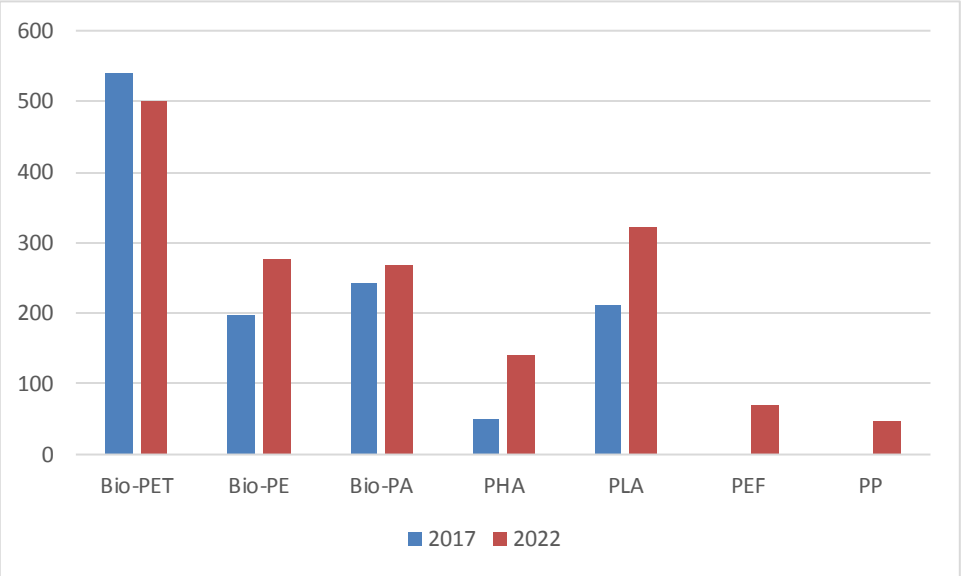


Source: European Bioplastics (2017)

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 11).

Figure 11: 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).

3.3.4.3 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 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

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

[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.

and knowledge between them and encourage the joint development of strategies and R&D&I priorities along the value chain.

3.3.5 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).

3.3.6 Scenarios

Scenario 1: "Derisking strategy"

Starting point: There is a comprehensive, coordinated policy (P4B) regarding bio-based plastics: while funding for R&D&I remains considerable at the status quo level (P3A), additional financing of risky business with strategic importance is implemented (P4B). This takes the form of e.g. flagship projects, public-private partnerships or investment financing and specifically address private funders and higher TRL stages (e.g. pilot/demonstration scale, near commercialization) (P4B). In addition, coordinated market pull measures (e.g. public procurement, tax exemptions etc.) are implemented in the EU (P6B). Moreover, labels and transparent information about bio-based plastics and their

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

benefits (e.g. indicating bio-based content, biodegradability, recyclability) are widespread (P5B).

As a consequence of these coordinated policy efforts, many new market opportunities arise: Bioplastics become increasingly competitive in a wide range of applications (B2C) and are incorporated into a greater diversity of products from a number of industries (B4B). Brand-owners drive the demand for bio-based plastics. In these market segments, some bio-based plastics achieve commodity status and earn more than 1 % of the overall commodity market (B5C). Regarding the share of drop-ins vs. new materials, price, policy and functionality all play an important role (T4C). Due to the diversity of products on the market, bio-based plastics are produced both in large and small scale processing plants (T2B) via many production pathways (T5B). Due to the high production volume of bio-based plastics, more feedstock is drawn to this market with the risk of feedstock shortage. Therefore, the use of a wide diversity of feedstocks is required (T1C, B1C), depending on regional capacities, product specifications etc. The positive market development is further supported by awareness and positive perception in the population (B3A). No special attention is given to plastic waste, so that incineration of plastic waste (both fossil- and bio-based) predominates (T3A).

Scenario 2: High oil price, no additional specific policy measures

Starting point: The oil price rises considerably (e.g. to 127 €/bbl or even 200 €/bbl) (P1B) and thus creates much more favourable market conditions for bio-based plastics than today, making certain bio-based plastics, mostly drop-ins, marginally competitive as commodity (B2B). Price determines the share of drop-ins in the overall plastics market (T4A). Brand owners (e.g. Coca Cola, LEGO) become the primary drivers of producing and bringing bio-based plastics to the markets (B5A). However, the spectrum of products remains limited (B4C) and the demand for bio-based plastics is mainly determined by the brand owners demand (B3C). Production of few bio-based plastics in large amounts takes place in large scale plants (T2A) via few production pathways (T5A), using conventional feedstocks (mainly sugar, starch, fats and oils) (B1A, T1A). No special attention is given to plastic waste, so that incineration of plastic waste (both fossil- and bio-based) predominates (T3A).

Scenario 3: (Micro)plastics receive high attention by policy and consumers

Starting point: There is very high awareness and concerns of (micro)plastics in the environment. This creates a climate in which much stricter policies regarding plastic use and plastic waste are enforced (P6C): there is a trend to ban short-lived plastics which do not

degrade readily under environmental conditions. On the one hand, this creates novel niche market opportunities for certain, biodegradable bio-based plastics (T3B, B2A). They can be easily identified via transparent and widespread labels (P5B). Moreover, recycling of plastics becomes a priority (T3C, T3D), and in addition, water treatment technologies are implemented to remove plastics from water. Functionality, in this case biodegradability, determines the share of bio-based plastics (T4B). On the other hand, there is social resistance to bio-based plastics which do not degrade readily (B3B), and innovation in this field is stifled (B3C). As only few bio-based plastics fulfill all the requirements, the bioplastics markets stagnate or even contract (B4A). Brand-owners drive the demand for bio-based plastics (B5A). Production mainly takes place in small-scale plants (T2C). Due to the recycling-friendly climate, waste is used as feedstock (T1B, B1B), in addition to conventional feedstocks (e.g. starch) (T1A, B1A). As a consequence of feedstock variety and small processing plants, a multitude of production pathways are used (T5B).

3.3.7 Conclusions & Recommendations

Bio-based plastics is a key value chain for IB. Bio-based plastics range from low-cost mass products (drop-ins) to lower-volume-higher-value specialty products, targeted at the Business-to-Business as well as the Business-to-Consumer market. Moreover, it has received significant attention by the public, as there is a rather good understanding of products and applications and a strong interest in environmental issues. Furthermore, the course of evolution of innovation of this value chain, the type of products commercialized, and the future development of the demand for bio-based plastics may have a signalling function for the development of IB in general and for other value chains (e.g. bio-based chemicals, bio-based surfactants, etc.).

The value chain is heavily influenced by a range of factors, from relative feedstock prices, technology innovations, or demand pull to various framework conditions. Today, the cost competitiveness against fossil-based products is often limited and hampers future expansion. Although higher oil prices and a strong support by R&D&I policy are very important, they will not be sufficient to achieve significant changes in the bio-based plastics market. Against this background, rather strong impulses for an uptake may result from an increasing demand pull support for bio-based plastics with improved sustainability (e.g. sustainability assessment, labels, public procurement, B2B success stories).

To foster the development of the value chain in the EU in such a way that it contributes to economic and societal goals the following actions should be taken:

R&D&I policy should continue to support the scientific-technological development of bio-based plastics from basic research to near-commercial phases. Specific attention should be paid to the following issues:

The identification and development of novel bio-based plastics should be primarily market- and application-driven so that the bio-based plastics are tailored to technical and economic requirements of the targeted applications and uses.

R&D&I should be continued to improve cost competitiveness of bio-based plastics from both 1st and 2nd generation feedstocks, with a specific focus on scale-up issues.

Non-food biomass feedstocks, including lignocellulose, CO_2, waste streams, should be explored further. In addition to technology and process-related issues, logistic concepts for collection and storage of feedstocks are required, and concepts for sustainable forestry to avoid deforestation, climate change, loss of soil fertility and desertification. Another focus should be on solutions for fluctuating feedstock composition and quality.

In addition to biotechnology, green chemistry approaches play a major role in bio-based plastics development. A focus should be on the intensified cooperation between chemists, biotechnologists, (bio-)process engineers and material scientists.

Bio-based plastics R&D&I should have a focus on reducing the environmental footprint of products and processes. Specific attention should be paid to water use in processes which comprise both process steps in aqueous media as well as organic solvents, with the aim to bring the different reaction requirements closer together (e.g. novel catalysts, water reuse).

The neglected issue of dealing sustainably with bio-based plastics in their after-use phase should be addressed by educating consumers on concepts for recycling and biodegradation, which are also relevant to fossil-based plastics.

To improve the access to sustainably produced biomass at reasonable prices, e.g. by supporting valorisation of side or waste streams from industrial production processes, by intensified collaboration between EU countries with strengths in biomass production conversion, and by intensified collaboration between actors from feedstock provision and feedstock conversion sectors.

Risk-sharing is of major importance for bringing bio-based plastics to the market. Therefore, financing of (near) commercial activities in the TRL range of 6-8 should be improved. This includes flagship projects, Public-Private Partnerships and financial instruments for industry (e.g. new type of financial instrument by ESIF or others). These instruments could target pilot and demonstration units in the EU, upscaling and commercialization.

Continuation of EU standardization/ labelling activities for bio-based plastics by aiming to enable claims for sustainability issues and to provide distinction between ”bio-based” and “biodegradable". Recognized standards for sustainability assessment and corresponding trusted certification schemes are needed in order to facilitate the assessment

and communication of benefits of IB processes and products both for company decision-makers as well as consumers.

In order to support market- and application-driven development of bio-based plastics, efforts should be taken to attract novel actors into value-chain oriented R&D&I projects and information campaigns. These novel actors should be from high-volume markets for traditional fossil-based plastics (e.g. automotive, construction etc.) which are potential application sectors for bio-based plastics, but would not join respective efforts on their own initiative because it would not be their present core business.

Ensure that bio-based plastics play an important role in the EU Circular Economy and in the future implementation of the Plastics Strategy, which may include relevant market uptake measures. Those measures may include for example improved recycling systems for bio-based plastics as well as a stronger consideration of bio-based plastics in public procurement.

Consideration of bans of fossil based plastics where bio-based / biodegradable plastics have demonstrable environmental benefits.

3.4 Enzymes

3.4.1 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.

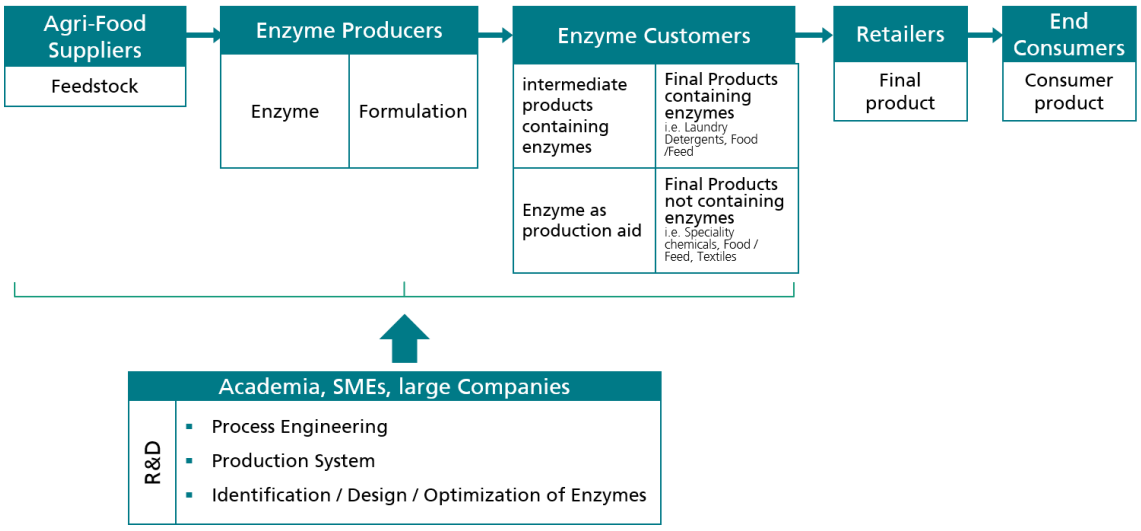
While enzymes are already established for many application areas, there is a demand for novel or improved enzymes to enable economically competitive and more sustainable solutions (van de Velde et al. 2013), as enzymes are key enablers for substituting fossil feedstocks by renewable ones.

Enzyme producers sell enzymes after purification and formulation as intermediate products to business customers (Figure 12). 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 12: Value chain for Enzymes



3.4.2 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.

3.4.3 R&D&I needs

Table 5 summarizes R&D&I needs for enzymes which result from the technology and innovation potential.

Table 5: R&D&I needs for enzymes

Topic	*State-of-Art*	*R&D&I needs*
Broadening the spectrum of enzymes in IB	Very few of the enormous abundance of naturally occurring enzymes are used in IB processes. Most of the industrial bioprocesses are based on biotransformations using single enzymes. Mainly hydrolases are used for bulk applications, for speciality enzymes, the spectrum of enzyme classes is broader than the enzymes that are commercialized or in industrial use	• Identification of novel enzymes (see below), de novo design and generation of novel enzymes • Optimization of enzyme properties for industrial use (see below) • Development of novel enzyme production concepts (see below) • Development of novel concepts for enzyme-catalysed processes (see below), e.g. engineering of enzyme cascades/multienzyme reactions, co-factor regeneration, etc.
Identification of novel enzymes	Currently established methods to identify new enzymes are: screening of enzyme producers from natural sources, metagenomics and in silico screening, high throughput screening and de-novo design of tailored enzymes	• Enzyme classes, reaction types: There is a need to expand the number of enzymes for industrial use which catalyse 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) • Further technological improvements of high-throughput screening methods which are either applied for the screening of naturally occurring enzymes or in the process of enzyme engineering: – Developing different screening concepts: 1) cells as reaction compartments, 2) in vitro compartmentalization via synthetic droplets, 3) micro-chambers. – Screening of genomic libraries without cloning step, using cell-free translation, thus overcoming limitations posed by the expression host *E. coli*; further miniaturisation (e.g. microsystems, microfluidics); – 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, novel detection systems (i.e. beyond fluorescence) for high throughput screening

Topic	*State-of-Art*	*R&D&I needs*
		– Screening of still "underinvestigated" sources/ecosystems with a higher likelihood of success: e.g. screening of microbiomes, marine sources, or extreme environments – de novo design and generation of enzymes. see below
De novo design and generation of enzymes	There is knowledge on the structure-function and dynamics-function relationships, but not yet sufficient for de novo design of tailored enzymes from scratch	• For *de novo* generation of enzymes the ultimate goal in rational design of industrial enzymes is to *de novo* generate enzymes with new and robust catalytic functions for industrial processes. For that R&D&I is needed to advance knowledge on the structure-function and dynamics-function relationships. • New/improved models to predict structure/functions relationships in order to improve in-silico predictions.
Optimization of enzyme properties	Protein engineering both by random mutation, by evolutionary and rational approaches is well established. The number of targeted alterations that can be introduced with reasonable effort (e.g. number of amino acid exchanges) has risen considerably.	• There is a general need to optimize enzymes for industrial purposes, to enhance their properties, as their application in industrial processes requires properties that do not exist in naturally occurring enzymes. • Properties of interest for engineering enzyme activity are e.g.: broadening tolerance to harsh process conditions (e.g. pH, temperature, chemicals), 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. K_m-value, velocity of the reaction, reduced product inhibition, inducibility/conditional activity), stability under reaction conditions, activity in organic solvents. • Properties of interest for engineering enzyme production are e.g.: optimisation of overexpression in the production host, e.g. by optimising codon usage, folding, protein export, ease of downstream processing (e.g. tags for purification), minimising protein degradation • Properties of interest for enzyme application are: reduced sensitisation potential (e.g. allergic reactions), performance in the target application, stability and robustness during logistics, storage and under reaction conditions • Enzyme engineering applied in the context of/for the purpose of metabolic pathway engineering: protein engineering strategies employing protein scaffolds for

Topic	*State-of-Art*	*R&D&I needs*
		enzyme co-localization or substrate channelling can enable higher pathway efficiency • Enzyme engineering could be further improved if the general lack of structural and mechanistic knowledge about enzymes could be overcome. More specifically, main R&D&I needs include deeper understanding of: substrate/product inhibition, enzyme stability, substrate specificity and enantioselectivity, and the ability to model and simulate these properties in order to support rational approaches in enzyme engineering. • Enzyme engineering with the aim to establish more complex biocatalytic systems and processes, e.g. artificial multi enzyme complexes, reactions cascades, e.g. by co-localising enzymes on scaffolds, enabling substrate channeling etc.
Hosts for enzyme production	Currently, Bacillus subtilis is the most widely used host organism in industrial enzyme production. Alternative concepts (e.g. cell-free protein synthesis) are established at laboratory scale.	• There is a general need for secretory hosts to enable large–scale production and therefore an R&D&I need to establish novel host organisms (e.g. fungi, yeast) with the ability to effectively secret proteins into the medium, by improving tools for engineering the host, e.g. by the ability to introduce or delete genes and to improve the level of protein expression, and by applying systems biology, modelling and simulation. • Development of synthetic biology approaches (e.g. chassis and cassettes, genome reduction), and their application to construct efficient enzyme production hosts. • Developing alternative concepts (e.g. cell-free enzyme production) to industrial scale maturity.
Production process for enzyme production		• There is a general need to further optimise enzyme production processes with respect to biotechnological, economic, ecologic and safety parameters. • Further automatisation and integration of unit operations, process analytical technologies, digitalisation of production.

Topic	*State-of-Art*	*R&D&I needs*
Development of novel enzyme applications, optimisation of enzyme applications		• See also other PROGRESS value chains, all require novel or optimized enzymes for innovative or improved processes and products. • Combination of chemical and enzymatic synthesis • Enzymes and enzyme cocktails for using novel carbon and energy sources, e.g. for waste and valorisation of production side streams, for CO_2 as substrate and for lignocellulose. • Transfer of enzyme production skills to recombinant protein production and engineering, e.g. new protein-based materials (e.g. made from silk protein).
Novel approaches		• Development of enzyme production in cell-free systems for different purposes (e.g screening, research, commercial production). – Development of novel, cell-free reaction compartments for enzymatic reactions – Development of complex biocatalytic systems for cell-free metabolic engineering, e.g. enzyme cascades by choosing or engineering suitable enzyme combinations (matched by their substrate specificity, catalytic activity and reaction conditions), targeted and ordered immobilisation (co-localisation), e.g. on scaffolds or as artificial multi-enzyme-complexes, scale-up to industrially relevant scales.

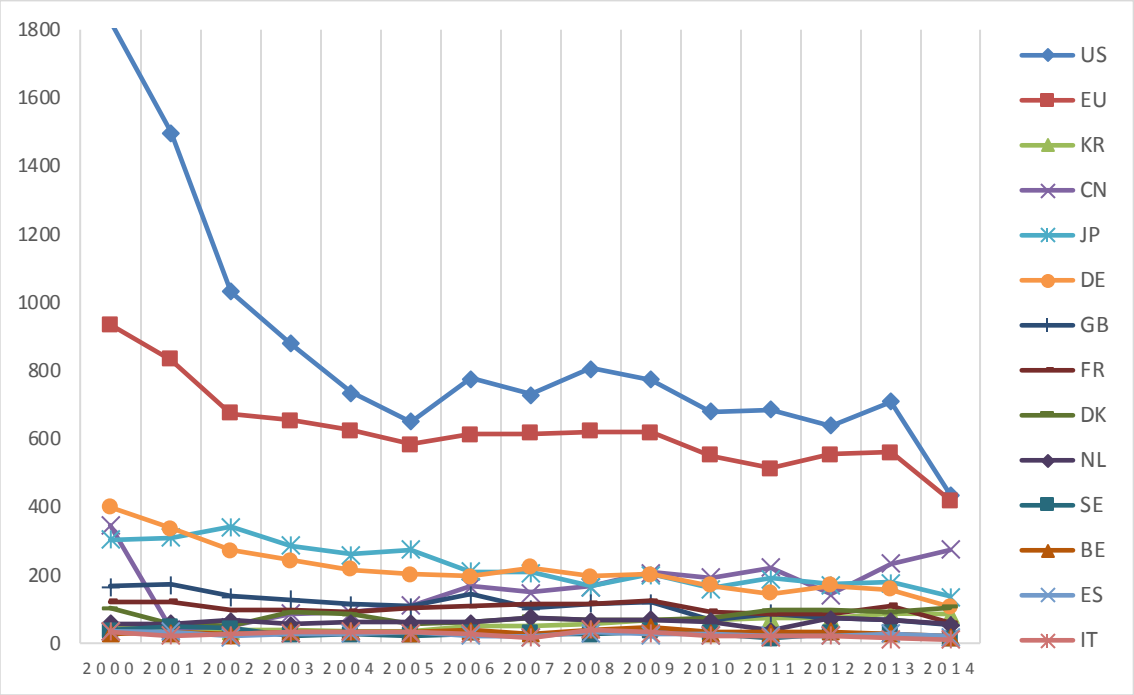
3.4.4 Economic analysis

3.4.4.1 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 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.

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

Figure 13: Transnational Patent Applications in Enzymes



Data Source: Fraunhofer ISI based on WIPO

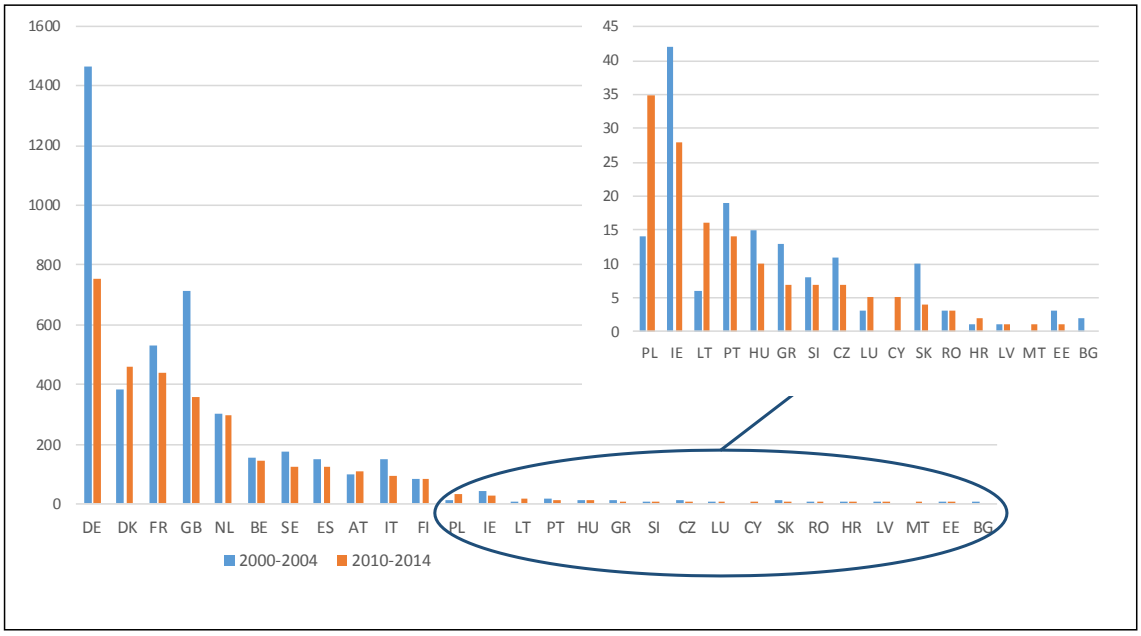
Along with the US, the main countries with intensive innovation activities in the field of enzymes are Japan, South Korea, Germany, Denmark, France and Netherlands (Figure 13). These countries recorded significant shares of total global enzyme related patent applications during the entire observation 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 Member 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 14: EU Countries: Transnational Patent Applications in Enzymes



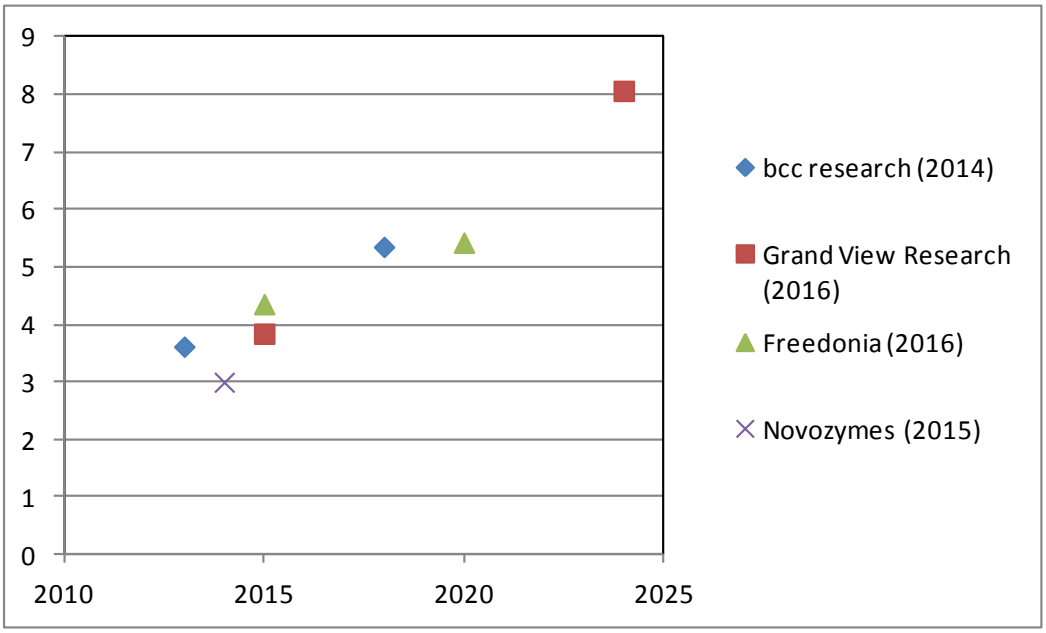
Data Source: Fraunhofer ISI based on WIPO

3.4.4.2 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).

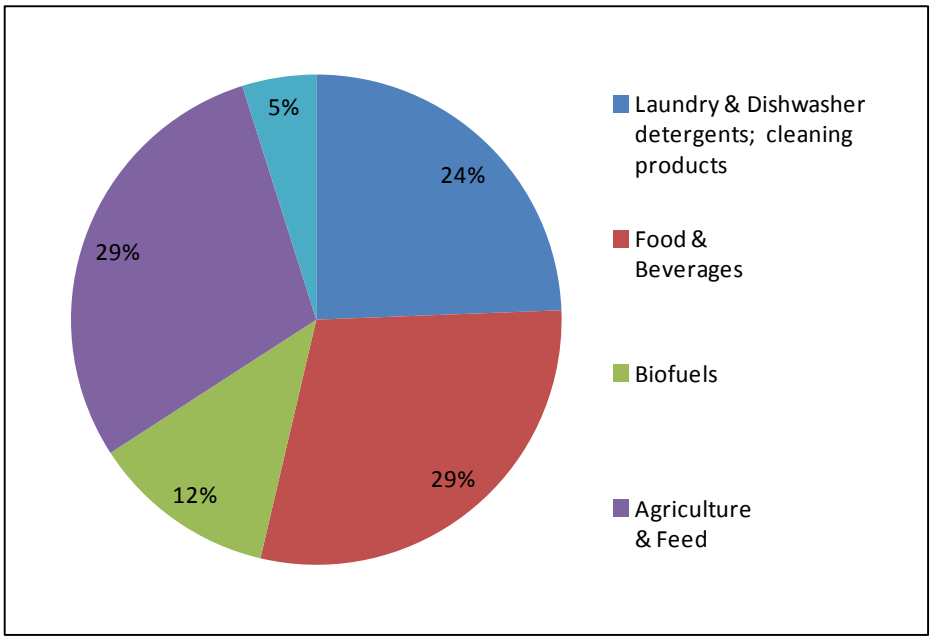
The global market for industrial enzymes was estimated to be around 4.2 billion US-Dollars in 2014 and was expected to reach 6.2 billion US-Dollars (Singh et al. 2016) to 7.2 billion US-Dollars (Freedonia 2016) by 2020 – at a compound annual growth rate (CAGR) of 7% (Singh et al. 2016). Other market studies' assessments of the enzymes market fall in with it and predict high growth for the next years (Figure 15). 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 15: Market estimations for enzymes (world market in billion Euros)



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

Figure 16: 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).

3.4.4.3 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).

3.4.5 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.

3.4.6 Scenarios

Scenario 1: Technology push, everything is optimal

Starting point: Substantial technological progress is higher than in Scenario 2, new options (e.g. production hosts, cell-free systems, rational improvement) are quickly developed and taken up by industry (T1C, T2B, T3C, T4B, T5B, T6C, T7aB, T7bC). The IP framework supports intensive cooperation of academia, SMEs and large enzyme companies (B3C/D).

New enzymes and new applications thrive. Markets expand in all segments (B1A/B, B2A/B, B5A). Europe maintains a leading position in enzyme innovation (B6C), in production (B4A) - there is even relocation of enzyme production from Asia to Europe (B4D)! Enzymes are perceived positively by customers and end-users (B7B). Regulation becomes clearer and more transparent without limiting enzyme applications (P3B).

Scenario 2: Coordinated bioeconomy policy, but global competition

Starting point: Rather favourable conditions for R&D&I (P1A), market pull measures = market expands (P2A), but increasing competition from Asia (B6A, B5B, B4B, B4C). This competition remains limited, because European players can maintain certain market shares due to their technological excellence (T7abB).

Rather favourable conditions for R&D&I result in good progress in R&D, both in academia and industry. There is a moderate knowledge transfer between the big enzyme industry and innovative SMEs, but not between academia and big enzyme companies because of the IP framework (B3B). R&D&I efforts result in moderate broadening of industrial production platforms, but established ones remain most important (T1B). Random approaches for optimization of established enzymes increase significantly (T2C) due to progress in high throughput screening (HTS); another option is, that rational optimization also increases due to favourable conditions for R&D&I (T2B) and increasing competition from other players/countries. The identification of new enzymes receives a push from screening technology breakthroughs (T3B). There is also progress in formulations through computational tools and knowledge-based understanding (T4B). New enzymes are evaluated for their potential applications, especially for example for valorisation of wastes and by-products (T5B). Process development remains a challenge, but

market pull creates sufficient incentives to overcome hurdles (T6B). European players have a competitive advantage over Asian competitors because they use new processes, e.g. enzyme cascades or continuous processing at industrial scale (T7B) or use synthetic biology, the latter having, however, a minor role for industry (T7B).

There is a considerable extension of the market for enzymes, both for industrial as well as laundry enzymes, because the replacement of chemicals by enzymes is favoured by high oil prices and environmental concerns/regulations (B1B). New industrial processes using established and also newly developed enzymes are implemented (B2B). Moreover, positive perception of enzyme use by end-users has an additional positive impact (B7B), the favourable perception of enzymes is partly due to awareness raising campaigns which focus on the innovation aspect and the positive environmental impacts. Due to growing wealth in developing countries, emerging players in developing countries get big enough to become global players and compete with present leaders (B5B). Present market leaders loose shares of the (expanding) market to Asian competitors (B4C); European producers especially withdraw their production from Asian countries, but still distribute their products globally (B4B). Saturation in Western markets triggers R&D&I into customer-specific solution, e.g. through novel combinations of laundry components, and into novel product forms (e.g. lower water content) (B1B). With respect to R&D&I investment, talents and competencies, Europe and the US remain among the leading countries, but China/Asia catch up quickly and obtain a leading position in certain segments (e.g. commodity enzymes) (B6A). Safety aspects of enzyme exposure are no major issue; it is being dealt with by standard operating procedures in industry (B8A).

Scenario 3: High oil price, but consumer concerns

Starting point: The oil price is high and thus creates favourable conditions to replace fossil-based chemicals and processes by enzymes (P2C, B2C). However, there is growing concern of consumers of genetically modified organisms and adverse health effects of enzymes (B7A). NGOs run anti-enzyme campaigns. As a consequence, regulations for enzymes become stricter (P3A).

The progress in R&D&I and innovation is less than in scenario 1, because there is less revenue from the markets and thus less private investment in R&D&I (e.g. T3D, T5C, T1A, T2A, T4A, T3A). Public funding of R&D&I remains on a comparable level as today and is focused on certain fields (P1B, T2D). The high oil price favours R&D&I bioeconomy initiatives (P2C). The R&D&I focus shifts to fields which are compatible with the enzyme regulations and public concern, especially to non-GMO production, natural production processes, synthetic chemistry, non-sensitizing enzymes and their formulations, and cell-free production systems for enzyme applications close to end-consumers (T4B,

T2D). In fields which are hampered by negative public perception (e.g. synthetic biology) (T7bA), enzyme development is significantly slowed down, redirected or moved to other countries (T1D, T2D). The enzyme industry sticks to the established expression systems (T1A). The high oil price favours the replacement of chemicals by enzymes in industrial processes, but the full potential cannot be exploited due to negative public perception (T3A). Process development is improved for industrial processes not hampered by public perception. It remains on status quo level in the other segments (T6A). There is certain progress in academic R&D&I in rational optimization of enzymes, but is not taken up by industry (T2A). One of the reasons may be that big enzyme companies reduce their cooperation with SME and academia (B3A).

The market also becomes segmented: applications develop positively, where the high oil price drives enzyme use and which are not significantly impaired by negative public perception and regulation: here, new enzymes are introduced, also for new applications (B2C). Enzyme applications close to consumers and of public concern decrease, e.g. food and drink, personal care products (B1D). There is increasing competition of enzymes with non-enzymatic alternatives on a case by case basis, depending on labeling requirements, public concern, oil price and benefits from enzyme use (B1A, B1D). New applications of new enzymes are being developed in certain segments (B2C). With respect to the geographical distribution of activities, Asia takes over in R&D&I because investment, talents and competencies are developed and supported in the whole enzyme field whereas Europe focuses strongly only on certain segments and has given up development in other segments (B6B). Emerging enzyme producers in developing countries become global players, replace present leaders in certain segments (B5C) and compete with them in other segments (B4C). Production of enzymes mainly takes place in Asia, the share of Europe and the US decreases (B5C).

3.4.7 Conclusions & Recommendations

Enzymes are key enablers for the

- substitution of fossil by renewable feedstocks,
- optimisation of environmental performance of industrial production processes,
- novel products, processes, services, and applications in a broad range of process industry sectors and consumer goods.

Thereby enzymes usually significantly contribute to the added value of final products and strongly support the transition process towards a bioeconomy.

While Europe is still leading in technology development as well as in production of enzymes, this position is increasingly challenged by competitors in the Asia-Pacific region, since 2015 the second largest enzyme market in the world. A European strength and opportunity in the challenge to stay at the forefront is to focus on technological excellence and innovative products and applications. Here, public R&D&I policy will be important, but R&D&I priorities and marketing strategies of the large leading companies will be equally important to shape the innovation paths, as those companies clearly dominate the whole market. However, SMEs also have an important role in innovation as fast-acting and pioneering actors which provide substantial input into product pipelines. While modes of cooperation between large companies and SMEs are established, high profile collaborations between large companies and university and research institutions are often hampered by disagreement on IP issues.

For successful commercialization of R&D&I results favourable market conditions and demand pull are indispensable. Such impulses can result from increasing oil prices, required environmental standards that are easier to fulfil by using enzymes and/or by positive public perception of enzymes in various applications. The present perception is rather positive for the enzyme industry. However, there are latent concerns regarding the use of certain technologies (e.g. genetic engineering, synthetic biology) especially in applications where enzymes come in direct contact with the human body (e.g. food, personal care products), related safety issues, and labelling requirements for product ingredients which may trigger the layman's perception of a "dangerous" product. These concerns may become more prominent in the future.

To foster the development of the value chain in the EU in such a way that it contributes to economic and societal goals the following actions should be taken:

- With respect to R&D&I policy funding, projects aiming at broadening the spectrum of enzymes for use in IB should be prioritised. This comprises the following R&D&I topics:
    - identification of novel enzymes with a focus on other enzyme classes/reaction types than hydrolases, technological improvement of high throughput and in silico screening methods, the screening of still "underinvestigated" sources/ecosystems, and the *de novo* design of novel enzymes. An emerging research field for redox reactions are bioelectrochemical systems.
    - for the *de novo* design of novel or improved enzymes from scratch, R&D&I is required on the structure-function and dynamics-function relationships and the development of new or improved in-silico models for the prediction of structure/function relationships, and the application in the design of industrially relevant enzymes with new and robust catalytic functions.

  - There is a constant need for optimization of enzyme properties for industrial use; the enzyme properties of interest for optimization are various aspects of enzyme activity, enzyme production, enzyme application in industrial processes, for the purpose of metabolic engineering and for the establishment of more complex biocatalytic systems.
  - the optimisation of enzyme production hosts, e.g. by synthetic biology approaches and systems metabolic engineering, the development of novel secretory enzyme production hosts and the required tools for engineering them, and the development of alternative enzyme production concepts (e.g. cell-free enzyme production) to industrial scale maturity.
  - the further optimisation of enzyme production processes with respect to technical, economic, ecologic and safety parameters. Specific attention should be paid to further automatisation and integration of unit operations, process analytical technologies, and the digitalisation of production.
  - Optimisation of enzyme applications and development of novel ones, specific for the respective value chains. Additional foci should be on the combination of chemical and enzymatic synthesis, on enzymes and enzyme cocktails for using novel carbon and energy sources (e.g. waste, CO_2, etc.), and on the transfer of enzyme skills to recombinant protein production and engineering, e.g. new protein-based materials.
  - Emerging approaches such as enzyme production in cell-free systems for different purposes (e.g. screening, research, commercial production), complex biocatalytic systems for cell-free metabolic engineering, e.g. enzyme cascades and multienzyme reactions, co-factor regeneration should also be addressed.

- Continuation of activities towards the transition to the bioeconomy, as new market opportunities for enzymes are created. Hence, a potential revision of the EU bioeconomy strategy with ambitious actions to support demand-pull in new and/or strategic sectors would create strong incentives to use enzymes (see section 5 demand pull).
- Balanced regulation that limits on the one hand current constraints for the authorisation and use of enzymes, reduces the administrative burden, minimises delay of time-to-market and provides more clarity for industry (e.g. regarding implications of Nagoya-Protocol), but on the other hand takes up latent concerns of the public seriously.
- The complex issue of access to genetic resources and the fair and equitable sharing of benefits arising from their utilization should be explored further: the present regulations, laid down in the international agreement of the Nagoya Protocol to the Convention on Biological Diversity, may pose an obstacle espe-

cially for innovative enzyme SMEs in the exploitation of digital sequence information. It should be explored whether an innovation-friendly option for the access to digital sequence information without compromising the requirement that interests of all involved parties must be taken into consideration.

- Support SMEs to develop innovative capacities and to pioneer new possibilities (e.g. dedicated R&D&I funding for SMEs) as well as provide possibilities for engagement in later TRL stages like demonstration or near-commercial prototyping.

3.5 Production of Biopharmaceuticals

3.5.1 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 17) (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.

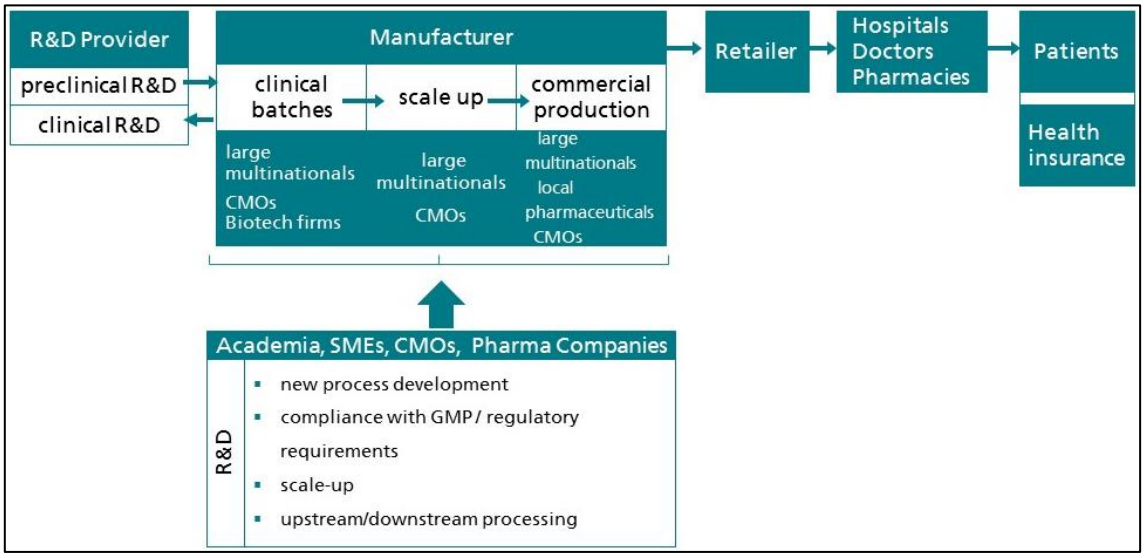
Production challenges can significantly impact the development process and its duration. Manufacturing of biopharmaceuticals is significantly more complex and costly than producing traditional chemical drugs or other bio-based products (Gennari et al. 2017; Behme 2015; Otto et al. 2015). The production 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 17: Value chain for biopharmaceutical production



3.5.2 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).

3.5.3 R&D&I needs

Table 6 summarizes R&D&I needs in the production of biopharmaceuticals which result from the technology and innovation potentials.

Table 6: R&D&I needs in the production of biopharmaceuticals

Topic	State-of-Art	R&D&I needs
Novel production paradigms	The current predominant manufacturing paradigm for biopharmaceuticals is characterised by complex and sophisticated 20+ step processes. They are usually carried out in large volume unit operations in cGMP facilities, equipped with stainless steel reactors, large filtration and chromatography skids, as well as associated piping and hardware. These manufacturing facilities are investment capital intensive and have high operating expenses, mainly due to expensive chromatography resins and large buffer volumes. Due to the trends of personalised medicine, orphan drugs and smaller disease paradigms, these production paradigms are no longer needed for most biopharmaceuticals. A number of advanced biomanufacturing technologies have been or are being implemented in various process steps but the integration into holistic novel concepts is still on its way.	• To synergistically combine different technologies into novel holistic manufacturing processes for biopharmaceuticals which allow the manufacturing of several different products of smaller volumes instead of one single product of large volume. These facilities are scalable and small-volume, with less capital expenditure that enables flexible multi-product manufacturing on demand, responding to current trends in the biopharmaceutical market. • R&D&I needs with respect to different technologies and steps in the manufacturing process are described in more detail in the table below. • Nevertheless, further improvements of established production paradigms need to be continued. They comprise – USP: improvements in cell line development and engineering, cell clone selection, media and feed development, cell harvesting, bioprocess development, reactor design and scale up – DSP: general optimization of individual unit operations, further development of non-chromatographic operations (e.g. to develop alternative technologies to Protein A affinity chromatography for MAb purification, i.e. membrane-based procedures, aqueous two-phase extraction (ATPE), precipitation, crystallization or affinity alternatives). – For process development and optimisation, modelling and simulation of unit operation is needed, as well as mini-plant facilities

Topic	State-of-Art	R&D&I needs
Continuous biomanufacturing	Continuous biomanufacturing means that the processed products are continuously/automatically moved to the next step as each unit process is completed. Currently, continuous biomanufacturing is predominantly implemented in upstream processing (USP): with the help of sophisticated single use technology, e.g. perfusion bioreactors. Productivities much larger (e.g. factor 4) than in conventional fed batch culture can be achieved.	• To develop equipment and instrumentation for integration of unit operations so that a continuous flow of material from raw input to finished product can be achieved. • To combine continuous up and downstream manufacturing technologies to enable higher process intensification. • USP: further improvements of perfusion reactors, e.g. reducing the usage of large volumes of medium; reducing the complexity of the process, as it is currently requiring specifically trained personnel • USP: To establish stable cell lines which maintain their high productivity over longer periods, e.g. two to three months. • USP: To reduce microbial contamination risks, especially during long-term operations • DSP: implementation of continuous purification processes and continuous non-chromatographic separation technologies to overcome continuous processing capacity constraints. • Issue of regulatory relevance: how can a "batch" be defined in continuous manufacturing; role and implementation of quality-by-design principles
Process analytical technology (PAT)	At-line and on-line process analytical technologies have been implemented for process monitoring.	• To expand the range of analytical parameters, especially for product purity and product quality (e.g. control of glycoforms) in on-line or at-line monitoring. • Development of novel sensors or improved systems for such parameters. • Development of novel sensors or improved systems that can be used in small scale single-use systems (e.g. development of a real time release testing approach). • To increase process understanding to the extent that closed loop control for feeding can be implemented (the cell culture receives at any time the amount of nutrients it requires). • Development of PAT solutions in down-stream processes unit operations, e.g. on-line, at-line determined product concentration in TFF steps or on-line, at-line determined control of product for appropriate collection of the desired product pool in a chromatography step.

Topic	State-of-Art	R&D&I needs
		• To develop non–invasive accurate, on-line, real-time monitoring instrumentation which enable further automation of processes (e.g. industry 4.0). • Use of synthetic biology to improve the detection of cellular metabolites with biosensors.
Single use systems (SUS)	Viable upstream and downstream SUS processing options exist (especially in mammalian-cell based processes) and there is a trend towards higher use of SUS.	• The performance of single-use systems needs to be optimised further: – USP: To broaden the applications beyond mammalian cell culture processes, increase the SUS suitability for microbial processes, e.g. by increasing the maximum gas transfer rates – Scale up SUS production capacities – Compatibility of single-use equipment solutions from different suppliers needs to be increased by standardisation.
Manufacturing of novel biopharmaceutical classes and advanced therapy medicinal products (ATMPs)	Novel biopharmaceutical classes such as antibody drug conjugates as well as advanced therapies (i.e. gene therapy, cell therapies) are emerging therapeutic paradigms which require specifically developed manufacturing processes. They have the potential to complement and even replace many biopharmaceuticals	• Further R&D&I needed to adapt manufacturing systems to new types of therapeutic molecules, such as antibody drug conjugates (ADCs), and optimize them • Development and optimisation of novel production paradigms for ATMPs
Established production organisms	Transgenic bacteria and mammalian cell lines are the workhorses in biopharmaceutical manufacturing. Alternative production hosts only play a minor role	• To improve established production organisms, especially with respect to the following aspects – Improvements in cell lines to reduce contamination and protein impurities such as host cell proteins. – Improvements of biopharmaceutical quality e.g. desired glycoforms or other desired post-translational modifications. – Production strains adjusted to reactor capability rather than the other way around (e.g. strains or cell lines that cope with the low oxygen transfer capabilities of SU bioreactors).

Topic	State-of-Art	R&D&I needs
Novel production organisms		• To develop new production organisms: R&D&I towards human cell lines, replacement of avian eggs for vaccine manufacturing, and "pharming" of transgenic crop plants, animals • Find solutions for regulatory approval issues of novel production organisms
Cell free production systems/platforms	Cell free systems exist that could be used as potential production systems for nonglycosylated proteins.	• Cell free systems for non-glycosylated proteins need improvements regarding productivity and product quality • Scale up of cell free systems to commercial scale • Expand the range of proteins that can be produced in cell-free production systems, e.g. establish cell free production systems/platforms for glycosylated proteins, for tailored glycosylation, and specifically modified proteins (e.g. with non-natural amino acids).

3.5.4 Economic analysis

3.5.4.1 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

[25] http://top1000bio.com/

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 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).

3.5.4.2 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 7 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 7: 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).

3.5.5 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

[26] http://top1000bio.com/

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 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).

3.5.6 Scenarios

Scenario 1: Increasing Demand for Biopharmaceuticals

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

Starting point: This scenario is mainly market/ demand driven with a dynamic growth for biopharmaceuticals (in absolute numbers, but also in market shares) that demands for increasing production (B1B). Stratified medicine is widespread and will lead to a diversification of the product and service portfolio, as the development of respective biomarkers and devices as well as testing will be provided complementary to the biopharmaceuticals.

On the technological side, the current "one line, one product" setup stays the predominant production mode for larger volume products (T1B); flexible multiple product operations are only established slowly, as they require too high quality control efforts. The availability of data available in real-time will grow enormously (T3A). Related infrastructure will be set up and related knowledge for data interpretation will grow cumulatively.

Breakthroughs will be reached in terms of more productive upstream methods via new improved organisms (e.g. plants, insects) (T2A). Moreover, respective downstream process are established to improve the process (continuous production, process intensification, new methods). Those advances in manufacturing, e.g. establishment of continuous manufacturing, will lead to slightly declining prices, which will be requested by the moderately continuation of cost containment pressures.

Regulation for biopharmaceutical manufacturing will continue to get stricter, but a higher transparency and growing consensus between regulators and manufacturers enables for a more efficient addressing of regulatory requirements (P3A). In particular, new biopharmaceuticals will receive considerable price reimbursement when they can prove high medical value. (P2C).

Europe is able to take advantage of this development. The number of biopharmaceutical facilities increases smoothly, while the output increases significantly (B1B). The share in production capacities in the EU remains constant and technological expertise can be secured in the EU (B2B). But also the markets and production in emerging countries may grow, as technological innovation and reduction of production cost enables to deliver products to patients there that cannot afford those medicines yet.

Scenario 2: Status Quo Development

Starting point: This scenario reflects incremental evolution in the production of biopharmaceuticals with rather slow technological progress and a rather modest market growth (B1A).

While the manufacturing of existing product groups (e.g. monoclonal or derived antibodies) with known production organism continues to work smoothly, difficulties in manufacturing processes for new types of product arise (T1A, T2C). This may lead to that the

market entry of some new product groups is significantly delayed and hampered. Regarding process analytics advances regarding real time and online monitoring will be achieved, but not all data will be available online (T3B).

The market for biopharmaceuticals grows steadily, but no high growth rates will be achieved (B1A). An important reason is the increasing cost containment pressure for biopharmaceuticals around the world (P2B). Incentives for biosimilars production are enforced, but to a lesser extent for the production of new biopharmaceuticals. For production, this may mean that the demanded volume (but not necessarily turnover because of falling prices) may rise, but also the pressure for more cost efficient solutions will rise. Because of limited probability especially for new products pharmaceutical companies will be rather reluctant in biopharmaceutical production, as the financial outlook is too modest to build capacities for new biopharmaceuticals in development. Flexible CMOs will step in; here, new firms from other fields (e.g. firms such as the already active firms Samsung Biologics, Fujifilm) will increasingly enter the market (B3A). Globally, Asia will catch up and increase their production capacity enormously (B2C). In Europe, the production capacities will fall in absolute numbers and world-wide share. Moreover, the advantages in technological expertise in Europe can hardly be preserved.

Scenario 3: Gene Therapy Breakthrough[29]

Starting point: This scenario is characterized by the establishment of gene therapies in clinical routine, enabled by advances of CRISPR / CAS methods (T1C). This could change medical delivery profoundly: for example, in mono-genetic diseases a one time treatment could become possible compared to medical treatment (e.g. enzyme replacement therapy) over a period of time or even life-long. New therapy forms with new manufacturing requirements will gain importance. While the industry structure will not change profoundly, new SMEs active in gene therapy enter the market (B3B).

In addition to advances in gene therapy, there will be significant advances in biopharmaceutical production, especially in process analytics (T3A). The availability of real-time data will grow enormously (e.g. CO_2 / O_2 / pH values available in real time). Related infrastructure will be set up and knowledge for interpretation will grow cumulatively. Further advances may come from cell-free synthesis, implemented for biopharmaceuticals production on industrial scale (T2B). The distribution of R&D&I activities increases all over the world (B2A). Emerging countries will increase their R&D&I activities along with production capacities. Instead, Europe suffers some decline in share of production capacities.

[29] This scenario was considered as very unlikely by some participants, because of high technology challenges and unclearness of technology design.

The market for biopharmaceuticals grows will grow (B1C), but the product portfolio becomes more diversified due to advanced therapies. Cost containment pressure will continue with significant efforts to link price setting to the additional medical benefit (P2A). Overall, prices will remain high.

3.5.7 Conclusions & Recommendations

Biopharmaceuticals are high-value products, which can only be manufactured economically with the help of IB. Presently, the EU possesses a strong position in global competition, as these complex manufacturing procedures with high quality requirements can hardly be performed by actors in emerging countries. Hence, offshoring plays only a limited role at the moment.

The market for biopharmaceuticals, which determines the production volume, is strongly affected by the development of healthcare budgets worldwide. However, manufacturing comprises only a minor share of the product costs and prices. Therefore, advances in manufacturing will only marginally influence the total biopharmaceutical market size. Nevertheless, there is high pressure to cut production costs, as they significantly affect profit margins, location decisions and the competitiveness of biosimilars against original molecular entities. However, due to the trends of increasing importance of personalised medicine and orphan drugs and due to significant production process intensification, the current predominant manufacturing paradigm for biopharmaceuticals with large capital intensive production facilities for large volume single products are no longer relevant to most biopharmaceuticals. Instead, scalable, small-volume facilities with less capital expenditure that enable flexible multi-product manufacturing of smaller product volumes on demand, are required in order to respond to current trends in the biopharmaceutical market. In addition, emerging therapeutic principles, such as advanced therapy medicinal products (ATMPs; medicines for human use that are based on genes or cells), also require the establishment of highly sophisticated manufacturing procedures. Hence, high needs exist for innovation in biopharmaceutical manufacturing. Globally, the challenge for Europe will be to maintain its strong position against emerging economies that could catch up quickly, especially in the production of biosimilars because of the rising demand in their home market.

To foster the development of the value chain in the EU in such a way that it contributes to economic and societal goals the following actions should be taken:

- R&D&I policy should support industry with the aim to successfully implement the transition from the current biopharmaceutical manufacturing paradigm to novel scalable, more flexible, multi-product facilities.
- Support R&D&I into continuous manufacturing, especially in the development of equipment and instrumentation for continuous manufacturing, in the combination of continuous up and downstream manufacturing technologies to enable higher process intensification, and in addressing the increased risk of contamination and loss of productivity.
- Single-use systems (SUS) play an important role in small-scale, flexible multi-product facilities. The SUS suitability for microbial processes should be increased in order to broaden their application range beyond mammalian cell culture processes.
- R&D&I in process analytical technology (PAT) should aim at expanding the range of analytical parameters in on-line and at-line monitoring, especially for product purity and product quality (e.g. control of glycoforms), for real time release testing approach, for closed loop control for feeding, and at PAT solutions in down-stream processes unit operations.
- Moreover, accurate, on-line, real-time monitoring instrumentation is required which enable further automation of processes (e.g. industry 4.0).
- Development of manufacturing processes of novel biopharmaceutical classes (e.g. antibody drug conjugates) and advanced therapy medicinal products (ATMPs) (e.g. cell therapies, gene therapies, immune therapies).
- In addition to the above-mentioned small scale flexible multiproduct facilities, which are still based on established productions organisms, R&D&I into other production organisms and paradigms is required in order not to lose competitiveness in emerging fields. These are novel production organisms (e.g. human cell lines, transgenic crop plants and livestock ("pharming") and cell-free production platforms developed to industrial scale production.
- In order to align innovation and regulation, it should be defined for quality assurance how the equivalent to "a batch" can be defined in continuous manufacturing. Moreover, to support the implementation of single-use systems, efforts in standardisation should be taken in order to ensure compatibility of equipment from different suppliers. With respect to novel production platforms, solutions for regulatory approval issues of novel production organisms must be sought.
    - It has to be ensured that regulation becomes consistent and transparent, as companies need to know what to expect before investing into developing and producing biopharmaceuticals.
    - Collaboration and accessible infrastructure should be fostered in such way that closed networks are avoided and newcomers (e.g. SMEs) may enter networks to provide new impulse.

- Promote competencies and infrastructure in the public sector and public research on biopharmaceutical manufacturing to ensure quality, control as well as knowledge and personal exchange between private and public sector in the long-term. New technological developments must be taken up by public institutions to keep quality standards in control and to qualify academic research to get industry-relevant competencies to enhance mobility between public-private sector.

3.6 Biotechnologically produced Flavors and Fragrances

3.6.1 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 8). 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 8: Overview of major routes of industrial F&F production, their characteristics, and their specific strengths and weaknesses

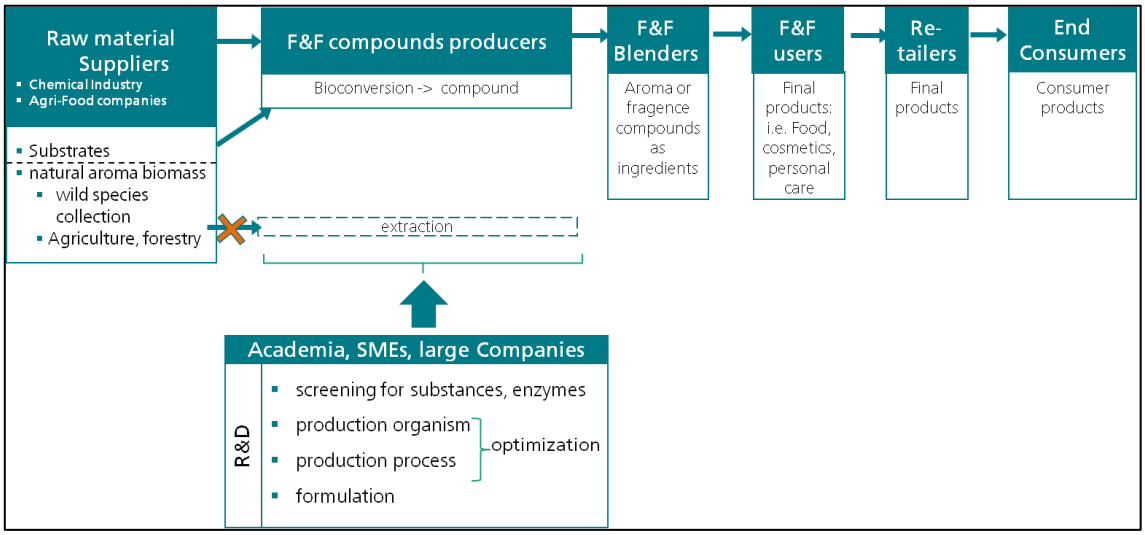
Extraction from natural sources	Chemical synthesis	Biotechnological production
aroma often a complex mixture	aroma made up of one or few major components	aroma may be a complex mixture or aroma made up of one or few major components
aroma produced under natural conditions by the source organism	F&F chemically 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 18). 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 18: Value chain for biotechnological Flavors & Fragrances



3.6.2 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.

3.6.2.1 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).

3.6.2.2 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 8 and Table 9):

- 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 9: 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

3.6.2.3 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.

3.6.3 R&D&I needs

Table 10 summarizes R&D&I needs in the production of F&F which result from the technology and innovation potentials.

Table 10: R&D&I needs for biotechnologically produced flavors and fragrances (F&F)

Topic	State-of-Art	R&D&I needs
Strategic focus of R&D&I efforts	F&F are mainly developed on a case-by case basis. F&F ingredients have to meet the taste specifications of the food or beverage in which they will be incorporated, have to meet national regulations and must cater to - often regional - consumer preferences. Technology experts may lack this knowledge and may focus on F&F and issues which do not make sense from a market perspective.	• Synergistically bring together profound knowledge of technological potentials and of market perspectives for the identification of top F&F candidates for R&D&I • Identify substance families with a broad spectrum of diverse F&F and different uses (e.g. terpenoids) • Identify novel uses and applications beyond the F&F sector for specific compounds or substance families
Identification of novel F&F	Compound libraries and sample collections can be screened for new flavor and fragrance compounds. A major challenge is to produce enough products for further characterisation, as the expression levels or concentrations of the target compounds are extremely low	• Expand the libraries and collections, expecially by underinvestigated sources (e.g. unculturable organisms, extreme environments) • Develop analytical techniques further which are employed to evaluate the aromatic profile (e.g. GC-MS, "electronic nose"), also automated, miniaturized, high-throughput methods • Establish precursor-providing platforms which provides sufficient precursors for testing and characterising novel F&F (and biosynthetic elements, see below)

Identification of novel biosynthetic pathways and enzymes (= biosynthetic elements)	Organism collections and gene databases can be screened for new genes involved in the biosynthesis of F&F. Relevant genes are often organised as biosynthetic gene clusters (BCGs), which encode the enzymes, regulatory elements and transporters that are necessary to produce, process and export a given metabolite. Significant efforts in genome mining for natural product biosynthesis (not restricted to F&F) have yielded several hundreds of novel molecules in the past decade.	• *in silico* screening of genome sequences of mostly unexplored microorganisms (e.g. unculturable organisms, extremophiles) • Further development and use of computational tools in the field of natural product research (e.g. identification of BCGs, annotation of functions based on DNA sequence information, prediction of target compound structures from DNA sequence information of key enzymes) • Develop good practice to narrow down the immense genomic diversity to a limited number of biosynthetic pathways which is feasible to be evaluated. For this purpose, algorithmic approaches for the identification, classification, dereplication and prioritization of biosynthetic gene clusters (BGCs) in genomes and metagenomes are required. Moreover, there is a need to further develop high-throughput and automated procedures, and combinations of bioinformatics and mass spectroscopy • Develop and apply bioinformatic tools which link genomic data on enzymes and pathways to data from the screening of compound libraries or to data from proteomic and metabolomic analyses • Establish precursor-providing platforms which provides sufficient precursors for testing and characterising novel F&F and biosynthetic elements • Feed newly discovered biosynthetic elements and their characteristics into repositories and databases in order to build a resource of a large diversity of biosynthetic elements that can easily be accessed for further targeted engineering

Construction of F&F overproducing strains, suitable for industrial production	As F&F are usually produced by organisms only in minor amounts, substantial engineering of heterologously expressed genetic constructs is required to reach industrially relevant production rates, yields and titers (appr. more than 1g/L). Often, more than 20 genes have to be altered. Therefore, systems metabolic engineering has to be applied. However, classical in vivo metabolic and host engineering is too resource- and time-consuming. Targets of engineering are central metabolic pathways to ensure sufficient F&F precursor supply, reduce flux to competing metabolic pathways, enhance flux to the target metabolic pathway, balance supply of energy and reducing equivalents (ATP, NAD(P)H), establish an appropriate regulation of this system, and address the potential toxicity of overproduced F&F precursors or target compounds.	• Develop a profound understanding of metabolic pathways, required biosynthetic elements and underlying mechanisms, by quantitative characterisation of the required elements (e.g. kinetics, regulation etc.), and by building and refining in silico models of the pathway • Identification (supported by bioinformatic tools) of the best performing biosynthetic elements (e.g. enzymes), ideally from large databases or repositories/collections (see above), and assembly into a functional biosynthetic pathway • Establishment of reconstituted biosynthetic pathways in vitro, • Proteomics and/or metabolomics analyses of in vitro reconstituted biosynthetic pathways with the purpose to better understand rate-limiting steps and to guide further pathway engineering • Broaden the amount of available bioparts (e.g. promotors of different strengths, ribosomal binding sites, regulatory elements) to be easily accessed and used in generating gene and pathway variants, e.g. made available through repositories • Improve and apply combinatorial approaches for generating large numbers of pathway variants and test them in vitro, ideally in high throughput manner for the best performing variants • Improve methods for the assembly of large multi-gene operons (e.g. bacterial artificial chromosomes, BAC) and their integration into the production host genome (e.g. by developing and using faster and more robust genome editing techniques, by providing integration cassettes that facilitate unlimited sequential integration of genetic elements) • Further optimisation of the genes/functional pathways finally introduced into engineered production hosts (chassis) that are most suitable for production, addressing the issues of sufficient F&F precursor supply, reduced flux to competing metabolic pathways, enhanced flux to the target metabolic pathway, balanced supply of energy and reducing equivalents (ATP, NAD(P)H), appropriate regulation of this system • If relevant for the target compound, toxicity of overproduced F&F precursors or target compounds must to be addressed. Further R&D&I is needed for strategies such as – compartmentalization of the pathway, e.g. in peroxisomes in yeast and proteinaceous micro-compartments in bacteria

		– establishment of in-vitro biosynthetic systems on a production scale (see below) – engineering of uptake and efflux systems for the toxic compounds
Optimisation of (key) enzymes involved in F&F synthesis	Metabolic engineering in de novo synthesis of F&F or biotransformation/bioconversion usually requires the optimisation of individual enzymes with respect to their substrate and reaction specificity and selectivity, kinetic properties, and other production-relevant characteristics (e.g. long-term stability). Bioinformatic tools to guide optimisation as well as strategies of (semi-)rational design, (sub-)domain swapping and other combinatorial approaches, and evolutionary approaches have been developed.	Depending on the substances of specific interest, certain enzyme groups are of key importance and may be one of the bottlenecks to be addressed, e.g. key enzymes are terpene cyclases for terpenoids, carboxylate reductases (CARs) for the production of aldehydes, or chain-tailoring enzymes for linear, medium-chain (C8–C12) hydrocarbons. R&D&I needs are the application of the existing approaches and strategies for enzyme engineering to enzymes involved in F&F and tailoring the approaches to specific requirements: • For *in silico* screening and genome mining, the refinement and further development of bioinformatic tools is required, e.g. tools for the identification of gene clusters and the prediction of specific enzymes, assessing the novelty of the detected clusters and genes by comparing the predicted genes with different cluster and compound databases. A more standardized procedure for genome mining for natural products and the corresponding enzymes would be desirable • Identification and establishing genetic parts of sufficient diversity and with the required properties for the engineering of target enzymes • Broadening the knowledge of structure-function relationships, elucidate the enzyme reaction mechanism • Application of established enzyme optimisation strategies in order to alter the substrate specificity of key enzymes in a synthetic pathway – high specificity for industrial-scale production of the target compound of higher purity – broad specificity (= promiscuous) for generating product diversity, e.g. for the creation of natural product libraries with many structurally diverse molecules • Develop applications for the engineered enzymes, improve yields in de novo biosynthesis and integrate enzyme into reaction cascades in in vitro systems

Process engineering for de novo biosynthesis	On laboratory scale, optimisation is often still done in Erlenmeyer flasks. However, state of the art process design and equipment (bioreactors, regulation of important parameters) should be routinely employed.	• Process design and engineering in order to reduce the toxicity of F&F intermediates and target compounds, e.g. by feeding strategies, or in situ product recovery • Process design and engineering in order to overcome low solubility and volatility, e.g. by feeding strategies and biphasic systems • Exploring the potentials of solid state fermentation, as it may have higher yields than submerged fermentation • Optimisation of the environmental performance of the production process by applying the principles of Green Chemistry, especially by reducing energy, replacing organic solvents by alternative solvents (e.g. supercritical fluids (e.g. CO_2),pressurised liquids, ionic liquids), reducing hazardous substances, minimizing water demand and waste water production
Process engineering for biotransformation, bioconversion and synthetic biochemistry	Industrially relevant complex biomolecules (e.g. monoterpenes) can be produced in vitro directly from glucose. ATP and Acetyl-CoA are provided by glycolysis. High titers, yields and production over several days can be achieved. It is the method of choice for producing (semi)toxic chemical compounds, for the optimization of individual enzyme steps or their combinations, and for the production of chemically diverse compound libraries, especially when optimizing the production of high-value chemicals in a high-throughput manner. For industrial scale production, production rates are still too low and costs too high.	• Long-term productivity of the systems must be achieved, e.g. by further optimization of reaction conditions as well as in vitro evolution of enzyme stability and activity, and especially by the development of novel systems for regenerating ATP and NAD(P)H • Further development so that more complex reactions can be performed in vitro • Reducing the enzyme cost, e.g. by more stable enzymes which can be used longer, (= increase total turnover number), by recycling of enzymes • Development of inexpensive purification methods • Explore the exchange of enzymes in the system in order to diversify the products

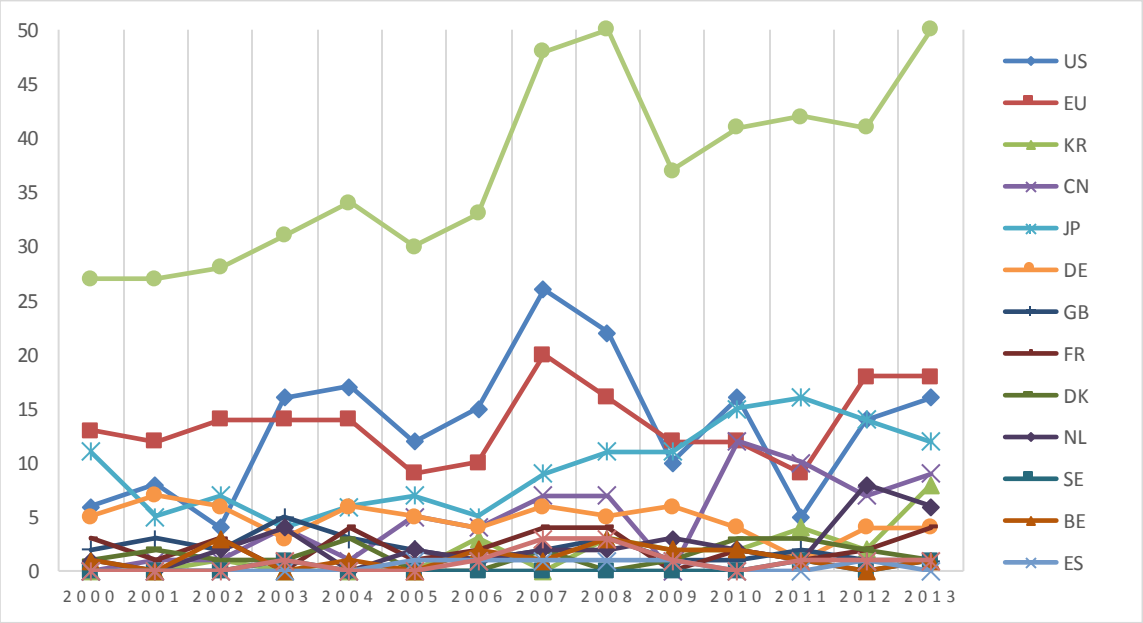
3.6.4 Economic analysis

3.6.4.1 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 19). 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 19: Transnational patent applications in Flavors & Fragrances

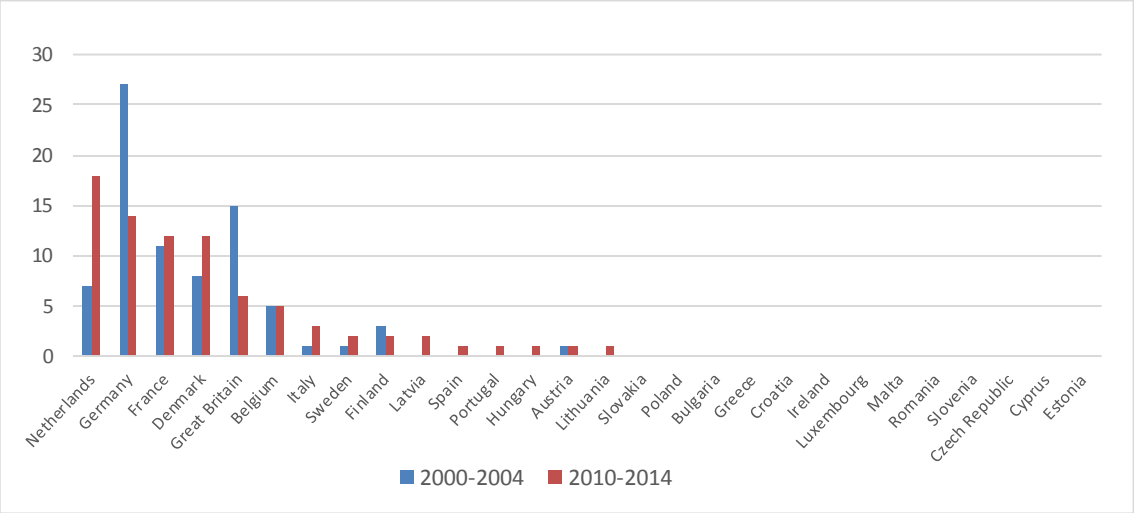


Source: Fraunhofer ISI based on WIPO

Among the EU Member States, the highest patenting activities in this technology field is found in the Netherlands, Germany, Denmark and France (Figure 20). 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 20: EU Countries: Transnational Patent Applications in Flavours & Fragrances



Source: Fraunhofer ISI based on WIPO

3.6.4.2 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.[30]

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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30 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:

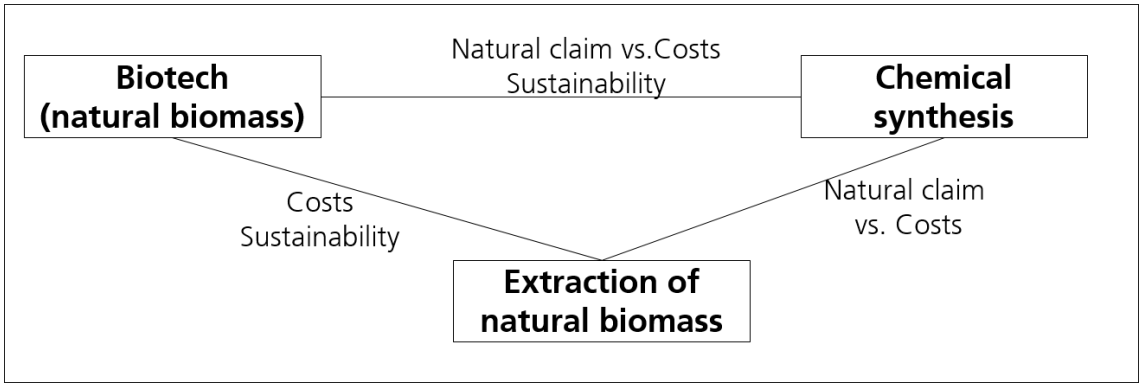
A main hurdle is the high fragmentation of the market. While most of the F&F user industries are dominated by multinational firms, these firms have to serve different geographical markets, which differ in consumer preferences and regulation. Hence, products and market strategies are highly diversified. 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 21.

Figure 21: 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.

3.6.4.3 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.[31]

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 11: 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)

[31] 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 12: 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 12 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 11 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.[32] 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.

3.6.5 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.[33] 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

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

33 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.[34] 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).

3.6.6 Scenarios

Scenario 1: Price driven scenario

Starting point: This scenario is characterized by price driven market developments. While regulations stay mostly unchanged (P2B), technology is optimized mainly regarding cost reduction (T1C).

An increased level of R&D&I funding (P1B) will support the development of basic tools in synthetic biology and the understanding of fundamental metabolic and regulatory processes and the application of synthetic biology approaches to new biosynthetic pathways (T3B). Moreover, problems in the transfer of results from lab to production are increasingly solved (T2C). This will lead to increasing cost competitiveness for biotech products, which is enhanced by the fact that costs for plant-derived ingredients are increasing (B4A).

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

The considerable extension of the biotech F&F market is driven by the key importance of the price for the consumers, also for the "natural ingredient" segment (B1aC, B1bC). And on the same side, regulations will continue to allow flavors claimed to be natural (P2B) even if they are produced by modern biotechnological methods. This is accepted by the consumers: they do not necessarily link the biotechnologically produced compound to the natural ingredients isolated from fruits or plants. However, the price is most important, and the similar aroma is regarded as sufficient. From a geographical point of view, the US will gain a leading position, as the higher availability of Venture Capital leads to strengths in commercialization of synthetic biology (B3B).

Scenario 2a: non GMO scenario – alternative niches for the EU

Scenario Starting point: In this scenario GMO produced flavors are either not accepted as natural by the consumers or are not allowed to use this claim due to an amended regulation (B1aA, B1bA, P2A). While this hampers the diffusion of biotech in the F&F markets there are quite some successful attempts of European actors in advances in non-GMO biotech fields.

Conventional Biotechnologies will continue to dominate the biotech developments (T1B). In particular, the combination of chemical synthesis + enzymes becomes more powerful. However, dedicated funding support for alternative pathways to GMO in Europe leads to some interesting developments: Growing high-content plants are more and more established as alternative for IB (T3C). On the production side, hurdles in scale-up are avoided by the establishment of either small scale production sites or even 3-D printing approaches that lead to widespread production activities (T2A). Europe may gain from such opportunities as it is less focused only on advances in GMO modified production than the US actors (B3A).

On the market side, biotech F&F suffer most from limited cost competitiveness compared to ingredients extracted from natural sources and to chemical synthesis (B4B). Hence, biotech is mostly relevant in niche markets (B3B), e.g. when it is not possible to extract ingredients from natural sources in sufficient quantity or in sustainable ways. Regarding regulation, a new label will be established that declares the use of biotechnology (P2A). Although products with this label will in total be less popular among consumers compared to products with natural claims, higher transparency may lead to an acceptance in the described niche markets.

Scenario 2b: non GMO scenario – status quo development

Starting point: In this scenario GMO produced flavors are either not accepted as natural by the consumers or the regulation is amended in a way that it is no longer allowed to

use this claim for this type of products (B1aA, B1bA, P2A). This leads to a continuation of incremental advances of biotech in F&F markets, but rather slow growth.

Conventional Biotechnologies will continue to dominate the biotech developments. In particular, the combination of chemical synthesis and enzymes becomes more powerful (T1B). Focus of research keeps on the known pathways (T3A), among others as funding opportunities for new approaches are not sufficiently available (P1A). Problems regarding the scale-up prevail (T2A), leading to missing investments for biotech in this sector. As a consequence, expertise in Europe in bio-processes / downstream processing is lost while respective expertise is built up in Asia. In particular China may profit from this development, and use its strength in conventional biotech expand its market shares (B3C).

On the market side, biotech F&F suffer most from limited cost competitiveness compared to ingredients extracted from natural sources and to chemical synthesis (B4B).

Scenario 3: Carbon footprint scenario

Starting point: In this scenario, environmental concerns will gain significant importance as a driver of changes and rules in the market (T1A, B2A). Environmental footprint of F&F will become a major issue, which is usually favourable for biotech (at least compared to natural extraction from plants, but also to chemical synthesis). The trend to valorize waste may lead to new feedstock possibilities for biotech F&Fs.

An increased level of R&D&I funding (P1B) will support the development of basic tools in synthetic biology and the understanding of fundamental metabolic and regulatory processes and the application of synthetic biology approaches to new biosynthetic pathways (T3B). Moreover, problems in the transfer of results from lab to production are increasingly solved (T2C). This will lead to increasing cost competitiveness for biotech products (B4A). However, the main market driver for biotech will be environmental concerns. Sustainability will increasingly determine purchase decisions taken by consumer (B2A). Overall, market diversification for F&F will continue and considerable markets will evolve for Natural Identical (non-biotech), for natural ingredients (biotech) and organic ingredients (non-GMO biotech) (B1aB, B1bB). Regarding regulation, a new label will be established that declares of use of biotechnology (P2A). This label will have a positive connotation for favourable environmental footprint, but also enforce the pressure to find alternative values such as sustainability for biotech F&F, as the advantage to use the same natural claim as for extraction of ingredients from natural sources applies in fewer product cases than currently.

3.6.7 Conclusions & Recommendations

The F&F value chain is very interesting regarding the emergence and development of IB. While biotechnology has been applied for already a long time in selected niches, there is recently technology push by synthetic biology firms. These methods bear the potential to reduce costs significantly, which may enable the diffusion into segments where biotech products haven't been competitive before. Biotechnologically produced F&F have the advantage that they may, according to current EU regulation, be labelled as "natural", a characteristic that is highly appreciated by F&F customers and consumers and premium prices may be charged - which is not the case for chemically synthetized products. Hence, all leading actors in F&F sector have biotechnology methods in their portfolio (either via M&A, collaboration, in-house R&D). Currently, European actors are well positioned in the value chain, but networks are rather regionally concentrated and networks across Europe are rather limited. Moreover, there is strong global competition in conventional (mostly form Asia) and advanced biotech methods (U.S.) for F&F.

Because of the high product diversity in the market it is very challenging to recover R&D&I costs of new products or process innovations. Moreover, for the further development of this value chain a key issue will be whether consumers will accept flavors for food and beverages which have been produced with the help of advanced bioengineering. A major concern is that consumers usually have a different understanding of "natural" F&F than is allowed according to current regulation. It is an open question whether regulation will have to be amended in order to better balance consumers' and industry's interests. Therefore, alternatives to GMO technologies should not be disregarded.

To foster the development of the value chain in the EU in such a way that it contributes to economic and societal goals the following actions should be taken:

R&D&I policy should play a significant role by:

- Supporting the formation of strong networks between European actors from academia, SMEs and key players in the F&F industry
- strategically focussing R&D&I efforts. Top F&F candidates for R&D&I funding should be jointly identified by technology experts and F&F business and market experts because scientific-technologically attractive approaches are likely to fail if the market perspective is not taken into account. It would be desirable to identify substance families with a broad spectrum of diverse F&F and different uses
- funding a broad scope of technology solutions, from synthetic biology to non-GMO approaches
- exploiting synergies between F&F R&D&I and natural product R&D&I especially for methods and R&D&I resources (e.g. compound libraries, culture collections, data bases), as both rely on similar toolboxes and sources for target compounds.

- support the discovery and characterisation of novel F&F and of novel biosynthetic elements (e.g. genes, enzymes, transport proteins, regulatory elements) involved in the biosynthesis of F&F by screening of compound libraries and organism collections, and by data mining, especially from so far under investigated sources. For this purpose, bioinformatic tools and analytical techniques need to be developed further.
- support the expansion and use of repositories and databases as a resource of a large diversity of compounds and biosynthetic elements that can easily be accessed for further targeted engineering.
- support the construction of F&F overproducing strains, suitable for industrial production, by applying state-of-the-art systems metabolic engineering and synthetic biology, and the further development of the corresponding toolbox.
- support the application of the existing approaches and strategies for enzyme engineering to the optimisation of (key) enzymes involved in F&F synthesis both in the context of metabolic engineering of production strains, as well as for in vitro biotransformation and bioconversion.
- support the creation of F&F diversity also with respect to compounds and aromas not found in nature
- Support process engineering for de novo biosynthesis of F&F, with a special focus on scale up
- Support process engineering for biotransformation, bioconversion and synthetic biochemistry, with a special focus on long-term productivity, cost reduction and suitability for complex biosynthetic pathways (e.g. by compartimentalization)
- Support the reduction of the environmental footprint of F&F production processes

Research into consumers' perception and acceptance of F&F produced by extensively engineered organisms and dialogues should be carried out and effective measures should be set up how to balance potentially differing interests of consumers and industry.

- Amend the regulation for "natural claim" to improve transparency for consumers, without posing high administrative burden on industry or hindering communication of attributes that are important for selling

While the regulations on flavors are in principle already uniform in all European countries (EC1334/2008), it still has to be implemented consistently in all EU Member States.

Funding for stronger networks between European actors in the field of biotechnological F&F, e.g. additional COST actions, Research and Innovation Actions (RIA) or Coordinated and Support Action (CSA) with the aim to facilitate EU-wide collaboration.

3.7 Microbiomes for food and healthy nutrition

3.7.1 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 here[35]. 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.

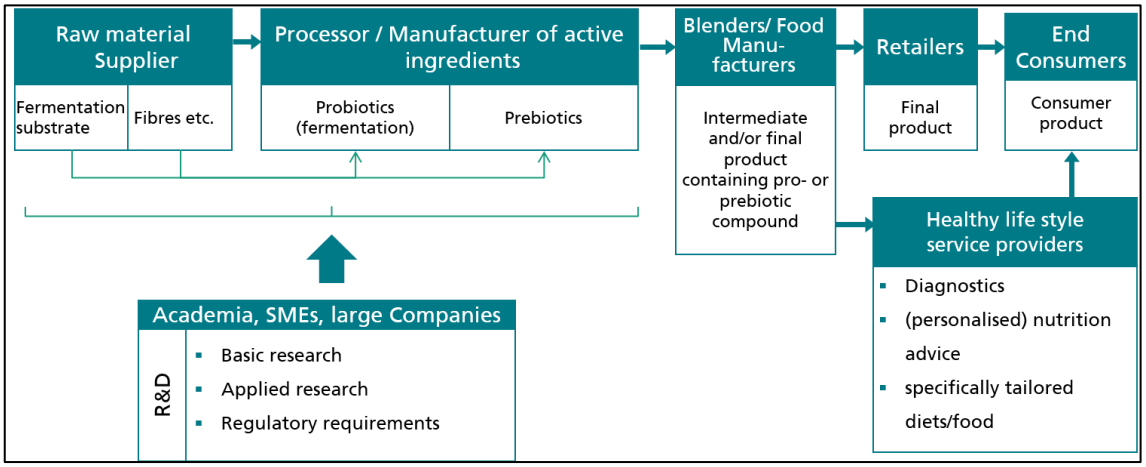
This value chain has the focus on healthy nutrition, lifestyle and prevention. However, the borderline to medicine, disease, and treatment is blurred. This field offers opportunities not only for companies firmly established in the food sector, but also for new entrants, such as diagnostic companies, pharmaceutical companies, bioinformatic companies, big data handlers, and technology providers such as developers of apps or wearables (Figure 25). 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

35 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.

for 177 M €). These EU funded activities covered microbiomes from several body sites (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-BIOME[36], MetaHIT[37], and MyNewGut[38].

Figure 22: Value chain for microbiomes for food and healthy nutrition



3.7.2 Technology and innovation potentials

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.

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

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

38 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).

3.7.3 R&D&I needs

Table 13 summarizes R&D&I needs Microbiomes for healthy food and nutrition, which result from the technology and innovation potentials.

Table 13: R&D&I needs for microbiomes for healthy food and nutrition

Topic	*State-of-Art*	*R&D&I needs*
Microbiome composition	The presence and composition of microbial communities in the human host has been studied and described in different age, ethnic and geographical groups and associations with different health and disease states have been established	Further refinement of the analysis of the structural composition of microbiomes is required by further developing the methods applied, e.g. with respect to • Spatial resolution. Methods for molecular cartography comprise e.g. imaging mass spectrometry (IMS), fluorescently tagged bacteria, transparent model host organisms • Quantitative determination of genus, species, strains • Quantitative determination of metabolites, e.g. by matrix-assisted laser desorption ionization–time of flight mass spectrometry (MALDI-TOF MS) • Establishment of R&D resources, such as inventories, catalogues and "reference microbiomes" for better annotation and assignment of functions to genes, transcripts, metabolites, and organisms, such as well annotated clinical repositories with deep phenotype
From microbiome composition to microbiota functions and mechanisms	Associations of microbiome composition and shotgun approaches with different health and disease states have generated many new hypotheses about causes, and many modes of action have been postulated. However, the molecular mechanisms related to health and disease in host-microbe and microbe-microbe interactions still remains a large knowledge gap.	Need for improvement of methodologies, with the goal to apply these methods to the elucidation of mechanisms of action • Establishment of R&D resources, such as comprehensive catalogues of genes, metabolites, synthetic pathways, and their characterization in order to reduce the number of unknown genes, metabolites etc • Overcome silos in -omics technologies, integrate different -omics technologies, including shotgun metagenomics, metatranscriptomics,and metabolomics, and specifically find solutions to the challenges – choice of appropriate statistical methods and tests – differentiating signal from noise, e. g. by tracking changes in perturbed systems via accurate quantification – identification of genes and metabolites and their annotation, assignment of functions to these genes and metabolites, identification of the origin of metabolites (whether from host, microbiota, or environment) • Identify, characterize and use attractive model organisms and model systems to study various aspects of microbiota functions. Combinations of in vitro, ex vivo, and in vivo models should be used.

Topic	*State-of-Art*	*R&D&I needs*
	Technologies which are able to help define the function of a system comprise omic technologies (metagenomics, metatranscriptomics, metaproteomics, metabolomics) and related bioinformatic tools, the ability to culture diverse intestinal microbes, to genetically manipulate bacteria so that the effects of gain or loss of particular functions can be evaluated, in vitro models, and animal models such as gnotobiotic mice for establishing causality. However, the function of many genes and metabolites is still unknown, the properties of many bacteria are poorly understood, especially if they evade cultivation or if tools are lacking to genetically manipulate them.	Model systems to test hypotheses of microbiota functions should cover a wider range in complexity, such as organoids and bioreactors (e.g. artificial gut) • improve culture methods for until now unculturable microorganisms and for defined mixed cultures • overcome the limited applicability of tools for genetic engineering and genome editing of microbiota members (e.g. probiotic strains) with the aims to introduce subtle genome edits without the need for antibiotic selection and to make the methods less challenging and time-consuming Apply the above mentioned methods and different approaches for the elucidation, testing and validation of proposed mechanisms of actions on the molecular level • Approaches should combine -omic technologies with classical bacterial genetics, bacterial physiology, protein engineering, and biochemical characterization • Approaches should dissect the function of each bacterium alone and in concert with complex bacterial communities in well characterized systems • Approaches should explore the relevant mechanisms alone and in concert (if there are more than 1 mechanism) Apply the above mentioned methods and different approaches to targets, to functions and to mechanisms of specific interest, for example to the mechanisms underlying • the beneficial effects of probiotics (e.g. (temporary) alteration of the microbiota composition, regulation of the epithelial barrier function, modulation of immune responses, interaction with the gut-brain barrier). Research could address probiotic effector molecules, such as specific pili, S-layer proteins, exopolysaccharides, muropeptides, as well as more widely produced metabolites such as tryptophan-related and histamine-related metabolites, CpG-rich DNA, and various enzymes such as lactase and bile salt hydrolases • the chemical communication in host-microbe interactions mediated by specialized metabolites (SMs), by which microbial communities can influence the health of their host (e.g. bile acids, short chain fatty acids etc) • the colonization of the gut by beneficial or undesired microorganisms

Topic	*State-of-Art*	*R&D&I needs*
Hypothesis- und knowledge-driven approaches	Due to the limited knowledge of the modes of action of microbiota in total or with respect to individual members of the microbial community, rational, hypotheses-driven approaches are difficult to pursue.	Apply the growing knowledge to design hypothesis- and knowledge-driven approaches, e.g. • Rational, reproducible probiotic strain selection, based on knowledge of the underlying mechanisms by which probiotics elicit their effects • development of tailored probiotics with increased stress tolerance, or enhanced metabolic activity • validation by in vitro assays, animal models, and genetic manipulation of bacteria (e.g. loss/gain-of-function experiments)
Taxonomic distribution of mechanisms	There is evidence that some mechanisms of action of microbiota are confined to specific strains whereas other mechanisms are shared by wider taxonomic groups.	Once mechanisms have been eludicated, there is a need to study the taxonomic distribution of mechanisms in order to identify shared mechanisms of taxonomic groups. This knowledge could be used, e.g. • for the rational selection of probiotic strains or strains with the targeted property (e.g. ability to synthetize beneficial molecules or specialized metabolites) • for metaanalyses of clinical trials by pooling of data from trials in which the intervention is based on the same mechanism (but may apply different strains) • for the further development of the EFSA health claims approval procedures.
Host-microbiota interaction and mechanisms	The analysis of microbiota structure and function remains incomplete if the specific host is not taken into account. However, host-microbe interactions have not yet been studied intensively.	There is a need to include also the host into the analysis of functions and mechanisms, as described above. R&D needs in studying host-microbe-interactions comprise e.g. • Studying in model systems the chemistry and mechanisms of host-microbe communication • Expansion to other host-microbe systems to investigate whether there are conserved mechanisms in different bacteria • Design and test targeted interventions into the host-microbe communication
Exploring the host-microbiota-environment interdependence	The analysis of microbiota structure, function and host-microbiota remains incomplete if the specific environment (e.g. lifestyle, diet) is not taken into account. There is still a lack of approaches which integrate all these issues.	There is a need to include also the environment into the analysis of functions and mechanisms, as described above. R&D needs comprise e.g. • Improvement and validation of tools to monitor diet and lifestyle with respect to accuracy, reproducibility, reliability, usability • Integration of lifestyle, nutrition, and environmental data into the analysis

Topic	*State-of-Art*	*R&D&I needs*
Development of novel interventions precisely targeting the microbiota	Mechanistic insight into microbial drivers of maintenance of health or in disease phenotypes is essential for translation to novel interventions. Different approaches have been proposed: • Additive approaches (e.g. probiotics, ranging from single strains via genetically engineered strains and defined mixed cultures to undefined microbial mixtures) • Subtractive approaches (e.g. engineered bacteriophages, antibiotics) • Modulatory approaches (e.g. prebiotics, selective non-lethal small molecules that target defined (and causal) microbial or host pathways Most studied probiotic organisms to date are several Lactobacillus strains and bifidobacteria. Only very few examples of microbiome-targeted small molecules are known.	The proposed approaches and strategies aimed at modulating the gut microbiota should be explored. An ecological perspective grounded in theory should be applied to design, predict and interpret the impact of microbiome-modulating strategies. R&D needs comprise • Screening for beneficial bacteria, molecules and functions • Characterisation of the mechanism of function • Validation of function in in vitro tests • Validation of function in animal model • Validation of function by genetically engineered strains • Clinical trials • Integration of lifestyle, nutrition, and environmental data into the analysis
Substantiation of health effects and health claims	There is still a substantial lack of evidence for the causation of microbiomes and disease. For example, in most cases of probiotics, it is not yet confirmed whether the known probiotic effector molecules are the actual drivers of the clinical effects observed in human trials.	• Properly designed clinical trials in human subjects are needed • Further research is needed to confirm the link between a given mechanism and clinical benefit and to establish associations between the presence of specific mechanisms and clinical benefits more broadly than up to now. • The clinical study design has to be based on comprehension of mechanism of host-microbe interaction or microbe function, and the trial should be performed with dedicated isogenic knock-out or knock-in mutants of the probiotic microorganisms or with proper formulated isolated bio-active compounds

Topic	*State-of-Art*	*R&D&I needs*
	It is known that many factors influence the clinical effects, e.g. the potency of the probiotic strain itself, but also dose, viability, formulation, targeted pathogen, targeted host response, targeted host site, prevention or treatment set-up. Difficulties of measuring certain biomarkers, combination effects, time frames for the probiotic activities (seconds, minutes, hours, weeks) need to be taken into account	• Clinical trials should also be used to explain inter-individual variation in responses to the interventions
Ensuring safety, quality and claimed health benefit of novel microbiota targeting interventions	On EU level, a health claim approval system is implemented at EFSA in order to ensure that the claimed effects are evidence-based and consumers are properly informed. Safety and quality of the food-based health interventions has to be ensured by the manufacturer.	• There is a need to investigate implications of microbiome research for health claims, product labelling and communication of health effects, as a basis for adapting the EFSA health claims system to the state of the art in science and technology. • R&D is required for the manufacturing, formulation, storage and consumption of food-based health interventions in order to ensure safety and quality, e.g. with respect to the effective dose and to standardization.
Food surveillance system	Research is underway to establish a food surveillance systems along the entire food value chain which is based on microbiome sequencing.	R&D needs comprise • Improvement of sensitivity, specificity and reliablity/reproducibility of pathogen identification • Broadening of the scope of pathogens that can be identified by generating sequence data of more food pathogens • Validation for different foods and locations • Development of a web-based platform to store, process, and analyze the data and to quickly generate easy-to-read food safety reports • Investigate the implications for regulation, guidelines and surveillance practice

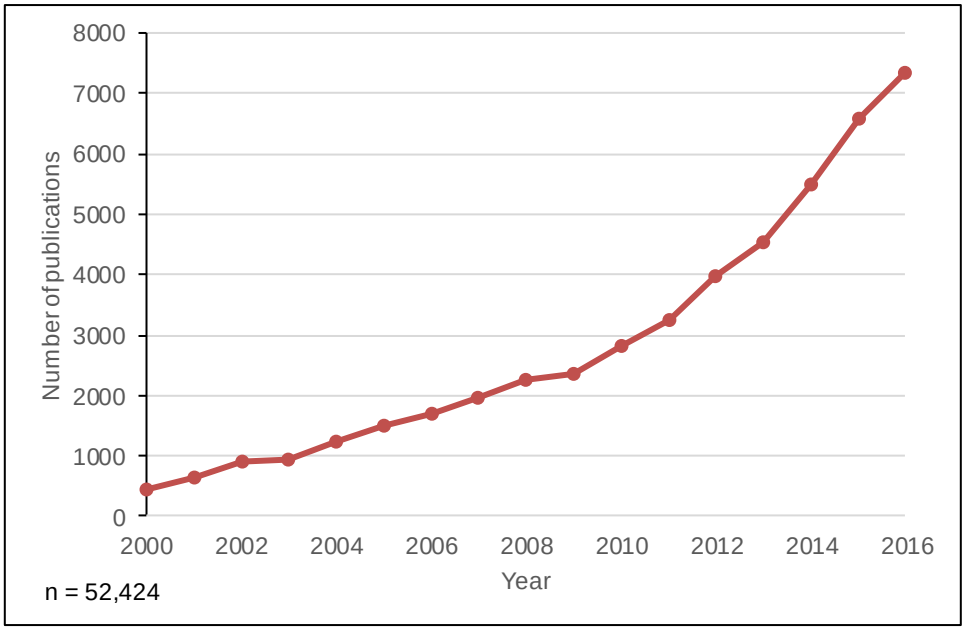
3.7.4 Economic analysis

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.

3.7.4.1 Publication and Patent analysis

The scientific publication activities in microbiome research have grown dynamically in the last years (see Figure 23), 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 $)[39], 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 23: Scientific microbiome publications worldwide, 2000-2016



39 https://hmpdacc.org

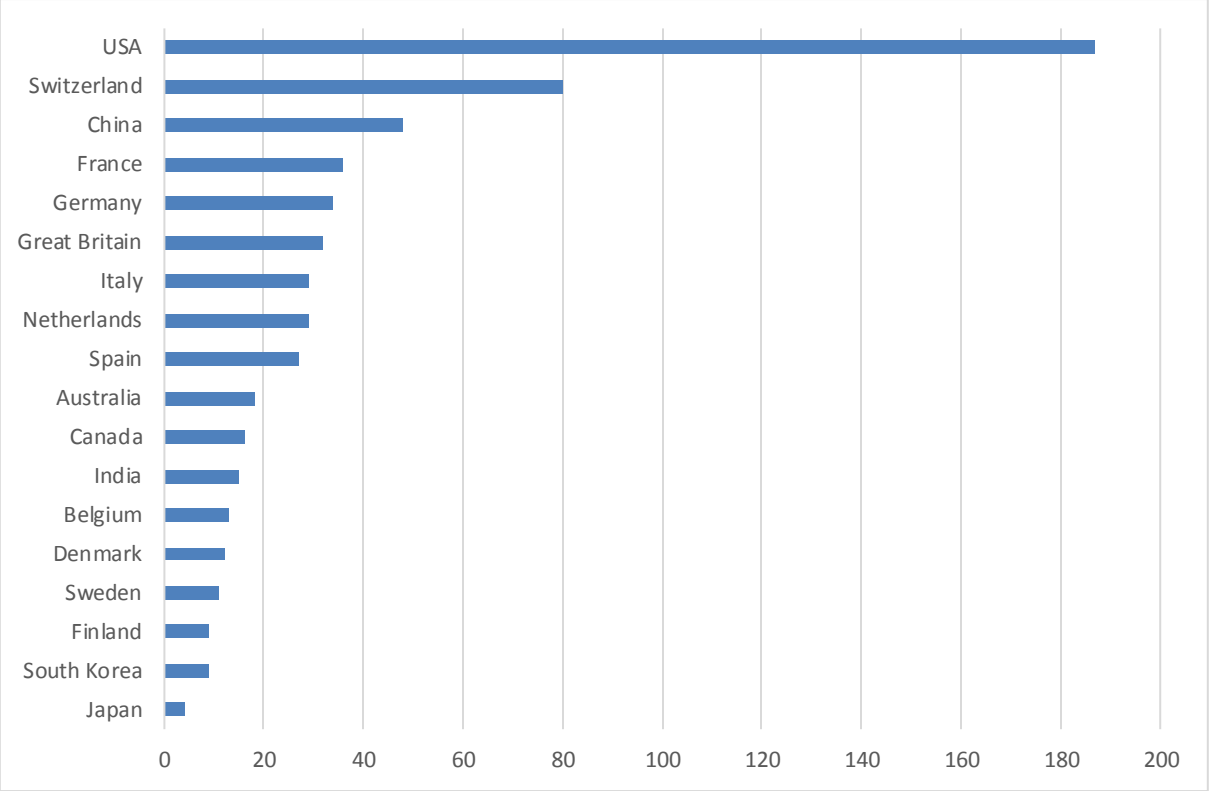
Source: SCOPUS database, search terms in title, article, keywords: microbiome* OR prebiotic* OR probiotic*

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.[40] 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.

[40] 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.

Figure 24: Transnational Patent Applications in Microbiomes (2010 – 2014)



3.7.4.2 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.[41]
- 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.[42]
- 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. [43]

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 und 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.

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

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

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

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 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.[44] 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.[45]I

3.7.4.3 Industry Structure and actors

Potential products address the microbiome can be placed in the continuum between food and pharmaceuticals. Figure 25 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 com-

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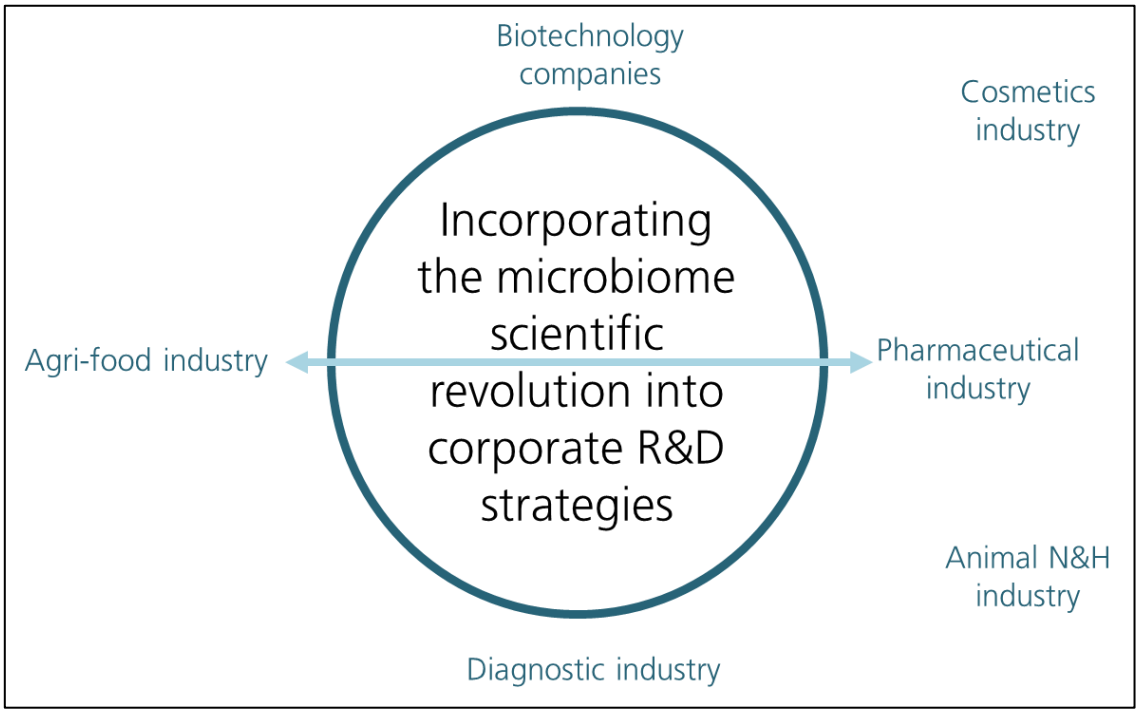
44 https://www.nutraingredients.com/Article/2016/08/26/EU-rejects-more-than-90-of-all-health-claims-Study;

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

panies, 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 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 25: 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)[46] 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 14.

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[47]. DuPont's first partnership through the venture is with the APC Microbiome Institute in Cork, Ireland. Table 15 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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46 https://www.nestlehealthscience.com/about-us/key-investments; last accessed 18.4.2018

47 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 14: 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 15: 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, North-Carolina, 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

3.7.5 Policy and 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 im-portance.

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). Nutri-tion and health claims for food products are only allowed when listed on a so-called pos-itive list. The European Commission bases its approvals on European Food Safety Au-thority (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 chal-lenging requests (Bröring et al. 2017; Khedkar et al. 2016).

3.7.6 Scenarios

Scenario 1: optimal future development

Starting point: The regulation is changed. Publicly funded core studies are performed (long term cohort studies plus intervention studies) and a biobank is publicly financed over the long term. Thus, better data are generated, and the public perception is positive.

Technology development is driven by significant public funding of research (P1B). Moreover, specific measures are implemented to support international collaboration (B3A), public-private cooperation, IP protection for companies and SME support (B4A) so that an active, diverse innovation landscape develops. R&D&I is characterised by the following aspects:

It becomes possible to define certain features of healthy and unhealthy microbiomes over the entire life span (T1A/C) and to establish evidence-based interventions for engineering the microbiome. Next generation microbiome products are developed which comprise well-known bacteria, a broad spectrum of probiotic bacterial strains, phages and parasites, prebiotics, and also active molecules etc. (T6D). Many modes of action are exploited; it even becomes possible to engineer microbiomes and maintain the engineered microbiome for a long time (T7A/B/C). Several evidence-based interventions become personalised (T5C). This progress is to a large extent due to research infrastructure (e.g. biobanks), international collaboration in large-scale projects, small-scale projects, an appropriate balance between flexibility, openness and innovativeness in research on the one hand (T2C) and comparability and standardisation on the other hand (T2A/B/C). Large epidemiological cohort studies and clinical intervention trials of highest standards are performed (T4A/B/C).

There are many opportunities for companies. Large research-intensive companies as well as highly specialised SMEs are active. Microbiome addressing foods and interventions are perceived very positively and consumer demand is high (B1A/B), both in the premium segment with official health claims (B1B) and in the segment where official health claims are of little importance (B1A). Social media, peer-to-peer advice and DIY

microbiome monitoring play a significant role (B5C). Frame conditions support collaborations between academia and companies (B3A), the development of SMEs and start-ups (B4A) and thus contribute to product development. Multiple new regulatory categories are implemented (B6C). Regulations for health claims are clear (P3C), harmonized within the EU (P2B) and moves towards a global regulatory framework (B2A/B) which opens new market opportunities but at the same time increases competition from producers in non-EU-countries.

Scenario 2: Focus on publicly funded research

Starting point: The regulation is not altered and remains as it is (B6B, P2A, B2 = status quo) and differences in terminologies prevail (P3A). However, public R&D funding in the EU is significantly increased (P1B) and allows intensive US-EU-Asia R&D cooperation. The data generated must be made publicly available. This increases the generation of basic knowledge about microbiomes considerably. Companies do not play an active role in the generation of this knowledge base, as the requirement to make the data publicly available is not attractive for them. Companies, however, use the publicly available knowledge base for product development.

Technology: Due to considerably increased public funding, the knowledge about healthy and unhealthy microbiomes and ways to modify them deliberately is significantly expanded (T1A/C/D). This deeper understanding of microbiome functions is to a significant extent due to global cooperation in research (EU–USA–Asia) and the integration of different –omics-data (T3C). Significant contributions to this integration stem from the standardisation of data acquisition, analysis and interpretation on a level that depends on the innovation phase (T2A/B/C): in research, comparability (e.g. sharing samples) is more important than extensive standardisation (T2A), and research has a high degree of flexibility in order to develop new technologies, algorithms and approaches, whereas in applications outside research, SOPs for sampling and data collection are implemented (T2C). But not only preclinical laboratory work is being publicly funded. Significant research budgets are also allocated to population studies and targeted human intervention studies (T4B/C). A set of validated biomarkers is established (B2A) In addition, citizen science projects contribute to sample and data collection (T4C). As a consequence, a broad spectrum of probiotic bacterial strains is being developed which go beyond the established well known bacteria and also comprise GMO and novel prebiotics (T6A/B). The mode of action is modification of the microbiome and also maintaining the altered microbiome (T7A/B). There is also a trend towards personalisation of interventions. While life style and demand driven interventions with unproven health effects dominate

(T5A), few evidence-based interventions are also personalised (T5C). Research is predominantly carried out in academia. Data and findings from publicly funded research must be made publicly accessible which is not attractive for companies.

Business: Microbiome addressing food gains broad positive perception and is readily consumed (B1A). Official health claims are of little importance (B1A) for marketing. Companies use the publicly available research data to develop a broad range of products (B2A) which are in part personalised (T5A), but not necessarily evidence-based, as official health claims do not play a major role for consumer behaviour (B1A). There are significant efforts in marketing (high profile marketing campaigns, celebrity usage) which bear the risk that market success is only a short-term hype cycle but not sustainable (B5B).

Due to lingering IP issues, industry mainly focusses on product development but not on basic knowledge generation (B3C). Public R&D&I Policy implements new forms of public-private cooperation in order to address this hindrance to knowledge transfer, innovation and product development (B3A). These measures also specifically address SMEs and start-ups (B4A). However, there is global competition in the research and supply services offered by SMEs, making the situation for EU-based SMEs nonetheless difficult (B4C).

Scenario 3: Favourable regulation, but negative public and consumer perception

Starting point: In regulation, the FSNP category with widened scope[48] is established for microbiome targeting food/products (P2B; B6A). NGOs transmit, however, a negative perception (B5A). Public R&D funding remains at a comparable level (P1A); increase cannot be justified due to negative public perception.

Regulation: the (improved) regulation is shaped significantly by consumer/public concerns and therefore has mixed impacts: on the one hand, the more clearly defined regulations support the development of microbiome products and services. On the other hand, requirements to comply with the regulation and obtain market approval/official health claims are high and in addition differ within the EU. As a consequence, the ratio of pre-marketing efforts to market size is unattractive for more advanced products and services. Companies therefore focus their efforts on only few (well-known) product categories for which a health claim can be readily obtained and on countries with more permissible regulation. The company landscape is dominated by few large, multinational or highly specialised players; SMEs play a minor role.

48 It has not been specified in the workshop in which way the scope is widened. We assume that due to negative public perception, rather strict consumer-oriented issues (privacy/data protection; regulatory oversight, level of evidence for claims) will be implemented.

Research: Public funding remains on a comparable level and scope as today. Funding budgets cannot be increased due to public concerns. However, funding is focused on certain issues which relate to the health claim regulation, e.g. definition of microbiome functions..., standardisation, large cohort studies. Regulations in the category “Food for Specific Nutritional Purposes (FSNP)” require compliance with Standard Operating Procedures (SOPs) for sampling and data collection for dossiers; there is also a high level of standardisation in research, which hampers innovation (T2D).

In the FSNP category, a positive definition is given for certain functions or metabolites (T1C); a comprehensive definition of a healthy microbiome remains, however, scientifically impossible (T1B). Regulation in the FSNP category is backed by knowledge from large cohort studies, for which funding has been made available (T4C). However, additional research into causal associations mainly remain restricted to case-control studies. Due to public concerns, rather strict consumer-related aspects are enforced, among them a strict data protection policy/regulation for microbiome data (P4A). As a consequence, only highly professionalized players can integrate omics data which have appropriate privacy/data protection procedures established (T3B). Moreover, the regulation protects against unsafe or misleading services or products (T5B). Although the scope of the regulation is rather broad and comprises also microbiome-targeting products beyond bacteria, and more clearly defined regulations support the development of products, the efforts focus on only certain product categories (B3A): e.g. market approval is only readily obtained for well-known bacteria with GRAS status (T6A) or well-established prebiotics; there are only few products on the market which make use of a broader spectrum of probiotic bacterial strains or novel prebiotics (T6B) because the requirements to provide evidence for this broader spectrum are too high in relation to the size of the market segments. Therefore, the dominating mode of action is modification of microbiota (T7A). Due to the public concerns, EU-wide regulation is complemented by additional national (in part even stricter) regulations so that a common EU market does not fully exist (B2C).

Business: The market is divided: on the one hand, there is a high demand by health conscious consumers who prefer food with official health claim labeling and pay premium prices (B1B); on the other hand, large population groups reject microbiome-addressing food because it is perceived as unnatural (B1C); this negative public perception can be knowledge-based or not (B5A) and influences markets, regulation and public and private R&D funding. Due to the public concerns, EU-wide regulation is complemented by additional national regulations so that a common EU market does not fully exist (B2C). This fuels divergence in regional development and marketing of products because national/regional actor networks develop primarily products specific to local/national market demands and regulatory frameworks (B3B). The uneven development also impacts SME and start up scene negatively (B4B).

3.7.7 Conclusions & Recommendations

This value chain represents an emerging, science- and technology driven field at the (blurred) interface of healthy nutrition, lifestyle and prevention on the one hand, and medicine, disease, and treatment on the other hand, and is closely related to personalized nutrition. Large scientific-technological, economic and public and individual health potentials have been assigned to this field and spurred substantial publicly funded R&D efforts as well as strategic high-risk investments of the private sector. The field bears the potential of novel products, which can only be produced by biotechnology or novel services and interventions 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. However, only few novel services, mainly microbiome profiling analyses coupled with dietary advice, have been commercialized yet. The majority of activities take place in R&D. 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. This does not exclude the possibility that novel products without health claims will be successfully commercialized earlier.

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. It will be a challenge especially for SMEs in the food sector - the majority being not research-intensive and focussed on incremental product and process innovations - to develop the required absorption capacity for these complex competencies.

From a public health and consumer protection point of view, such high standards are desirable to indispensable in order to achieve public health goals and not mislead consumers. For this purpose, a health claim approval procedure has been established in the EU. Nevertheless, it has to be adapted to scientific progress in the microbiome field and international harmonization across world regions should be strived for.

Scientific evidence for health benefits of food based microbiome interventions can only be generated if the knowledge of microbiome functions and the underlying mechanisms is significantly expanded. This will require substantial funding of basic research for several years, and there is a need for dedicated R&D resources, such

as biobanks, data bases, reference catalogues, standard operating procedures and standards, cohort studies etc. Despite the need for basic research, in the nearer future additional efforts should be devoted to translational research in order to establish evidence-based interventions, which target human gut microbiota.

To foster the development of the value chain in the EU in such a way that it contributes to economic and societal goals the following actions should be taken:

R&D&I policy should play a significant role by continuing R&D&I funding on the EU and member state level. Specific attention should be paid to the following aspects:

- Substantial funding of basic research will still be required for several years in this science- and technology-driven field. However, the focus of research should shift from studying microbiota composition to elucidating microbiota function and mechanisms. Moreover, the scope should be widened from microbiota-centred research to studying also host-microbiota interactions and host-microbiota-environment interactions (lifestyle, nutrition). In addition, the descriptive, exploratory, shot-gun approaches should complemented by hypothesis- and knowledge-driven approaches, informed by the growing insight into underlying functions and mechanisms.
- These shifts in research focus have to be enabled by further development of methods and technologies, especially by integration of -omics technologies to multi-omics approaches, by the establishment of model organisms and model systems of different levels of complexity, by improvement and validation of tools to monitor lifestyle, diet and environmental factors. These technologies should be combined with bacterial genetics and physiology, protein engineering, and biochemical characterization in order to elucidate, test and validate proposed mechanisms of action on the molecular level.
- Support for the establishment of microbiome research resources (e.g. inventories, catalogues and "reference microbiomes", well annotated clinical repositories with deep phenotype) should be continued. A pooling of resources should be strived for. Moreover, standards and practices should be supported which allow the exploitation and combination of existing data (e.g. for multi-omics approaches), so that the generation of new data could have the main purpose to fill data gaps.
- Improvement of methods and technologies for microbiome research, although developed in one subfield of microbiome research (e.g. medicine), could most likely also be applied in other subfields (e.g. agriculture, food, environment). Platforms and forums should be established which allow the exploitation of synergies between different microbiome research subfields and which avoid the duplication of efforts.
- Interdisciplinarity is very important in microbiome research. Therefore, efforts to overcoming disciplinary silos should be an integral part of public R&D funding.

Despite the need for continued funding of basic research, additional efforts should be devoted to translational research in order to establish evidence-based interventions, which aim at modulating the human gut microbiota, based on mechanistic insight. The following aspects should be taken into account:

- This comprises the engineering of probiotics, prebiotics, bacteriophages, small molecules, based on mechanistic insight, and the validation in in vitro tests, animal models, and by gain or loss of function experiments, as well as properly designed clinical trials. Further research is needed to confirm the link between a given mechanism and clinical benefit and to establish associations between the presence of specific mechanisms and clinical benefits more broadly than up to now.
- R&D is required for the manufacturing, formulation, storage and consumption of food-based health interventions in order to ensure safety and quality, e.g. with respect to the effective dose and to standardization.
- In order to implement translational research, the establishment of novel collaborations should be supported in order to bring the required expertise of academia, and relevant industries (e.g. industrial biotechnology, food, pharma and ICT and data industries) together.

Implications of microbiome research results for health claims, product labelling and communication of health effects should be investigated, as a basis for adapting the EFSA health claims system to the state of the art in science and technology. Moreover, international harmonization across world regions should be strived for.

3.8 Overall assessment for Industrial Biotechnology

The analyses and scenarios for these six value chains point out that for a favourable development of IB in Europe a set of different factors has to evolve positively, such as maintaining competitiveness in future technological developments, aligning supply to customer needs, adjusting policy instruments, etc.

The following section summarizes findings from a cross-value-chain analysis as well as assessment of current trends for the whole field of Industrial Biotechnology in the PROGRESS project.[49] Where appropriate, the differences between the heterogeneous value chains are pointed out, by using the examples of the analysis in section 3.1.

Cost reduction

A key challenge for technological development and economic activities in many IB segments is the reduction of cost. This applies even to those value chains without direct competition to chemical synthesis or fossil-based products, for example, the production of biopharmaceuticals and some applications for enzymes where regulatory or market pressures exist to reduce the costs.

Advanced technologies

Advanced technologies, such as synthetic biology, genome editing, next generation sequencing etc. have a high potential for the commercialization of bio-based products. They may strongly contribute to reducing the costs and environmental impact of IB processes as well as enabling the provision of new functionalities. A key characteristic of IB disruptive potential is that it is unpredictable because developments are very fast.

For the value chains Flavours and Fragrances and microbiomes the potential is most impressive: Advanced metabolic engineering, systems and synthetic biology in the case of Flavours and Fragrances and next generation genome sequencing and bioinformatics in the case of microbiomes are of major importance for the further advancement in these value chains. Moreover, the conjunction of biotechnology with different processing technologies & sciences (e.g. nanotechnology, information technology, chemical catalysis) as well as the use of biotechnology in fossil-based processes becomes of key importance.

Feedstock use

[49] In two workshops overall findings of the value chain analyses were presented and discussed regarding generalization for IB. Moreover, a set of interviews has been conducted targeted to discuss developments in the field of IB as a whole.

The demand for feedstock differs highly across IB value chains. While for those value chains that require large amount of feedstocks the availability, logistics, prices and innovation are key factors for commercialization, for some other value chains feedstock supply has a limited role (e.g. microbiomes, production of biopharmaceuticals). In some cases, IB methods are already being used for processing non biomass feedstock, such as CO_2, or in combination with chemical methods to process fossil fuels.

For those value chains with significant biomass use demand, a stable supply of sustainable feedstock is a decisive driver for market development. Here it is widely assumed that lignocellulose, side-streams in industrial production, waste and CO_2 bear a high, yet untapped potential of non-food feedstocks for IB. Technological and logistic challenges, including the heterogeneous and variable composition of many of these feedstocks, as well as their wide dispersal, need to be addressed in order to valorise these feedstocks.

For that purpose, an increasing collaboration between feedstock suppliers and users are needed. These communities are often separated with a lack of knowledge of each other's competences and resources.

Effective collaboration networks within the value chains

The current status and challenges for effective collaboration networks differ between the value chains. For example, on the one hand for the value chains Flavours and Fragrances and microbiome European-wide networks still have to be firmly established and expanded. On the other hand, for the value chains production of biopharmaceuticals and enzymes collaboration networks are well established. However, the question arises whether they are sufficiently open to address the challenges from alternative, competing concepts (e.g. cell-free production, advanced therapies). For enzymes, collaboration between large companies and academia has decreased because of IP issues. This may represent a hurdle for taking up R&D&I impulses from academia into commercialisation.

Collaboration across European countries

Currently, innovation and commercialisation activities in innovative biotechnology products and processes are geographically highly concentrated. This is because European regions are highly heterogeneous with respect to their technological capacities and resources (skills, biomass, etc.) in IB. Higher collaboration between the EU countries and integration of more countries into the various value chains may lead to a build up of critical mass and a better use of complementary competencies and resources that eventually leads to a higher quality of R&D&I. Moreover, a wider spread of economic and societal benefits of IB may be achieved.

Specific challenges lie in the appropriate combination of scientific-technical excellence and geographic coverage, pointing at the need for "smart specialisation" of regions and mutual learning, rather than supporting "me-too"- activities and duplication of efforts.

Skills

Industrial biotechnology is a highly specialised area with a need for a specifically skilled workforce (Bio-TIC 2015). It needs to change dynamically with new science and technology developments as well as increasing commercialisation activities. The multidisciplinary nature of industrial biotechnology requires that experts specialised in one field have additional understanding of other competencies, for example molecular biologists of bioinformatics or process issues and vice versa bioinformaticians or process engineers of biology issues. Moreover, specific skills for scaling-up processes from lab to production as well as business skills for commercialisation are increasingly needed.

Technology transfer and scaling up

While an increasing number of R&D&I projects get more and more mature, the transfer of innovations from R&D&I settings to commercial applications in Europe is gaining importance. This in particular the case for value chains in a medium maturity stage such as ligno-cellulosic ethanol, bio-based plastics, flavors & fragrances

Typical problems at that stage are becoming increasingly crucial for the whole value chain, such as:

- the high complexity of scaling up biotechnological solutions,
- the need for closer collaboration between academia and industry,
- unclear market perspectives from the view of potential investors and consequently the lack of funding for pilot and demonstration activities,
- the lack of skilled people in scale-up (see "skills" above).
- High financing needs for scaling-up, because of limited awareness of investors or accordance to overall company strategy.

Regulatory environment

Product regulations have a significant impact on growth opportunities in IB. The effects of regulations are often complex and not positive or negative per se. Moreover, effects can differ between being short and long term as incentives for actors in the markets may change. Value chain-specific regulations, which create a rather favourable environment for commercial activities exist in the value chain biopharmaceuticals (securing a competitive advantage for EU players over competitors due to high requirements), Flavours and

Fragrances (opening opportunities for IB to produce substances which can be claimed as being “natural”), and enzymes (no need for labelling and / or intermediate products with enzymes produced in genetically modified organisms). It is an open question to which extent this rather favourable commercial environment will be maintained in the future.

On the other hand, in three value chains, amendments of existing or even novel regulations are called for: In the microbiome value chain, it is being discussed whether existing regulations regarding both food for specific nutritional purposes or medicinal products should be amended in order to specifically address microbiome products at the borderline between food and medicinal products, clarifying the requirements and procedures for health claims for the respective products. In the case of lignocellulosic ethanol and bio-based plastics, demand-side regulations such as mandates, tax exemptions or bans of competing products are called for.

Acceptance and perceived benefits of IB

Awareness of IB products and trust in the claimed benefits by the general public as well as decision makers are necessary preconditions for the successful commercialization of IB. Generally, the overall public attitude towards IB products is assumed to be mostly positive, but may differ substantially depending on the target group, product segment, application, technologies used or benefits perceived: For example there is scepticism towards some advanced technologies and applications (e.g. for food, textiles).

Moreover, for many value chains the “willingness-to-pay” of consumers for more healthy, more sustainable, natural products is still limited or restricted to small consumer groups. An important reason is the lack of awareness of the existence of IB products and in particular their benefits to consumers. While there are single best-practice cases, it is challenging to provide information and to communicate benefits for a broader range of products and processes. Because of these challenges, for quite some value chains a strong market uptake is expected, if additional demand side policy activities are set in place (e.g. for lignocellulosic ethanol, bio-based plastics) or, in the case of production of biopharmaceuticals, existing reimbursement policies aren’t cut.

4 Role and potential of EU Member States in IB

Within the EU, there is a diversity across countries with respect to the framework conditions determining the extent and scope of their activities in the field of IB. In fact, countries differ from each other considerably in terms of their research and innovation capabilities in IB. Closely related to different innovative capabilities is the variety of deployment of IB and the development levels of the IB sector in different EU countries. Moreover, the availability and effectiveness of policy support mechanisms aiming at fostering the deployment of IB differ from country to country to a considerable extent. Furthermore, there are significant differences between EU countries in their potential of biomass supply and biomass production.

Taking into account the diversity and different potentials of European Member States in IB, a one-size-fits-all strategy approach to foster it in different countries would be neither useful nor viable. Consequently, when elaborating policy recommendations for the uptake and development of IB, specific situations of countries must be considered, and their potentials and needs identified and thoroughly analysed. This enables to develop a package of measures, which is tailored to the specific framework conditions of different countries to respond best to their needs and potentials. This way an additional value can be created from the diversity by combining complementary expertise and gaining synergies across countries, which would also make a positive contribution to the regional cohesion of the EU.

In the PROGRESS project extensive desk research and data analysis of official statistics were performed to identify the capabilities and potential of individual countries within the EU with respect to the following dimensions:

- research and innovation (patents, R&D&I expenditures),
- industrial sector capacities (existence of relevant actors),
- policy framework conditions (I&B related strategies and policy measures
- availability of the biomass resources (relative abundance of land and forest biomass) 50.

50 The estimation is based on the biomass potential assessments made within the Biomass Policy project (see Elbersen et al.2016) and on the Eurostat data on forest areas and land use. .

The evaluation of EU countries according to the above mentioned aspects led to the identification of four groups of countries[51] sharing common characteristics:

1. Countries with advanced industrial biotechnology sector
2. Countries with strong innovative capacities in selected IB fields
3. Countries with modest innovative capacities in IB
4. Countries with hardly any innovative capacities in IB

The description of the country groups as well as the summary of their main characteristics are given in Table 16.

[51] EU-countries with less than 1 Million inhabitants, such as Luxembourg, Malta and Cyprus, were excluded from the analysis.

Table 16: Characterization of country groups

Country Groups	Countries	Policy Framework Conditions	Innovation Capabilities	Characteristics of IB Sector	Potential of Biomass Supply
1. Countries with advanced IB sector	Broad spectrum of activities: Germany, Belgium, Netherlands, France Special focus: Finland, Sweden (woody biomass based IB), Denmark (microorganisms / enzymes)	Strong commitment to foster bio-based industry Recognition of IB as strategically important field Broad range of measures and instruments to support IB High level of public sector investments in IB	High R&D&I and innovation intensity in IB related fields Number of research institutions involved in different IB related research topics Strong academic base in IB	Availability of a well established and highly competitive IB sector Large number of innovative and dynamic companies, specializing in various niches of industrial biotechnology High levels of business expenditure in R&D	High agricultural biomass potential: France, Germany High potential of woody biomass: Sweden, Finland, Germany
2. Countries with strong innovative capacities in selected IB fields	Ireland, Austria, United Kingdom, Spain and Italy	Commitment to foster bio-based industries has risen continually in recent years Acknowledgement of the potential of IB	Research expertise and strong innovative potential in selected IB related fields	Availability of a large number of important industrial players in IB, mostly active in some specialty sectors	Limited agricultural biomass resources High potential of forest biomass: Austria

		Some important initiatives and promotion schemes aimed at fostering IB in place		High concentration of business R&D&I investments in selected fields of IB	
3. Countries with modest innovative capacities in IB	Portugal, Slovenia, Czech Republic, Slovakia, Poland, Estonia, Greece, Hungary, Latvia and Lithuania	Little targeted policy aimed to foster bio-based industry Increasing recognition of the relevance of IB in recent years IB related projects are supported mainly through EU support schemes	Some academia and research centers are active in selected topics of IB Moderate R&D&I intensity and innovation performance in IB related fields Strong tendency towards healthcare BT in some countries	Few business sector players specializing in selected fields Availability of a few domestic research intensive companies specializing in niche products FDIs are one of the main source of technology transfer in industrial biotechnology	High potential of agric. biomass resources in: Poland, Hungary, Czech Rep., Slovakia, Lithuania Woody biomass: Poland, Czech Rep., Lithuania, Latvia, Estonia
4. Countries with hardly any innovative capacities in IB	Bulgaria, Croatia, Romania	No strategies or policy measures dedicated to the promotion of bio-based industries and IB Poor awareness of the potential of IB	Lack of critical mass to conduct scientific research in IB related fields Low level of investment in R&D&I Extreme weak innovation performance in IB	Massive FDIs led to the establishment of the traditional IB sector, where modern technologies are applied to produce traditional IB products (e.g. food and feed, fertilizers, chemicals, cosmetics etc.)	High potential in agricultural biomass resources: Bulgaria, Romania, Croatia Woody biomass: Romania

Based on assessment with experts on the IB related research and innovation policy under the consideration of identified framework conditions of different country groups the following major strategic priorities for stimulating IB within the EU have been elaborated.

Policy Framework

For the countries with the advanced IB sector it would be essential to continue their efforts in fostering IB and to continuously update the IB policy framework to make sure that policy and strategies remain effective to be able to respond to new developments and challenges. As the second group of countries generally lacks a targeted IB policy, the development of such could be helpful to clearly define the thematic priorities in IB as well as to ensure the government commitment to foster IB by taking concrete policy measures and actions. For country groups with little innovative capacities (country group 3 and 4) it is considered essential to increase the awareness of the relevance of IB at government level and to enhance commitment among policy makers to promote IB. Careful consideration should be given to the definition and specification of strategic foci in IB and to the identification of thematic priorities according to the potential and framework conditions of each individual country.

R&D&I Capability

Continuous improvement of the R&D&I capabilities in IB is another priority of crucial importance for the EU. The main challenge for countries with advanced IB and for countries with strong innovative capacities in selected fields of IB is to be able to maintain their leading position in IB in the future by investing in cutting edge technologies, exploiting emerging topics and ensuring closer cooperation between biomass production and biomass conversion. In view of increasing international competitiveness in IB, it would be advisable for countries, which specialize in selected topics to explore, which existing strengths and capabilities in these selected fields they can use in order to broaden their strategic focus and to move into some novel fields. For the country group with modest and very little innovative capacities in IB, it was considered essential to strengthen the efforts in fostering research and development and to expand capabilities in the existing fields. To establish the necessary R&D&I infrastructure, EU regional development funds should be used in a more targeted and efficient way.

IB Sector

One of the most central challenges for countries with advanced IB and for countries with strong innovative capacities in selected fields of IB remain the exploitation of knowledge and transfer of R&D&I results into commercialization generating economic value of them. Targeted policy measures are needed to incentivize the commercialization of research and to support the diffusion of industrial biotechnology into different industrial sectors. Apart from this, countries with strong innovative capacities in selected IB fields could gain more complementary expertise through stronger cooperation with partners from other EU countries or regions. It would enable them, among other things, to get access to the necessary expertise in the novel fields of IB. For the country groups with little innovative capacity in IB, it would be crucial to support the

expansion of relevant activities around the national champions (e.g. by means of the cluster policy) and to foster the cross-country integration into existing networks and value chains.

Biomass Resources

The role of each country depends largely on the country specific availability of biomass resources. As many of the EU countries from country groups 3 and 4 hold a high potential of biomass resources, they could be better integrated in the European value chains as feedstock suppliers. However, it is important to ensure that these countries do not position themselves only as raw material suppliers along the European value chain, but are able to build up their own industrial and innovative capability in IB in order to create opportunities for higher value added activities.

5 Recommendations

In order to maintain a strong and leading position of the EU in Industrial Biotechnology and to realize its socio-economic potential, a broad portfolio of IB technologies, products, processes and applications has to be supported: only a broad portfolio is robust and flexible enough to cope with unfavourable or changing external factors and frame conditions, allowing the full exploitation of the enabling character of IB for a bioeconomy and a circular economy that can contribute to mastering the grand challenges and to achieving the UN Sustainable Development Goals. Moreover, the diffusion into and adoption by new industrial sectors of IB methods should be in focus. However, this does not mean that all potential areas should be addressed equally by public funding. In order to achieve critical mass, and to efficiently allocate resources for R&D&I, production and marketing it is recommended to continuously support forward looking activities and identify areas of strategic importance, such as the value chains analysed in the PROGRESS project.

Therefore, policy has to address on the one hand the heterogeneity of value chains (see also specific recommendations for value chains in section 3). But, on the other hand, a comprehensive and coherent policy framework and a set of well-balanced, targeted policy actions is needed to support this portfolio. R&D&I and corresponding actions are an integral part of this framework, but must be accompanied by coherent activities that support the innovation system.

In the following, key recommendations and actions are outlined which would be key elements of a coherent policy framework for fostering IB in the EU.

Supporting advanced technologies

Advanced technologies play a crucial role in advancing IB and in maintaining international competitiveness, both in research and in commercial production. Support of R&D&I should enable leading EU countries in IB to keep at the cutting edge and enable emerging IB EU countries to adopt these technologies and to diversify into emerging IB industrial sectors.

In addition to value-chain specific R&D&I needs (section 3), the cross-cutting R&D&I and technology issues below are relevant to IB in general:

Actions to be taken

1. Demand- and market driven R&D&I, also for application in not yet addressed industrial sectors and applications, should be fostered, as well as IB innovations at all TRL stages.
2. In order to further strengthen the core competencies in established and emerging advanced life science technologies, R&D&I support should comprise the development of IB toolboxes and approaches which are broadly applicable in different value chains and industrial sectors. Examples are screening approaches based on still under investigated sources and on data mining of -omics data, toolboxes for systems metabolic engineering of production organisms and enzyme engineering, comprising, among others, improved genome assembly and editing tools, synthetic biology bioparts, bioinformatic tools, and (high-throughput) *in vitro* test systems for unblocking the test phase of design - build - test cycles.

3. Where appropriate, R&D&I projects should aim at integration of IB with other technologies, especially with environmentally benign chemical processes ("green chemistry") and with digital technologies and bioinformatics.
4. R&D&I efforts should be continued regarding the pre-treatment of biomass to yield fermentable substrates with the aim to develop robust, low cost processes for a large diversity of non-food feedstocks of variable qualities without compromising the following production processes. Combinations of physical, chemical and biotechnological technologies for pre-treatment, information and communication technology approaches for feedstock logistics, and model-based adaptation of process parameters to feedstock quality should be included.
5. R&D&I projects with the aim to tailor production organisms and biocatalysts to bioprocess requirements should synergistically combine competencies in metabolic engineering, bioinformatics and systems and synthetic biology in a coordinated way. Additional educational measures should be considered in order to develop competencies for successful and effective R&D&I work in such interdisciplinary teams.
6. The challenge of unblocking the test phase in design - build - test cycles of optimising production organisms and enzymes should be addressed by supporting the development of high throughput *in vitro* test systems, especially for more complex reaction cascades and with systems for the regeneration of energy and reducing equivalents.
7. R&D&I should address cost-competitiveness by optimising organisms and biocatalysts with respect to yield, product concentration and productivity, simplifying the overall process, and improving their robustness under production conditions.
8. R&D&I on production processes should focus on scale up and further optimisation of production processes with respect to biotechnological, economic, ecologic and safety or quality parameters. Digital technologies should be exploited for optimising production processes, e.g. by further automatisation and integration of unit operations, by process analytical technologies and by coupling them with process modelling. The lack of staff specifically qualified in scale-up should be addressed. Moreover, R&D&I efforts should be targeted at further developing and optimising integrated biorefineries.
9. The coordination of R&D&I infrastructures should be supported with the purpose that they offer complementary services and access to the specific services is facilitated (e.g. continuation of funding consultation and dialogues between R&D&I centres with the possibility to integrate new entrants in the networks; funding for R&D&I projects that encourages joint application of R&D&I institutions; supporting gap analysis of missing offers of R&D&I infrastructure with potentially high impact; funding of independent secretary for governance of R&D&I centres; flexible funding schemes)

Sustainable feedstock supply

In IB bulk product value chains (e.g. biofuels, bio-based plastics and platform chemicals), the expected growth goes hand in hand with an increased industrial use of biomass. The following actions should be taken in order to satisfy the growing demand for feedstock and at the same time prevent possible negative impacts for food security, on water resources and soil fertility, biodiversity, and net energy use:

10. In order to prioritize food use, the "food first" should be operationalized: A recognized IB expert committee (e.g. the EU Bioeconomy Panel, the Standing Committee of Agricultural

Research (SCAR)) could work out such a comprehensive concept, preferably in a process with public input. This should be followed by an implementation phase in all relevant policies and R&D&I programmes on EU and Member State level.

11. Efforts by IB expert committees, funding bodies and research should be undertaken to work out the concrete requirements that IB activities have to comply with in order to contribute to the UN Sustainable Development goals. These requirements should subsequently be implemented in all relevant policies and R&D&I programmes on EU and Member State level.
12. In order to ensure sustainability of biomass production for IB in a globally linked economy, there is an urgent need to strive for European and international agreements on standard definitions of sustainable production of feedstocks, and the related tools and indicators for measuring sustainability. Coordinated efforts by the EU Commission, EU bodies (e.g. CEN) and relevant non-governmental stakeholder groups should be pursued.
13. To satisfy the growing demand for feedstock, the following approaches should be pursued or intensified in combination with each other:
    - Support of R&D&I efforts aiming at raising the technological potential of land use in the EU: this comprises scientific-technological progress for using all fractions of biomass and non-food biomass (straw, wood, industrial and municipal waste, CO_2, aquatic resources), and the intensification of agriculture with land sharing and land sparing concepts.
    - More research is needed regarding possible unintended and harmful environmental impacts of increasing biomass use, as well as unintended impacts on other markets.
    - Implementation of a study or a monitoring system is needed which allows a consistent uniform assessment of the available biomass and type of feedstock across the EU.
    - Comparative mapping and characterizing different use paths of biomass in order to direct activities to products and processes with high resource efficiency and value added, and elaborate a "best use hierarchy"[52] for consistently applying the cascading principle.
    - Support the pan-European trading of biomass feedstocks with the development of a framework of standards and norms which allows the uniform assessment of the availability and quality of the traded feedstocks.
    - In order to overcome existing legal restrictions to exploit the potential of waste as feedstock for IB, it should be clarified in a revision of the waste regulations such as the EU Waste Framework Directive which types of waste could be allowed to be used further for recycling.

Address public perception and acceptance

Generally, IB has a rather positive public perception because of its potential to contribute to mitigating climate change and substituting fossil fuels. However, attitudes and acceptance dif-

52 Currently, such hierarchies are only available very generally in thy biomass value pyramid form (see e.g. http://www.betaprocess.eu/the-value-pyramid.php), but not for concrete products

fer substantially depending on stakeholder group, application, and technologies, requiring specifically tailored approaches. Particularly sensitive areas are any potentially negative environmental impact, governance, distribution of socio-economic benefits and scepticism towards advanced technologies in certain applications.

Actions to be taken

14. Constructive stakeholder dialogues and public participation should be continued on both EU and Member State levels, following the concept of Responsible Research and Innovation (RRI). The involvement of all relevant stakeholder groups, the neutrality and transparency of the process and actions taken based on the process results are key success factors.
15. Dialogues should be carried out in order to develop a commonly shared future vision for IB and to integrate the expertise of NGOs and lay persons in the elaboration of research and innovation missions for R&D&I programmes,
16. Public and consumer concerns should be addressed in specifically tailored (value chain and/or technology-specific) constructive dialogues.
17. It should be ensured that results and implications of these involvement processes are considered strongly in further policies: possible outcomes might be that for example funding of certain areas or use of certain technologies may be decreased, that presently neglected R&D&I topics may become more important or that value-chain specific regulations may have to be amended (e.g by revising product claims regarding sustainability, health issues, origin from nature). The PROGRESS scenario analyses show that such strategies, although they may at first sight seem to be counterproductive for the advancement of IB in the EU, also bear significant potential in international competition.
18. EU and Member states IB R&D&I strategies should be tailored in a way that they are guided by the requirements derived from the UN Sustainable Development Goals.
19. Develop and implement internationally recognised standards for sustainability assessment, certification schemes and labels in order to facilitate the assessment and communication of benefits of IB processes and products.
20. Continue to ensure that research into science, social and humanities (SSH) aspects is a substantial part of post-H2020 work programmes, both as integral part of technology development projects and as own research activities (e.g. as calls in programmes equivalent to H2020 “science with and for society”)).

Demand pull

Despite substantial scientific-technological progress, achieving cost-competitiveness in IB will remain difficult for many IB products in times of low prices for fossil resources. Therefore, a higher demand pull would be needed to enforce the development of IB. The broad range of IB products makes this very challenging as very different customer groups have to be addressed specifically: the spectrum ranges from highly different groups of end consumers to business customers, among them brand owners with substantial outreach to shape market and demand,

to public procurement by ministries and agencies. For these different target groups, efforts should be intensified to increase their awareness, to inform in a balanced way about IB products, to communicate the benefits or unique selling propositions of IB products and enable informed purchasing decisions. Those information and communication activities should be primarily conducted by private actors and organizations. But public actors and funding have an important role as well to contribute to objective knowledge about public perception (e.g. conducting Eurobarometer surveys), activate dialogues where necessary, prepare neutral information with high quality (e.g. development of education material), partly financing communication activities as part of broader projects (e.g. in CSAs).

Actions to be taken

21. provide target-group specific information for different age/consumer groups (e.g. contribution of IB based products to quality of life), using different communication channels (e.g. selection of appropriate media) and conduct dialogues with consumers
22. IB policy should ensure public funding for the development of appropriate sustainability assessment tools. Coordinated efforts between public policy makers and stakeholders are required for the implementation of the sustainability principles.
23. Publicly funded dialogues with consumers could be performed to identify preferred features, concerns and perceived benefits of IB products and processes and for the understanding of labels in early, precompetitive, stages of development of such products.
24. Market research should establish customers' and consumers' preferences with respect to IB products in order to establish the knowledge base for subsequent marketing campaigns.
25. Certification schemes and labels for IB processes and products should be developed, for cross-border markets, preferably on a supranational level. Implementation campaigns will be required to inform customers and the public about the purpose and content of the labels in order to support informed purchasing decisions.
26. Privately funded marketing campaigns for IB products and processes should make use of all modern marketing tools and communication channels, and be specifically targeted at all relevant groups of the population. A possibly effective message could be the contribution of IB products and processes to quality of life.
27. Member States should consider the implementation of public procurement programmes for IB products. It is recommended to include only those products in such a programme which conform to high environmental performance standards (higher standards than e.g. in the US BioPreferred Program).
28. An important target group to be addressed are decision makers in the B2B sector, large brands and retailers. A broader set of measures should be specifically targeted at this group by raising their awareness of the potential benefits arising from IB products, their unique selling propositions and their contributions to the company's environmental footprint, e.g. through events and information campaigns, possibly conducted by business associations or other intermediate actors, by providing incentives for joint research projects with technology developers, and by systematically collecting and communicating success stories from other companies.

Moreover, there are some specific regulatory issues for the value chains that have an impact on demand pull (e.g. mandate legislation for lignocellulosic ethanol). Related recommendations are described in section 3.

Multidisciplinarity of skills

The multidisciplinary nature of IB requires teams of highly specialised experts. In order to interact synergistically and effectively in these teams, experts should not only be highly competent in their own field of expertise, but also have a basic understanding of other competencies. In order to enhance the required skill formation a portfolio of instruments would be adequate.

Actions to be taken

29. Adaptation of curricula in higher education, universities and vocational training (support on EU level by developing specialized training programmes in (post-)H2020)
30. In order to intensify cross-country exchanges of expertise, check whether the existing instruments (e.g Marie Skłodowska-Curie Actions (MSCA) are sufficient, whether they should be specifically complemented for selected target groups (e.g. participants from countries without a strategic focus on IB; participants from industry), or whether potential candidates for exchange should be made more aware of the existing instruments and be encouraged to apply.
31. Public-private partnerships should be systematically exploited as an opportunity for students and scientists from academia to gain industry relevant experiences. R&D&I centres with an infrastructure for applied research and scaling-up could gain a more important role in skill formation both for staff from academia and companies, and dedicated facilities for training in IB-relevant disciplines may be set up: E.g. the National Institute for Bioprocessing Research and Training (NIBRT) in Ireland provides tailored training solutions for clients, ranging from operator through to senior management training, and training can be delivered in a realistic manufacturing environment (OECD 2017).
32. It should be considered whether there is a need to give additional incentives to companies (e.g. in the form of tax exemptions, or reductions of social and healthcare payments) in order to intensify upskilling and retraining of IB company staff.

Transfer of R&D&I results into commercialization

The economic, ecologic and social potentials of IB can only be fully exploited if R&D&I results are taken to commercialised processes, products and services. As an increasing number of (R&D&I) projects are entering a more mature stage the need to address the various - and well-known - barriers to commercialize IB products and processes becomes even more pressing. Existing efforts to overcome these barriers must be continued and intensified. They should comprise a set of actions that address shortages in know-how, capital and collaboration with a special focus on the following actions.

Actions to be taken

33. Continue supporting the collaboration along value-chains in R&D&I projects. In order to raise awareness of partners more downstream in the value chain, attractive networking and partnering events should be continued.
34. Continue public support for R&D&I in all TRL stages, but ensure significant R&D&I funding in higher TRL stages (e.g. providing flexible solutions for financing further scale-up of funded projects where appropriate).
35. Encourage the active participation of SMEs and support start-ups and spin-offs in R&D&I programmes. It should be checked whether this could be addressed appropriately by e.g. reserving a higher proportion of H2020 budget for SME.
36. Address the shortage of staff experienced in scale-up of processes, e.g. by education and qualification (see above), or by attracting staff from adjacent industrial sectors to IB.
37. Provide opportunities for actively bringing different experts (researchers, investors, intermediaries) closer together in order to develop teams with commercialisation-relevant expertise (e.g. scaling up, market intelligence). This may include networking events, platforms, making commercialisation-relevant activities a mandatory requirement of in R&D&I projects or providing incentives (e.g. funding) in addition to scientific work for integration of business expertise in finance, legal, marketing affairs in IB R&D&I.
38. Create favourable framework conditions for risk and venture capital for IB (e.g. consideration of tax regulation)

Co-evolution of regulatory environment and S&T development

The regulatory environment has a significant impact on IB growth opportunities and innovation incentives in many IB value chains, but cannot be assessed as being generally positive or negative for IB: In some value chains, rather favourable regulatory conditions already exist for industry, whereas in other value chains, a significant deployment of IB is rather unlikely without regulatory change. Moreover, relevant regulations and the implemented or proposed regulatory instruments differ highly between value chains and are often value-chain-specific.

Against this background, the PROGRESS scenarios show that co-evolution of S&T developments and regulations is of critical importance. The challenge is to align R&D&I policy with regulatory activities, both with respect to timelines and areas incentivized. Regulations should also be seen as part of Responsible Research and Innovation (RRI) and thus as instruments for establishing trust and credibility in IB by balancing incentives for R&D&I and industry with - potentially differing - interests of the public and consumers.

Actions to be taken

39. Regularly anticipate new, emerging scientific-technical developments (e.g. synthetic biology, genome editing) and check whether they make corresponding updates of regulations necessary,
40. Perform dialogues with stakeholders and citizens with the aim to inform the regulation-setting political process,

41. Reconsider regulations in the following fields, as outlined in other recommendations above: review of waste regulation, feedstock certification, regulations for public procurement

Moreover, there are specific regulatory issues for the value chains, which are described in section 3.

Collaboration along value chains

The collaboration of actors from different stages of the value-chain in R&D&I is a prerequisite for successfully transferring R&D&I results to commercialisation.

Although many new collaborations and networks of communities have been established in IB in the last years, fostering networks remains a key issue in emerging value chains (e.g. microbiomes) or in existing ones, where novel approaches enable an innovation push (e.g. flavours & fragrances). Moreover, the existing comparably weak linkage between biomass production and supply on the one hand and biomass conversion on the other hand should be addressed by adequate policies.

Actions to be taken

42. Continue the funding of R&D&I projects that include actors along the value chains and from different countries
43. Attractive networking and partnering events should be continued in order to attract novel partners to existing value chains and to establish networks for novel value chains. Specific support measures or incentives should be considered for the integration of novel partners into existing networks (e.g. via requirements for integrating new partners in R&D&I programs, promotion of novel, alternative approaches in research fields, etc.).
44. Support IB clusters both national and cross-border, as these may form important networks to bring actors from different value chain stages together
45. Provide R&D&I funding to specifically address research questions that require closer cooperation between biomass provision and biomass conversion actors, e.g. quality of biomass for certain industrial uses and applications, decentralized small scale biorefineries, logistics concepts, and digitization as a tool to link the sectors.
46. Flavors & Fragrances, Microbiomes: establishment of a platform that enables networking and further development of R&I agendas

Collaboration across European countries

Intensified collaboration between actors from EU countries and integration of more countries into the various value chains should be strived for, in order to build up critical mass, to combine complementary competencies and resources, to achieve a higher quality of R&D&I and to contribute to more balanced, more sustainable regional development within the EU. On the one hand, efforts should be targeted at enabling leading countries in IB to join forces, to maintain their internationally leading position, and to team up with countries with complementary

strengths. On the other hand, R&D&I policy and cohesion policy should jointly tap the potential contribution of EU countries, which have presently low activities in IB by addressing low visibility and network competency of actors from countries with few IB activities, their integration into existing networks, and the joint development of strategies for cross-country collaboration, e.g. between feedstock providers and converters. The actions below refer to measures that explicitly aim to foster EU-wide collaboration.

Actions to be taken

47. Support the establishment of cross-country value chains, e.g. between feedstock providers from one country and IB firms specialised in conversion of feedstock in other countries (support of joint projects, networking)
48. establish a pan-European mapping of relevant IB competencies as an information base for complementary competencies and for higher visibility of actors
49. further support of cross-border clusters
50. diversify R&D&I funding portfolio to foster EU-wide collaboration with a focus on excellence, but also on cohesion (e.g. requirement for participation of a number of partners from certain set of countries with modest / low IB activities)
51. in order to incentivize the participation of actors from countries with modest or low activities in IB the following modification of existing measures and procedures may be considered:
    - restriction of the national freedom to assign EU structural funds by linking part of those funds to IB relevant topics
    - further simplification of application processes for many programs, as those actors from lagging-behind countries often lack of skilled workforce to write proposals
    - increase the EU budget for programs like EUREKA, EUROSTAR, which currently high national co-funding, which isn't available in some countries

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7 ANNEX I: Value Chain Scenarios

7.1 Introduction

In the following sections, the results from the workshop on value chain workshops from 7th-9th March are summarized. The selection of the value chains has been explained in Deliverable 2.1. The aim of the value chain workshops was to elaborate possible future pathways (scenarios) for each value chain in Europe in the next 10-12 years. The guiding question was how may the value chain in Europe look like in 2025-2030 from a technological, business, societal and policy perspective.

For each of the value chains between 7 and 13 experts participated. In total 64 experts attended the workshops. For each value chain the following steps were taken:

- Assessment of factors and current situation for technology, business, policy based on pre-analysis of the project team
- Priorization of key factors and imagination of alternative future developments for the key factors along the value chain
- Elaboration of three alternative scenarios by combining possible future developments for each key factor

In the following, for each value chain a short narrative describing a selection of potential alternative scenarios is described together with respective supporting tables. The tables contain the current situation for the critical factors that were identified and prioritized as well as the different future assumptions attributed to different scenarios. The narratives or story lines for the selected scenarios include links to the respective assumptions for the corresponding scenario as shown on the tables (the links T,B and P stand for Technology, Business, and Policy, respectively; the following number corresponds to the line in the table; and, A,B,C,D to the specific assumption).

Main conclusions are presented as a cross-value chain analysis for all 6 value chains in chapter 8. The conclusions for each value chain are being presented separately (Deliverable 6.6) as a result of combining the value chain analyses (Del 2.2) with the scenarios described hereby.

7.2 Scenarios for Lignocellulosic Ethanol - Overview of Factors and Future Assumptions

Scenario 1 (green): Policy driven uptake

Scenario 2 (yellow): Partial established production

Scenario 3 (red): Stagnant development

Scenario Starting points:

Scenario 1: This scenario is characterized by demand-side policy measures, namely a modification of the current proposal of a new Renewable Energy Directive (RED II). The modifications provide strong incentives for advanced biofuels, but do not contain the currently planned significant reduction in first generation biofuels. As a consequence, existing producers or investors in bioethanol as well as potential new investors commit to advanced biofuels. The measure is integrated in a broader policy mix.

Scenario 2: This scenario presents a partial uptake of lignocellulosic ethanol. Rather favourable framework conditions with a rising oil price and modest biomass price increases go along with only partial established demand-side policies that may foster the uptake of lignocellulosic ethanol. More concretely the current RED II proposal with binding mandates for lignocellulosic ethanol, but a significant cut in first generation biofuels come into place.

Scenario 3: This scenario presents a stagnant development of lignocellulosic ethanol. There is neither a development of an external framework, which may drive activities, nor significant policy commitment to bridge the phase and overcome missing cost competitiveness. More concretely, oil price remains low and comparable to current price levels, public financial support for R&D&I is falling, there are no binding mandates for lignocellulosic ethanol or other demand-side policy or strong financing of (near) commercial activities.

7.2.1 Technology

T	Factor and Current Situation	Future Assumption A	Future Assumption B	Future Assumption C	Future Assumption D
1	**Sustainable provision of lignocellulosic biomass** - Depending on the feedstock (agricultural residues, forestry, municipal waste), different machines, infrastructures and logistics for collecting biomass are under development; sustainability remains an issue - Alternative use of biomass as key influencing factor	2 **Waste and residues for small scale production** - Agricultural/forest residues, organic (industrial/household) waste as biomass for fuel production or chemicals - Small scale production close to raw material sources more widespread	1 **Tailored non-food crops for large scale production** few large-scale versatile biorefineries, using different types of feedstocks, among others tailored biomass crops	**Diversified biomass feedstock** - certain types of lignocellulosic biomass (e.g. straw) which are in principle available cannot be used in a sustainable way for ethanol production because their conventional use (e.g. soil improvement) cannot be re-placed → Additional biomass needed, e.g. - CO_2 Fixation / Capture CCS - Marine based biomass (Blue biomass)	3 **Incremental advances** Mainly status-quo development, concepts based on straw and wood are further developed, but no major advances in cost reduction

T	Factor and Current Situation	Future Assumption A	Future Assumption B	Future Assumption C	Future Assumption D
2	**Pre-treatment and hydrolysis** - Different options: Chemical, thermal, mechanical, biological pretreatment or a combination of these - Biological pre-treatment not very efficient yet (a lot of water and energy needed) and quite expensive - Enzymes break down cellulose and hemicellulose fractions to fermentable C5 and C6-sugars - Costs have decreased in the past, but are still significant	1 2 **Novel pre-treatment and hydrolysis steps** - Novel pre-treatment and hydrolysis steps broadly implemented - optimized pre-treatment techniques leading to higher yields and limiting adverse inhibitors' effects,e.g. through better fractioning and use of novel solvents; - less costly and more efficient enzymes through optimization of enzymes (modification/stabilization) or better re-use of enzyme combinations; up-scaling of enzyme production - enzyme costs of total production costs < 10 %	3 **Gasification** - Gasification of biomass to syngas becomes the predominant process	**Biological pre-treatment and hydrolysis** - Deployment of bio-based technologies for converting biomass which replicate natural processes - Complete biological processes by using optimized microbes, microorganisms and enzymes (mainly by synthetic biology) - Simplification of processes, e.g. simultaneous saccharification and fermentation	

T	Factor and Current Situation	Future Assumption A	Future Assumption B	Future Assumption C	Future Assumption D
3	**Valorization of lignin and by-products** - Few high-value uses of by-products and residues, lignin mainly used in bioenergy production - Lignin can be applied both as material and aromatic chemical building block - Part of lignin will be used for process steam	1 2 **High value applications** - High value applications for lignin (e.g.: source of phenols in duroplastic and thermoplastic application) broadly established - Cellulosic ethanol production integrated into biorefineries; thus using multiple feedstocks and achieving highest value through broad spectrum of products - More advanced biorefineries would enable the production of purer and qualitatively better lignin - Lignin could be used for semi-bulk applications (e.g. as a glue for materials) - High-value uses for by products (extractives: tannins, lipids; fatty acids, bioactive compounds) established:	3 **Use for energy production** - By-products mostly used for energy production (= status quo)	**Less by-products** - Diversification of biomass used - Tailored use of biomass , reduction of by-products - Stronger valorization of biomass components - Use of marine biomass (salts, bioactives, antimicrobials)	

T	Factor and Current Situation	Future Assumption A	Future Assumption B	Future Assumption C	Future Assumption D
4	**Fermentation using production organisms*** - Different production options: using yeast-based, bacteria-based systems, or chemical conversion of the produced acetic acid into ethanol - Current challenges: limited ability to ferment C6 and C5 sugars, sensitivity of microorganisms to inhibitors , achieved yields and final EtOH concentration	• Broad use of genetically modified, metabolically engineered microorganisms on commercial scale*	• Use of thermophilic archaea (e.g. tolerating 80°C) in order to combine pretreatment and ethanol fermentation in one process step *	• Broad use of tailored microorganisms designed by synthetic biology*	

* This factor and assumptions haven't attributed to scenarios in the workshop

7.2.2 Business

B	Factor and Current-Situation	Future Assumption A	Future Assumption B	Future Assumption C
1	**Cost Competitiveness** - ligno-cellulosic ethanol is not cost competitive compared to fossil fuel and bioethanol 1 generation - Still a significant cost gap exist, literature assumes around 25-30% higher costs	3 **No cost competitiveness** - No cost competitiveness compared to1st gen. bioethanol and fossil fuels	1 **Increasing cost competitiveness** - Ligno-cellulosic costs converge to those of 1st generation bioethanol and fossil fuels - Preconditions: RED mandate for significant 2nd LC-Bioethanol; financing for new facilities available; scale up of facility and build up of at least 20 facilities	2 **Cost competitiveness for selected pathways** - Costs competitiveness only achieved for very few pathways of LC Bioethanol and only economic viable in certain regions - Preconditions: Favourable regulation (e.g. such as CO_2 tax in Sweden) and feedstock supply advantage in a region

2	**Commitment of users and financiers**
	- Large uncertainties regarding revenues, as
	  - no long-term commitments/contracts from user industry, as there is no advantage or must for them to provide fixed acceptance guarantees
	  - depends on policy mandates for LC bioethanol, which are unclear
	- consequently raising funding for build up of new plants is difficult
		1
		Increasing commitment
		- Blenders give long-term commitment
		- More financing programs for building plants available
			2 3
			Very limited commitment
			- Neither user industry nor financiers provide long-term commitment to build up new plants	

B	Factor and Current-Situation	Future Assumption A	Future Assumption B	Future Assumption C
3	**Industry Structure** - Large companies are dominating the market (for ethanol, not necessarily fuels) - SMEs are present in different roles, some as technology developer, as producer or as service provider (e.g. engineering concepts)	3 **Large firms and SME struggle** - Markets of large companies are declining → these firms move into new markets, - Small firms may not step in as market conditions are unfavourable - → less industrial dynamic in the ethanol sector	1 2 **SMEs on the rise** - SMEs become more and more successful and take shares of large companies → these become more agile and fruitful market concurrence emerges - SMEs are also active in creating markets for by-products of ethanol; e.g. firms that are (independent from ethanol) active in lignin markets. They create new value products and settle the path for other to use the lignin coming out from lignocellulosic ethanol production to produce those goods	**Large firms dominate (Status-Quo)** - Large firms are still dominant - As SMEs are not assumed to have a special role in this sector this may not necessarily hinder further developments, but market is highly dependent on large companies decisions

7.2.3 Policy and Framework Conditions

P	Factor	Future Assumption A	Future Assumption B	Future Assumption C	Future Assumption D
1	**Oil Price** - **50 US$/bbl**	2 **111 US$/bbl** - (From IEA New Policy Scenario)	**127 US$/bbl** - (From IEA Current Policy Scenario)	**85 US$/bbl** - (From IEA 450 Scenario)	3 **60 US$/bbl** - (From Expert Workshop)
2	**Biomass Price** - Varying between regions in feedstock in EU, prices for straw and wood in a range of around 50-70 €/t – 100 €/t - Biomass Prices will to some extent follow oil prices in the long run	3 **Constant/slight declining prices (up to10%)**	2 **Moderate Price increase (10-25%)**	1 **High price increase (> 25%)**	
3	**R&D&I Policy** - Considerable funding for lignocellulosic bio-ethanol available	**Public funding at constant level** - Funding opportunities for R&D&I remain at a comparable level.	1 **Extensive public funding made available for specific purposes** - Specific funding for lignocellulosic fuel projects throughout different TRLs	2 **Extensive public funding made available more generally** - Stimulation of general replacement of oil-based products (not only fuels)	3 **Less public financial support available**

P	Factor	Future Assumption A	Future Assumption B	Future Assumption C	Future Assumption D
4	**Renewable Energy Directive** - Indicative target for 2nd generation biofuels of 0,5 % and double counting to quota - Sustainability criteria: 60% GHG emission saving for new installations, 50% GHG emission saving for existing installations (from 2018 on)	3 **Continuation of existing RED goals until 2030** --> no stimulation of new investments in lignocellulosic ethanol	1 **Amendment of existing RED goals** - Continuation of 10% share for biofuels - introduction of obligatory mandate for lignocellulosic ethanol	2 **EC proposition for RED II** - cap on the contribution of food-based biofuels to declining to 3,8 % in 2030; - submandate for advanced biofuels (3.6 %) - Mandatory quotes would give a market with price pressure - Higher sustainability criteria (70% GHG savings for advanced biofuels) Policy Targets vs. penalties very important	
5	**Demand side measures** - Public Procurement/Price Guarantees hardly introduced yet	2 3 **Very limited demand side measures** - Very few, fragmented activities to support demand for 2nd gen. biofuels	1 **Broad range of demand side measures** - Price guarantees, e.g. via local tenders - tax exemptions for lignocellulosic ethanol	**Climate protection tax**	

P	Factor	Future Assumption A	Future Assumption B	Future Assumption C	Future Assumption D
			- Fossil fuel tax		
6	**Financing of (near) Commercial Activities** - Public/private investors are reluctant; rather low incentives for investment - Approach of banks important	2 3 **Limited financing** - Predominance of the status quo development	1 **Increasing public/private financing** - Comprehensive, coordinated policy funding or tax incentives for private funders for high TRL-stages or commercial production		

Workshop participants gave written comments to the policy factors. Some of these comments have been integrated into the factors listed above. The other comments can be summarized as follows:

- The need for several public support instruments was expressed as necessary
- For some instruments (e.g. mandates) the characteristics of the penalties are of key importance for the functioning of the instrument
- Also instruments should be considered that reach beyond fuels and the lignocellulosic feedstock, e.g.
  - Stimulate the replacement of oil-based products, not only fuels
  - R&D&I policy innovation on flexible processes that can be applied to using CO_2 / sugars / syngas / other as bio-based raw materials

7.3 Scenarios for bio-based Plastics - Overview of Factors and Future Assumptions

Scenario 1 (green): “Derisking strategy” scenario

Scenario 2 (yellow): High oil price scenario

Scenario 3 (red): Niche market scenario: Recycling of plastics as a priority, ban of short-lived plastics

Scenario Starting points:

Scenario 1: De-risking strategy: there is a comprehensive, coordinated policy which finances risky business with strategic importance, e.g. via flagship projects or investment financing. In addition, coordinated market pull measures (e.g. public procurement, tax exemptions etc.) are implemented in the EU. Moreover, labels and transparent information about bio-based plastics and their benefits (e.g. indicating bio-based content, biodegradability, recyclability) are widespread. Many new market opportunities arise. As a consequence, more feedstock is drawn to the bio-based plastic market, with the possibility of feedstock shortage. Brand owner roadmaps to bio-based plastics (including lignocelluloses sugar) become attainable.

Scenario 2: Favourable oil price (127 €/bbl), market pull measures remain status quo (=Standardisation/information about bio-based plastics, labeling: functionalities and benefits remain unclear or are partly unknown)

Scenario 3: (Micro)plastics in the environment receive high attention by consumers and policy. Recycling of plastics becomes a priority, and water treatment technologies to remove plastics from water are implemented. There is a trend towards the ban of short-lived plastics which do not degrade readily under environmental conditions, and water treatment technologies to remove plastics from water are implemented. However, there are only few niche applications for bio-based plastics which degrade under environmental conditions. In addition, new solutions for textiles are needed

7.3.1 Technology

T	Factor und Current Situation	Future Assumption A	Future Assumption B	Future Assumption C	Future Assumption D
1	**Type of feedstock** (= biomass used for the production of bioplastics) The factor refers to the respective shares of feedstock type. A certain flexibility in feedstock use is required (e.g.: start now with future assumption A, adapt to market, then switch to other feedstock). Efficient feedstock use is a prerequisite (expressed as e.g. kg bio-based plastics / ha)	2 3 **Sugar/ starch and fats/oils dominate as feedstocks** as they also have the following characteristics: - The feedstocks are globally available in large quantities, they are transportable, storable, they have a constant quality, - A high grade of preprocessing is required	3 **Nonfood feedstocks play a major role** Dominating feedstocks are - A: wood, reed, straw, hay - B: fresh biomass, e.g. green grass, and waste: from the food industry, municipal waste, agricultural waste Characteristics of these feedstocks are A feedstocks have similar characteristics as the feedstocks in Future Assumption A B feedstocks have the following characteristics: The feedstocks are locally available in small quantities, they are fresh, have a high water content, and require immediate processing There is the option that high value substances can be isolated from feedstock fractions	1 **A wide diversity of feedstock is used** - All the feedstocks listed in future assumptions A and B are used - In addition, gasous feedstocks are used (CO, CO_2, H_2, CH_4, exhaust gases, gasification of waste)	

T	Factor und Current Situation	Future Assumption A	Future Assumption B	Future Assumption C	Future Assumption D
2	**Infrastructure for feedstock provision, processing and logistics** The factor refers to the type of biomass processing plants where bioplastics or building blocks are manufactured, and the required supply chains and logistics Sustainable feedstock provision is a prerequisite	2 **Large scale plants processing plants** - Processing of feedstocks takes place in large scale plants, where only a few products are manufactured. This is state of the art and will be continued (business as usual) - They are part of global supply chains - Technology is improved continuously	1 **Large and small scale processing plants** - Technologies for the pretreatment of biomass, which meet bioprocess requirements, become cost-competitive - Logistics for waste collection and waste pretreatment are established - Processing of feedstocks T1A may take place in larger scale plants - Processing of feedstocks T1A and T1B takes place in small scale conversion plants	3 **Small scale processing plants** - Processing of feedstocks takes place in small scale conversion plants	

T	Factor und Current Situation	Future Assumption A	Future Assumption B	Future Assumption C	Future Assumption D
3	**Recycling technology for bio-based plastics**	1 2 **Thermal use of plastic waste predominates** - Bioplastics remain a disaster for recycling - Mixed plastic waste is incinerated or converted to fuels	3 **Degradation of plastic waste** - Environmental degradability becomes mandatory for short-lived plastics	3 **Recycling established for certain plastic products or types of plastic** - Collection systems and recycling technologies are established for certain plastic products which make a “bottle-to-bottle” recycling possible (example: PET bottles) - Technologies are established which allow to recover high quality plastics from recycling (e.g. no smell, high chain length, etc.)	3 **Recycling established for all types of plastics** - All plastic materials can be separated or sorted by types of plastics. They are channeled into high value (re)-uses

T	Factor und Current Situation	Future Assumption A	Future Assumption B	Future Assumption C	Future Assumption D
4	**Share of drop-ins vs. share of new materials**	2 **Price determines the share** - Drop-ins dominate the bio-based plastics segment, they compete by price with fossil-based plastics	3 **Functionality determines the share** - New bio-based materials dominate the bio-based plastics segment because drop-ins cannot compete with fossil plastics on a cost basis	1 **Price, policy and functionality play an important role** - The share of drop-in bio-based plastics in the bio-based plastics segment is determined by price and/or market uptake policy measures - The share of new bio-based materials in the bio-based plastics segment is determined by performance and functionality	
5	**Production pathway** - Different pathways for bio-plastics production, e.g. direct production from feedstock (e.g. PHA), or intermediate steps, where monomers (e.g. platform biochemicals) are formed	2 **Few production pathways** - Few pathways a established for few large scale production processes/plants	1 3 **Many production pathways** - A multitude of production pathways coexist		

7.3.2 Business

B	Factor und Current Situation	Future Assumption A	Future Assumption B	Future Assumption C
1	**Feedstock** - Currently, Sugar and Starch based feedstock have market dominance for Bioplastics. - Alternatives (like lignocelluloses) remain ineffective or cost prohibitive. - First generation feedstock is inherently unreliable in regards to their performance consistency. Though second generation feedstock are under development, it is likely that most will go to the production of biofuels (not plastics).	2 3 **Continue to use traditional feedstock (sugar and starch) for production of most industrial Bioplastics.**	3 **Major switch to non-food biomass** - This would require a major technological and procedural breakthrough, but if successful would radically shift the balance. - Many researchers are currently experimenting with lignocelluloses technologies.	1 **Wide diversity of conventional and non-food feedstock are used.** - Dependent on regional capacities and policy, - Product specifications, - Other factors.

B	Factor und Current Situation	Future Assumption A	Future Assumption B	Future Assumption C
2	**Competitiveness of „Drop-Ins“** - Due to currently low oil prices, cost competitiveness of Bioplastics has been impeded, and some bio-based companies have struggled to remain in operation and/or to move up the value chain. - This status is also closely linked to various policy threads, including national and international policy regarding sustainability. - There is steady interest in Drop-ins that can alter functionality and safety or result in novel materials within current production infrastructures.	3 **Limited or Constricted Competitiveness.** - The increasing availability of shale-oil based products could severely limit the growth potential for Bioplastics, and continue to push the industry into smaller niche provider directions. - If C2 based Drop-Ins (which are largely the product of shale-oil) continue to grow in quantity, Bioplastics could be pushed out of commodities entirely. Actors then will focus their efforts on other areas of the value chain and niche markets.	2 **Marginal Competitiveness**. - With strong, brand-owner led demand, Bioplastics could become marginally competitive as a commodity***. - Such demand could support a growing infrastructure for Bioplastics production, but it is likely that such development would occur in regions or nations where it was most fiscally profitable. - It was also put forth that Bioplastics could become increasingly competitive within niche or minor industries (aromatics, etc). (***It was estimated that, specific for C2 plastics, 1% of the commodities markets for plastics could equal upwards of 300 million tons)	1 **Broadly Competitive.** - Bioplastics might become increasingly competitive if demand can be encouraged through changes to policy and/or a heightened public awareness of their potentials. - Increasingly stringent policies (rooted perhaps in carbon caps) could greatly benefit the Bioplastics industry both as it exists and its future development. - As the public becomes more aware of Bioplastics and their range of functionality, they might be more insistent on such products in the market, and push for further policy reform.

B	Factor und Current Situation	Future Assumption A	Future Assumption B	Future Assumption C
3	**Societal Awareness and Actions -** - Currently, social awareness of Bioplastics seems restricted to their capacity to biodegrade – a concept both misunderstood and radically limiting of Bioplastics potential. Raising consumer awareness also carries the danger of public fear (for example public reactions to GMO products and the resulting legislation). - There are also few policies in place to differentiate Bioplastic products and incentivize consumer purchases. Official certification programs to promote consumer awareness and /or policy that impacts pricing of non bio-based plastics could have a strong impact on consumer decision making.	1 **Bio Plastics could see major expansion if an increased level of social awareness can fuel a growing demand in both B2B and B2C markets.** - Waste Policy that favors certain functionality from plastic products could create growth in Drop-in and Non-Drop-In production and development. Coupled with awareness raising campaigns regarding technological breakthroughs and advanced functionality of Bioplastics, social demand for bio-based products could be radically increased. - If Climate Change continues to shape social perception regarding product life cycles and their environmental impact, growing social awareness and demand for public and private Bioplastics consumption could greatly benefit the industry.	3 **Falling Demand for Bioplastics could arise from different social movements and policies.** - If food security becomes a growing social concern, then land usage policy could reduce feedstock availability by limiting its production. - Alternatively, resistance to new products (both by industrial and individual consumers) might prove an important obstacle to garnering public favor, and could be detrimental to existing Bioplastic markets..	2 **Demand for Bioplastics could reach a plateau in the coming years due to many converging factors.** - If Bioplastics either fail to deliver on publicly perceived functionality promises, they could come to be viewed as a “fad” technology and fall out of the public imaginary. This perception might not eliminate incumbent Bioplastic technologies or industries, but could reduce the amount of funds available for research, development, and innovation. 3 - Alternatively, if public policy and regulation raises functional requirements too high, Bioplastics innovation could be stifled (both by established large firms, and in SMEs/startups).

B	Factor und Current Situation	Future Assumption A	Future Assumption B	Future Assumption C
4	**Markets for New Materials and „Non-Drop-Ins“** - Currently, the majority of bio-based products are Drop-Ins for existing mass markets. These are cost-competitive with fossil based counterparts, particularly during times of higher oil prices. - B2B opportunities typically dominate the industry, though B2C opportunities are growing alongside consumer awareness.	3 **Contracting Bioplastics Markets** - Multiple factors could lead to a contraction of the overall Bioplastics market and the variety and quantity of products offered. - Continued low (or lower) oil prices can undermine what little competitive advantage Bioplastics once held. - Concerns over Food Security fuel a social movement regarding land usage for non-food bio production.	1 **Greater diversity of Products could come from a number of industries.** - For Bioplastics that can exhibit the required functionality, growing interest from architecture, industrial design (including automotive), and other high-volume markets for traditional fossil plastics could lead to competitive parity for bioplastics within certain niches. - Such interest could spurn R&D&I for more diverse Bioplastics as both building blocks and as finished products.	2 . **Stagnant Product Evolution** - This could be the result of a variety of factors, but primary drivers include continued low-oil prices, restrictive policies, or the development of alternative processes to achieve carbon neutrality. - The CO_2 process that is currently being developed and marketed by the Coca Cola Co. is one such instance of a competing process that undermines the stability of Bioplastics.

B	Factor und Current Situation	Future Assumption A	Future Assumption B	Future Assumption C
5	**Brand Owner Strategies**	3 2 **Brand Owner Driven Demand for Innovation** - If brand owners (LEGO, Coca Cola) become the primary drivers of demand for new products and functions - Bioplastics R&D&I institutions from academia to SMEs is likely to grow in scope and overall production. - It is possible that Brand Owner driven demand can help bio plastics pass critical tipping points, and become ever more competitive with fossil based alternatives across a growing variety of plastic types.	**As an extension of the status quo, Brand Owners continue to drive the market for all non-food biomass based products.** - Under such conditions, novel innovations in Bioplastics and their functionality remain specialized and marginalized in regard to the wider market.	1 **Brand owner driven demand for Bioplastics could result in commodity status, with some bio-based products earning more than one percent of the overall commodity market (a very large amount).**

7.3.3 Policy

P	Factor and Current Status	Future Assumption A	Future Assumption B	Future Assumption C
1	**Oil Price** - 50 US$/bbl	- 111 €/bbl (IEA New Policy Scenario)	2 - 127 €/bbl (IEA Current Policy Scenario)	- 85 €/bbl (IEA 450 Scenario)

P	Factor and Current Status	Future Assumption A	Future Assumption B	Future Assumption C
2	**Biomass Price** Varying between regions in feedstock in EU, prices for straw and wood in a range of around 50-70 €/t, white sugar 470 €/t	- Constant/slight declining prices (up to10%)	- Moderate Price increase (10-25%)	- High price increase (> 25%)
3	**R&D&I Policy (EU + national)** Considerable funding for bio-based plastics available	1 - Status Quo: Funding opportunities for R&D&I remain at a comparable level.	- Extensive public funding made available	- Less public financial support available
4	**Financing of (near) Commercial Activities** Public/private investors are reluctant; rather low incentives for investment	2 - Mostly status quo development	1 - Comprehensive, coordinated policy funding or tax incentives for private funders for high TRL-stages or commercial production	
5	**Standardization/Information about Bio-based Plastics, Labelling** Terms (e.g. “green”, “bio-degradable”, “bio-based”, “bioplastics”, etc. are not well defined Some EU standardization initiatives	2 - Functionalities and benefits unclear/partly known	1 3 - Transparent and widespread labels /information about bio-based plastics and their benefits (e.g. indicating bio-based content, biodegradability, recyclability)	

P	Factor and Current Status	Future Assumption A	Future Assumption B	Future Assumption C
6	**Market pull measures** Various measures debated (bans, mandates, public procurement, tax exemptions, etc.) Fragmented national policies for bans/procurement; no market uptake incentives	2 - Status quo, few fragmented national activities	1 - Market uptake measures (public procurement; tax exemptions etc.) coordinated in the EU	3 - Short-lived plastics, which do not degreade readily under environmental conditions are more and more banned - Recycling of plastics as a priority

Participants' comments for the Policy measures/factors and future assumptions:

- Oil price: Non-linear effects of oil prices should be taken into consideration, regarding plant size, fuels, and commoditization of specialities
- Biomass price: constant or slightly declining prices are expected for 2nd generation feedstocks; moderate price increases are expected for competitive pricing without subsidies
- R&D&I Policy: both EU and national policies should be taken into consideration
- Financing of (near) Commercial Activities: Flagship projects, Public-Private Partnerships and financial instruments for a "derisking strategy" are suggested. These instruments could target pilot and demonstration units in the EU (e.g. like in BBI), upscaling and implementation.
- Standardization/Information about Bio-based Plastics, Labelling: A clear distinction should be made between "bio-based" and "biodegradable". There are CENTC4II standards on bio-based products. Standards and certification should be for sustainability. It is warned against "over-marketing", as it bears the risk that no-one believes in "green" anymore.
- Market pull measures: Bioeconomy and bio-based products have important roles in the EU circular economy strategy. Bioplastics and market uptake measures have/should have a role in the upcoming EU plastics strategy. Market pull measures should be part of a coherent supportive policy framework. Life cycle thinking and the performance of new biomaterials should be taken into consideration. Green public procurement is expected to create a critical mass with the market.

7.4 Scenarios for Production of Biopharmaceuticals - Overview Factors and Future Assumptions

Scenario 1 (green): Broader Access to Biopharmaceuticals

Scenario 2 (yellow): Status Quo Development

Scenario 3 (red): Gene Therapy Breakthrough

Scenario 1:

Market demand leads to a dynamic growth for biopharmaceuticals (in absolute numbers, but also in market shares) that demands for increasing production.

Scenario 2:

Incremental evolution in the production of biopharmaceuticals with rather slow technological progress and a rather modest market growth

Scenario 3:

Gene therapies become established in clinical routine, enabled by advances of CRISPR / CAS methods (T1C). This will change medical delivery profoundly with one time treatment compared instead of medical treatment with pharmaceuticals over a period of time or even life-long. New therapy forms with new manufacturing requirements will gain importance.

7.4.1 Technology

T	Factor und Current Situation	Future Assumption A	Future Assumption B	Future Assumption C
1	**Technologies for new products** - Solutions for rare diseases gain importance - protein therapeutics -gene therapy - Push to develop technologies for true personalized approaches at affordable cost; e.g. oncology, diagnostics, orphan drugs - Maintaining expertise in microbiology (in academia – SME – large companies as challenge)	2 **Manufacturing difficulties for new products** - Difficulties in manufacturing process for new type of products. Market entry of some new product groups is significantly delayed and hampered - Monoclonal or derived antibodies still on the market	1 **One line- one product set-up** - current “one line, one product” setup stays the predominant production mode; flexible multiple product operations require too high quality control efforts - Single-use systems are suited - Virology + brain / nerves as important areas	3 **Gene Therapies established** - Gene Therapies more widely established by CRISPR / CAS - Drug device combinations (insulin)
2	**Production organisms for biopharmaceuticals** - Most biologicals are manufactured in bacteria or mammalian cell cultures. New production platforms (e.g. cell-free synthesis of recombinant proteins) are mainly in lab to pilot scale and are predominantly used in the research phase, but not yet in manufacturing - Important developments - - Improved cell lines (e.g. secreting cell lines) - New production organisms (e.g. plant cell lines, - Alternatives to engineered cell lines (e.g. transgenic crop plants or transgenic animals (“pharming”))	1 **Break through: more productive upstream methods** - new and/or improved production organisms (e.g. plants, insects) -> reduce downstream hurdles(-> GMP)	3 **Cell free synthesis established**	2 **Incremental Advances**

T	Factor und Current Situation	Future Assumption A	Future Assumption B	Future Assumption C
3	**Process analytics** Relevant aspects: - real time monitoring - - online analytics, single use - "Data integrity", Data management - Data evaluation - Process control for continuous production - Advanced models - Data handling - Need to understand / control the process: in-process analytics development	3 . 1 . **All data available in real time** - All Data (CO_2 / O_2 / pH values) available in real time - IT-infrastructure available - Knowledge for interpretation available - Process control for continuous processes - Intercellular devices - Molecular sensors"	2 . **Some data available offline**	

7.4.2 Business

B	Factor und Current Situation	Future Assumption A	Future Assumption B	Future Assumption C
1	**Market for new Biopharmaceutical Products** Mixed market developments for new biopharmaceuticals, which determine the needed production capacities and its utilization: - Unmet clinical needs and personalized medicine favor biopharmaceuticals - Payer pressure on cost of drugs increase - From the cost side, approval of product becomes increasingly expensive. This may hamper the R&D&I and commercialization of new products - Blockbuster model is losing importance	2 **Slow growth** - Market grows steadily, but no high growth rates	1 **Dynamic growth** - Market for of biopharmaceuticals (in absolute numbers, but also in market shares) grows very dynamically - Stratified medicine widespread - The value chain for the products will broaden significantly, as the development of respective biomarkers and devices as well as testing will be provided complementary (e.g. companion diagnostics) Cost reduction for companion diagnostics via improved methods in DNA sequencing	3 **Dynamic growth, diversified product portfolio** - Market for of biopharmaceuticals (in absolute numbers, but also in market shares) grows very dynamically - New therapy forms with new manufacturing requirements gaining importance

B	Factor und Current Situation	Future Assumption A	Future Assumption B	Future Assumption C
2	**Localization of R&D&I and production** - Europe strong in technology and production capacities - Increasing importance of emerging markets for (bio-)pharmaceuticals - Trend of localized production in many countries and also costs are very low in some locations	3 **World-wide distribution** - Increasing R&D&I distribution all over the world - Share of emerging markets in biopharmaceuticals rises significantly; - Emerging countries increase production capacity for these products - Europe suffers some decline in share of production capacities	1 **EU holds position** - The number of biopharmaceutical facilities increases smoothly, while the output increases significantly - The share in production capacities in the EU remains almost constant - Technological expertise can be secured in the EU	2 **Asia catch-up** - Asia will catch up and increase their production capacity enormously - In Europe, the production capacities will fall in absolute numbers and world-wide share - Significant technological expertise in Europe is lost
3	**Division of Work** - Increasing importance of CMOs, new firms from other fields entered the market (e.g. Fuji Films, Samsung) - Some large firms with production of own-developed pharmaceuticals and production for other firms - Some biotech firms with production capacities for clinical batches; role for CROs and SMEs in the production process unclear	2 **CMOs importance continues to rise** - Reluctant activities of large pharmaceutical companies - Flexible CMOs sill step in; here, new firms from other fields will increasingly enter the market	3 **SMEs on the rise** - Increasing importance of SMEs (in Europe) - New research areas are not occupied by big pharma; hence, fruitful fields of activities for SMEs exist	**Large companies dominate** - Status-Quo development Diversified landscape of actors, but large pharmaceutical companies have still a dominating role in the market

7.4.3 Policy

P	Factor	Future Assumption A	Future Assumptions B	Future Assumptions C
1	**R&D&I policy*** - Considerable funding for production technologies for biopharma available	**Status Quo: Funding opportunities for R&D&I remain at a comparable level.**	**Extensive public funding made available** - for R&D&I funding , but partly also for clinical trials	**Less public financial support available**
2	**Price regulations** - Increasing cost containment measures for (bio-) pharmaceuticals	3 **Significant cost containment, price regulations adjusted** - Price will be fixed according to additional medical benefit	2 **High cost containment, biosimilars incentives** - Incentives for biosimilars production, but to a lesser extend for the production of new biopharmaceuticals	1 **Moderate cost containment, new biopharmaceuticals favoured** - favourable reimbursement of new biopharmaceuticals
3	**Regulation for manufacturing** - GMP regulation sets up high requirements for manufacturing - Some discrepancies between regulators and manufacturers arise - Emerging compounds have to fulfill GMP when produced globally	1 **More Transparence and Consensus** - Transparent, partly more strict regulation - Growing consensus between regulators and manufacturers	2 **Less harmonization** - Less harmonization of regulations across world regions	**Much stricter regulations** - Increasingly strict regulations: Local advantages for industrialized countries due to a favourable regulatory framework and abundant endowment with advanced production factors

* Not identified as important driver in the various scenarios

7.5 Scenarios for Enzymes - Overview Factors and Future Assumptions

Scenario 1 (green): Technology push, everything is optimal

Scenario 2 (yellow): Coordinated bioeconomy policy, but global competition

Scenario 3 (red): High oil price, but consumer concerns

Scenario 1:

There is substantial technological progress: Enzymes can be designed on demand due to powerful prediction technologies. Enzymes can flexibly be produced by in vitro expression on large scale. Generation 3.0 enzyme production hardware is established.

Scenario 2:

There is a coordinated bioeconomy policy in Europe, which invests in R&D&I and establishes market pull measures. The regulation supports the replacement of chemicals by enzymes, the use of biomass, the saving of energy, environmental protection. Countries in the Asia/Pacific region advance significantly in enzyme-related skills as well as enzyme production, thus challenging the EU leadership in enzyme R&D/innovation as well as enzyme production.

Scenario 3:

The oil price is high (100 Euros/barrel). There a growing concerns of consumers of genetically modified organisms and adverse health effects of enzymes. NGOs run anti-enzyme campaigns. As a consequence, regulations for enzyme use become stricter.

7.5.1 Technology

T	Factor und Current Situation	Future Assumption A	Future Assumption B	Future Assumption C	Future Assumption D
1	**Expression Systems for Production (Production Host Systems)** - A small set of highly optimized production organisms (e.g. Bacillus, Trichoderma, Aspergillus) is used for most enzymes - Multinational enzyme companies often hold their proprietary technology. - New production systems provided by SMEs and academia.	3 . **Established expression systems (**e.g. Bacillus, Trichoderma, Aspergillus**) predominate** and determine which enzymes can be produced on an industrial scale. E. coli as cloning system has the advantage of high flexibility.	2 . Established expression systems remain the most important hosts, but a **larger choice of host systems** becomes industrially available.	1 **New expression systems are in widespread and growing use across multiple industrial applications.** Among them are - **Cell-free in-vitro protein expression**, which has the advantage of very high process flexibility. - **Whole cell biocatalysis using optimized enzymes** enters industrial applications.	3 . **Curtailment of Enzyme Process Development, including some of the established production organisms**. - Negative public attitude impacts use of some of the established production organisms. - Development in certain segments put on hold until public perception can be redirected. - R&D&I focus shifts to enzymes in fields with few public concerns (e.g. enzymes in industrial processes, manufacturing of intermediates)

T	Factor und Current Situation	Future Assumption A	Future Assumption B	Future Assumption C	Future Assumption D
2	**Optimization of Established Enzymes** - Mainly hydrolases (E.C.3) are in use for industrial and commercial applications. - The exploitation of other enzyme classes is hampered by ○ technical challenges (e.g. co-factor recycling) ○ lack of basic enabling technologies, including bioinformatics tools, HTS biochemical characterization, and databases of structural/functional knowledge.	3 . **Rational optimisation expands in academia, but doesn't scale and is rarely used for industrial enzyme optimisation.** - Rational optimization is applied to enzymes from all enzyme classes - has substantial impact on general understanding of enzymes - This progress in science and research leads to slow, but well understood, development of new enzymes.	1 2 . **Rational optimisation increases for most use cases** (random approaches for optimization are applied only in special cases). - Bioinformatics and data processing capacities lead to multiple breakthroughs. - more efficient or effective enzymes can be constructed with reasonable effort	2 . **Random optimisation increases for most use cases,** based on high-throughput-systems (HTS) - Bio-informatic capacities remain insufficient, enzyme modeling is too complex. - Bio-informatics research is hindered by access and non compatible data sets.	3 . **Optimization of established enzymes is slowed down and/or takes place only in certain segments** - Major shift to natural production processes - R&D&I focus shifts to non-sensitizing enzymes and/or non-sensitizing formulations

T	Factor und Current Situation	Future Assumption A	Future Assumption B	Future Assumption C	Future Assumption D
3	**Identification of New Enzymes** **There are bottlenecks between finding and using new enzymes:** - Evaluation of molecular diversity for potential applications - Genome Mining becomes a basic bioinformatics tool in new enzyme identification - Development of new functions is more difficult than optimization. - Software based forecasts and predictive models of expectable outcomes and risk assessments.	**Status Quo: Mainly hydrolases are used in industrial applications.** - Hydrolases continue to grow in applications like biomass conversion & bulk processes. 3 - The use of new enzymes in industrial applications is limited due to cost and risk of R&D, and limited integration into industrial processes.	2 **Screening Technology Breakthrough** - In-silico enzyme screening and design, in-vitro synthesis and automated HT enzyme analytics become routine. - Bioinformatics development enables in-silico promiscuity screening even for hydrolases - Fine-tuned biochemical characterization of enzymes, and evaluations of molecular diversity of new production enzymes are enabled through HTS.	1 **Identification of enzymes diversifies** - De novo design becomes feasible for first applications in industry. - Enzymes are designed according to predefined characteristics including non-natural reactions. - Technical difficulties are overcome enabling dream reactions through the discovery or design of new enzymes. - Enzymes from all classes see widespread industrial adoption and a broad range of new applications.	3 **Reduction in new enzyme research.** - Funding for new enzyme R&D&I dries up - R&D&I focus shifts to non-sensitizing enzymes and/or non-sensitizing formulations
4	**Formulation** - Formulation for enzyme applications in detergents - Addressing safety and effectiveness aspects by formulation (e.g. encapsulation) - Proprietary delivery systems	3 **Trial & Error formulation development remains the primary research mode**. - Better formulation is achieved through HTS approaches (allowing greater efficiency in testing).	1 2 - an increasing understanding of underlying principles makes more rational, knowledge-based research possible. More efficient formulation development is supported by computational tools	3 - **Formulation research slows to a halt** with a wide shift back to synthesis.	

T	Factor und Current Situation	Future Assumption A	Future Assumption B	Future Assumption C	Future Assumption D
5	**Enzyme Applications** - High development costs are a major hurdle. - Typically, the different steps within the R&D&I process are carried out independently resulting in a high risk of late-stage-failure. - Integrated approaches are also in place in industry, (especially for improving existing development processes) - Always a question of Host Ambivalence vs. Host Speciality	3 . **Lack of evaluation tools** - The use of new enzymes in new applications is hindered by a lack of evaluation tools.	1 2 . **New enzymes are evaluated for their potential applications**. - Potential use of co-products - Enzymes for use in the waste management industry, and waste management of the IB enzyme industry itself.	3 . **R&D&I efforts slowed down** Reductions in funding sources and market demand slow R&I efforts in new application development.	

T	Factor und Current Situation	Future Assumption A	Future Assumption B	Future Assumption C	Future Assumption D
6	**Process Development/Development time and cost** - High development costs are a major hurdle. - Typically, the different steps within the R&D&I process are carried out independently resulting in a high risk of late-stage-failure. - Integrated approaches are also in place in industry, (especially for improving existing development processes) - Always a question of Host Ambivalence vs. Host Speciality. - Expressability and Culturability factors - Space/time yield efficiency create conditions for technological and business development.	3 - **Process development is improved for some industrial applications**, but remains on status quo in other applications/market segments	2 **Process development** remains a challenge, but there are **sufficient incentives to overcome hurdles**	1 **The complexity in process development process becomes manageable.** **Water removal becomes new barrier or limitation** because enzyme technologies and technics are so far advanced.	
7a	**Production Processes** - Currently underrepresented in R&D&I, even though downstream benefits can be significant.	3 **New process designs (e.g. enzyme cascades, continuous processing) are not or only rarely implemented in industrial processes**	1 2 **New process designs (e.g. enzyme cascades, continuous processing) are implemented in industrial processes**		

T	Factor und Current Situation	Future Assumption A	Future Assumption B	Future Assumption C	Future Assumption D
7b	Production Processes	3 Synthetic biology is not used by industry	2 Synthetic biology plays a minor role for industrial processes	1 Synthetic biology is important for industrial processes	

7.5.2 Business

B	Factor und Current Situation	Future Assumption A	Future Assumption B	Future Assumption C	Future Assumption D
1	**New applications for established enzyme** - Industrial processes - today are based on chemistry, physics - could be biological (environmental friendly, more specific (chiral), more cost effective) - Reduced use of chemistry/chemicals, economics and environmental concerns drive growth of enzyme use - Scope to use enzymes in new applications is often limited by safety considerations (e.g. use in open systems) - Regarding both technology and business, there are fundamental differences between industrial enzymes and ”specialty” enzymes (very high value	1 **Enzymes are in competition with chemical catalysis** - **Industrial enzymes:** Enzymes replace chemical catalysis/chemicals on a case by case basis if their use saves raw materials, saves energy, reduces by-products - **Laundry enzymes:** the driver for replacement of chemicals by enzymes are the formulators’ needs; they want fast acting enzymes with broad specificities, replacement takes place if these needs can be met by enzymes - REACH effects are ambivalent; can either favour or disfavor use of enzymes (see also future assumption C)	1 2 **Extension of the market for enzymes** - **Industrial and laundry enzymes** Chemicals are replaced by enzymes in new applications (e.g. cleaning applications such as hand dishwashing, spray; in personal care products which are only in short contact with the skin, or use of proteases in peeling - Synergistic action of chemicals and enzymes can be exploited - A new process/product/solution becomes possible without existing predecessor, e.g. in biopharmaceutical production - High oil prices favour the replacement of chemicals by enzymes - Environmental concerns and strict environmental regulation favour the replacement of chemicals by enzymes - Saturation in Western markets triggers customer-specific solutions, e.g. novel combinations of laundry components, or novel product forms. As a consequence, enzymes become commodities and enzyme prices fall	**Market for established enzymes decreases** - **Industrial enzymes** Clean chemistry, chemical catalysis and certain chemicals outcompete enzymes, they are cleaner, well-defined, and cheaper - Low oil price disfavours enzyme use 3 - **Laundry enzymes**: Enzymes are used less in laundry detergents, because… - …New washing machine concepts without water are broadly introduced - …New synthetic fibres and functional clothes become more important than cotton - …Clothes have a shorter life time and therefore need less washing	3 **Use of enzymes in non-consumer products is favoured** Use of enzymes in food, drink, textiles, personal care decreases Laundry formula are changed in order to comply with labeling requirements

B	Factor und Current Situation	Future Assumption A	Future Assumption B	Future Assumption C	Future Assumption D
2	**New applications for new enzymes** - Enzymes are remarkable for their specificity - New applications for new enzymes exploit enzyme specificity; especially for high value products - Enzymes in Biocatalysis: value of enzyme is low!	1 **Enzymes are in competition with chemical catalysis** See above	1 2 . **Extension of the market for new enzymes** - Generation 2.0 production systems for enzymes become available, so that new enzymes can be produced on industrial scale which cannot be produced with the current microbial hosts - A new process/product/solution becomes possible without existing predecessor, e.g. in biopharmaceutical production - New complex compounds (e.g. peptide antibiotics) made by new enzymes - Synergies between chemicals and enzymes can be exploited (also: see above)	3 . - Enzymes replace chemicals/chemical catalysis in Industrial processes in certain segments/applications, because they save raw materials, save energy and reduce by-products	

B	Factor und Current Situation	Future Assumption A	Future Assumption B	Future Assumption C	Future Assumption D
3	**IP Framework** - High barrier to entry for SME to supply directly "ready to use" enzyme ingredients	3 **Big enzyme industry hardly cooperates** - Big industry reduces their collaboration with SME and academia to protect their IP / freedom to operate	2 **Big enzyme industry/SME collaboration** - Big enzmye industry collaborates with SMEs but not with academia in order to protect their IP/freedom to operate	1 **Swiss model for cooperation:** Big enzyme industry collaborates within publicly funded projects with academia, because the generated IP will be owned by the companies	1 **Alternative ways for co-creation/cooperation** - Ways are found for co-creation (open innovation) - Joint development by large companies, SMEs and academia - Patent protection 10 instead of 20 years
4	**Geographical distribution of activities: Production** - Western Europe is the only net exporter of enzymes.	1 **Global production by present market leaders** - Western Europe and the US remain market leaders, they produce globally	2 **Glocal production** - Enzymes are produced locally (= in a few leading countries, e.g. by present market leaders), but are distributed globally (as in the chemical industry))	2 3 **Production in Asia** - Enzymes are produced in Asia; the share of Europe and the US decreases (as in steal industry)	1 **Relocation to EU** - Relocation of enzyme production from Asia to Western Europe due to rising prices in Asia

B	Factor und Current Situation	Future Assumption A	Future Assumption B	Future Assumption C	Future Assumption D
5	**Geographical distribution of activities - Market** - Detergent/laundry enzyme use in Europe is a mature sector - Growth potentials lie in export to emerging markets - Specific adaptation to non European wash processes (e.g. non-soaking) and local markets required	1 **Globalisation 1** - Developing countries as major growth markets: detergents are produced by local companies. These local companies are the major customers of big global enzyme producers or are even bought by the global players	2 . 3 . **Globalisation 2** - Developing countries as major growth markets: emerging players in developing countries get big enough to become global players and compete with present leaders	3 . **Globalisation 3** - Emerging players in developing countries become global players and replace present leaders in certain segments	**National isolation** Global trade is severely impaired by national isolation strategies (e.g. the US/ Trump, EU breaks apart, tariffs)
6	**Geographical distribution of activities - R&D** - with respect to R&D&I investment, talents, competencies Europe and the US leading, China is emerging - Specific adaptation to local markets required (for laundry enzymes), is partly carried out locally	2 . **Europe, the US and China leading** Europe and the US remain leaders, but China also obtains a leading position in certain segments	3 . **Asia is world leader in industrial enzymes innovation**	1 **Europe is world leader in industrial enzymes innovation**	
7	**End-user-demand / perception**	3 .	1 2 . **Positive impact of end-user demand/perception on enzyme use**		

B	Factor und Current Situation	Future Assumption A	Future Assumption B	Future Assumption C	Future Assumption D
	- For detergents cold-active detergents are a major trend	**Negative impact of end-user demand/perception on enzyme use** - User gut feeling could switch a process - Non-bio-formulations due to consumer health concerns of enzymes 3. - Awareness raising campaigns are required	- User gut feeling could switch a process - Awareness raising campaigns support positive attitude		
8	**Safety aspects of enzyme exposure**	1 2. - Enzyme Exposure Limits			

7.5.3 Policy

P	Factor und Current Situation	Future Assumption A	Future Assumption B	Future Assumption C
1	**R&D&I policy** - Considerable funding opportunities in Europe and from national agencies.	1 2 - Funding opportunities for enzyme R&D&I increase	3 - Status Quo: Funding opportunities for enzyme R&D&I remain at a comparable level as today - Efforts are focused on specific fields	- Funding opportunities for enzyme R&D&I decrease.
2	**Bioeconomy policy** - Bioeconomy as a strong driver for enzyme technology. - Various initiatives exist at European and national level. - Instruments differ between various applications.	1 2 - European industry greatly benefits from the R&D&I investments and market-pull policy. New applications for enzymes with high value-added arise in Europe.	- Bioeconomy policy is losing importance.	3 - R&D&I Bioeconomy initiative continue to exists and are frequently revised resulting in a strong R&D&I base in Europe. - No/only few corresponding market incentives are implemented.
3	**Regulations and Standards** - Regulatory framework for enzyme applications depends on their applications. - SOPs for production safety are implemented	3 - Regulations concerning enzymes become stricter and more transparent. - As a result access to certain applications and markets also becomes restricted.	1 - Regulations concerning enzymes become clearer and more transparent without limiting applications of enzymes significantly. - As a result of higher certainty applications and markets for enzymes grow/open up.	- Status Quo: Regulatory framework differs between applications and is not always well defined. - Effects are unclear.

Workshop participants gave written comments to the policy factors. Some of these comments have been integrated into the factors listed above. The other comments can be summarized as follows:

- The EU bioeconomy strategy should be updated and/or revised.

- Several instruments for R&D&I funding are suggested:
  - significant funding of basic research, as this is the foundation for innovation;
  - synergistic combination of different funding instruments
  - specific funding instruments for SMEs; e.g. > 50 % public funding for SMEs
  - tax reductions for R&D&I investments within EU projects
  - in calls for project proposals, higher transparency which project volumes will be funded, perhaps separate calls depending on project volume (e.g. < 300 k Euros; 300-700 k Euros; 700 k Euros - 1,5 mio. Euros, >1,5 mio. Euros)
  - funding of company R&D&I at lower TRL stage (< TRL 6)
- The IP policy in the EU regarding academia is a disincentive for industry to cooperate with academia, leading to industrial R&D&I being carried out “in isolation". Novel connections would be desirable.
- Regulations should be specific for the targeted products or fields.
- Globalisation might lead to more permissive regulations in order to be able to stay competitive internationally.
- It is unclear which effort has to be taken by industry in order to comply with national regulation beyond REACH
- It is a realistic estimate that the status quo of the regulatory framework will remain, so that the framework differs between applications and is not always well defined.

7.6 Scenarios for Microbiomes - Overview Factors and Future Assumptions

Scenario 1 (green): Favourable regulation, positive public perception, science-based product development

Scenario 2 (yellow): Focus on publicly funded research

Scenario 3 (red): Favourable regulation, but negative public perception

Scenario 1:

The regulation is changed. Publicly funded core studies are performed (long term cohort studies plus intervention studies) and a biobank is publicly financed over the long term. Thus, better data are generated, and the public perception is positive.

Scenario 2:

The regulation is not altered and remains as it is. However, public R&D&I funding in the EU is significantly increased and allows intensive US-EU-Asia R&D&I cooperation. The data generated must be made publicly available. This increases the generation of basic knowledge about microbiomes considerably. Companies do not play an active role in the generation of this knowledge base, as the requirement to make the data publicly available is not attractive for them. Companies, however, use the publicly available knowledge base for product development

Scenario 3:

In regulation, the FSNP category with widened scope is established for microbiome targeting food/products. NGOs transmit, however, a negative perception

7.6.1 Technology

	Factor und Current Situation	Future Assumption A	Future Assumption B	Future Assumption C	Future Assumption D
T1	**Knowledge Base/** Healthy microbiome - "what is healthy microbiome over the entire life span"	2 1 . **"Negative" definition given (= definition of an "unhealthy microbiome")** - Unhealthy microbiomes can be defined for certain diseases	3 . **No definition possible** - Healthy microbiomes can never be defined due to heterogeneity and complexity dynamics host-environmental interactions	3 . 2 1 . **"Positive" definition given for certain functions or metabolites** - For certain mb functions & metabolites a "healthy state" can be defined -	2 **Healthy microbiome as basis for personalized medicine** Understanding of healthy microbiomes is basis for personalized medicines
T2	**Bio Informatics, Role of standardisation**	2 1 . **Standardisation vs. comparability** Comparability (e.g. sharing samples) more important than extensive standardization	2 1 . **Implementation of standardization depends on innovation phase** - In the development of bioinformatics standardisation is counterproductive - In the use of bio informatics: standardization is implemented	2 1 . **Medium level of standardisation** - High flexibility for evolving technologies - SOPs for sampling + data collection	3 . **High level of standardization** - Most approaches (sampling, data analysis) are standardized - But: stagnation

	Factor und Current Situation	Future Assumption A	Future Assumption B	Future Assumption C	Future Assumption D
T3	**Causal associations** **-Role of integration of omics data**	**Not helpful** - Integration of –omics data leads to more confusion	3 . **Highly professionialised players required** - Integration of omics data requires big data / bio informatics statistics companies (who owns the data?)	2 1 . **Very helpful** - Integration of –omics leads to deeper understanding of microbiome functions	-
T4	**Causal associations** - Role of studies and methodologies for investigating causal associations	3 . **Case-control-studies** - Remains restricted to case – control - studies	2 1 . **Targeted interventions** - Targeted interventions (from n=1 to larger group)	3 . 2 1 . **Large cohort studies** - large long-term prospective cohort studies are performed, funding is made available - (citizen science)	-
T5	**Personalisation**	2 **Life style and demand driven interventions** - Personalized interventions are offered - Not evidence-based, health effects unclear gadget /life style driven	3 . **Regulatory protection against unsafe procedures** - Regulatory oversight to prevent unsafe / misleading services / products	2 1 . **Evidence-based interventions become personalised** - Host microbiome analysis and integration with personalized medicine, is basis for personalized Nutritional advice and subsequent intervention	-

	Factor und Current Situation	Future Assumption A	Future Assumption B	Future Assumption C	Future Assumption D
T6	**Next generation microbiome products** - Need for “new” probiotics and bacterial products - Live biotherapeutic products (single strains, mixed strains)	3 . 2 **Well-known bacteria and prebiotics** - Lactobacilli and Bifidobacteria probiotics (GRAS) - Fructans etc	3 . 2 1 . **Broad spectrum of probiotic bacterial strains and prebiotics** - Broad spectrum of probiotic bacterial strains (genus, physiological functions), also GMO - Broad spectrum of prebiotics, also novel ones	1 . **Broader definition, beyond bacteria** - Probiotics comprise bacteria, microbial phages, parasites, …	1 . **Broadest definition, beyond organisms and prebiotics** - Microbiome products comprise every active ingredient which modifies the microbiome
T7	**Mode of action of microbiome products (microbiome addressing food)**	3 . 2 1 . **Modification of microbiome** Next generation products that modify microbiota to improve health	2 1 . **Maintaining altered microbiome** Next generation products that maintain altered microbiota	1 . **Engineering microbiomes and maintaining the engineered microbiome** Xenobiotics to eliminate microorganisms in dysbiosis and establish modified microbiota	-

7.6.2 Business

B	Factor und Current Situation	Future Assumption A	Future Assumption B	Future Assumption C
B1	**Consumer Demand** - Current consumer demand trends point to an increasing share of consumers with higher awareness and demand for healthy food. - While 'probiotics' tended to encapsulate much of the early Microbiome related consumer products, and still frames much of the popular understanding, more nuanced, specific, and impactful information is (slowly) gaining public awareness	2 1 . **Microbiome addressing food gains broad positive perception and is readily consumed, official health claim labels are of little importance.**	3 . 2 1 . **High demand of particularly health conscious end-consumers who prefer food with official health claim labeling and pay premium prices.**	3 . **Microbiome-addressing food is perceived as unnatural (ie. Infant formula) and therefore rejected by large population groups.**
B2	2 **Regulatory Issues** - The status quo in which regulations exist but are unclear and or too broad. - Under such conditions R&D&I remains a more open, and uncertain, endeavor. Without guideline to establish viable marketable products, R&D&I practices must cast a wide net (resource intensive) with fewer guarantees of success (higher risk).	1 . Clearly stipulated and evidence-backed procedures and cooperation standards established by the ENA/EFSA - Heightened focus to research - Companies to pursue more viable Microbiome-effecting products. - Enables the establishment of a set of validated biomarkers – a lynchpin issue for the R&D&I community.	1 . Movement towards a Global Regulatory framework. - Enable extension of industrial development of new products - Reach into new markets, - Increase in competition from producers in Asia, North America.	3 . Fragmented Regulation - Regulations and standards are developed on a national or geographic basis, - Increased complexity for product development. - Increase risk and uncertainty in R&D&I - New products might not be applicable to sufficient markets resulting in overall losses and fewer investments.

B	Factor und Current Situation	Future Assumption A	Future Assumption B	Future Assumption C
B3	**Collaboration and Knowledge Transfer** - Current trends show that collaboration between industry and academic or pure research institutions is declining. - In part this is due to issues of Intellectual Property regarding product development and sales based on research findings. - Knowledge transfer, between public and private research organizations, is inconsistent and adheres to few standards. - This slows down innovation and product development.	3 . 2 1 . **Increased EU wide collaboration clearly linked to faster product development could take two forms.** - On one side, more clearly defined regulations concerning IP produced in public/private partnerships could create Win-Win conditions for 2-party collaborations. - Alternatively, funding policies could be developed to encourage multi-party, transnational consortiums between industry actors and public research facilities. This alternative could favor more general acceptance of Microbiome-addressing foods and products, as it would encourage general awareness raising.	3 . **Collaboration that is divided among national lines could benefit the development of national Microbiome industry ecosystems.** - This would fuel divergences in regional development (likely favoring those nations with pre-existing, competitive industries. - It would also fuel the creation of national or regional actor networks, and develop more products specific to local market demands and regulatory frameworks.	**Reduced collaboration as a results of one or more of the following factors:** - 1 - Less public funding available - 2 - Less R&D&I funding available - 3 - Negative consumer perception - 4 - Lingering IP concerns 2 - 5 - Regulatory issues

B	Factor und Current Situation	Future Assumption A	Future Assumption B	Future Assumption C
B4	**Role of SMEs** - There is currently a considerable SME scene, primarily focused on providing research or supply services to larger industrial actors - Some research firms operate independently, and have even diversified their services to allow for the acceptance of VC funds, without threatening their daily operations.	2 1 . **Growth in SMEs and Startups** - "Incubator" programs increase opportunities for private equity and pharmaceutical companies to invest in early stage, higher risk research. New EU policies streamline processes to initiate and fund startup and incubator programs in Microbiome research. - In addition, the utilization of university programs as startup launch platforms (with shared IP) could further expand the SME space within the industry. - Open innovation approach becomes a new model for SME development – with open access to data and research being exchanged for EU funding, and community support through Creative Commons licensing.	3 . **Large Variation in Regional industrial biotechnology development** - If policies concerning regulation, funding, or VC investment vary wildly across national or regional borders, **an increasing variegation in the SME and Startup scene** could emerge. - While the biotechnology industry in general, and the Microbiome research specifically, would certainly be impacted, it does not lead to large overall growth. Rather, **growth prospects become unevenly distributed** according to regional or national conditions.	2 **The number of SMEs and the amount of services they are able to legitimately offer could decrease** - Based on **differing interpretations** of the standards and **mechanistic regulations** that might be passed to encourage growth in the overall bioeconomy. - Alternatively, **competition could come from overseas operations**, making the environment for EU-based SMEs more difficult.

B	Factor und Current Situation	Future Assumption A	Future Assumption B	Future Assumption C
B5	**Information and Education** - Currently there exist some significant gaps in the various communication channels between actor groups in the Microbiome-addressing research, producers, providers, and consumers. - Translating the science and knowledge of Microbiome-based studies and products to consumers is of highest concern, as this shapes public perception and consumer demand. - Also important is education and training of healthcare professionals (doctors and nutritionists) such that they can better assess patient microbiomic needs and suggest appropriate dietary and lifestyle changes. - A larger issue regarding health benefits vs. health claims looms over the industry as a whole. Without critical regulations and standardized metrics, health claims remain suspect and possibly deleterious to public perception (when products fail to improve health).	3 . **Public Perception Turns Negative** One or more of the following influential factors could negatively sway public opinion of Microbiome-addressing products: - **NGO's transmit a negative view** of Microbiome products (seen as comparable to the No-GMO movement and policies from the past 15 or more years). - **Meta-analysis publications** in peer-reviewed journals can provide negative viewpoints, without providing substantial evidence of their claims. - **Mass media** can sway public opinion quite dramatically, and often pick up on "attention-grabbing" research articles, regardless of their legitimacy. Any of these factors, acting alone or in conjunction with one another, could have an immediate impact on sales and consumer perception. It was also thought that any setbacks to public perception would take years to repair.	2 **Short-term Product-Use "Hype" Cycles** - It is possible that the industry sees a boom/bust cycle develop through a mixture of high-profile consumers, marketing, and misunderstanding of Microbiome-addressing products and processes. - **Celebrity usage** of a product could be a boon to fueling high consumer demand, particularly when used with high profile **marketing campaigns**. - However, while this could have a short-term dramatic increase in Microbiome-addressing product consumption, if such use is **not paired with appropriate shifts in diet and lifestyle**, it is likely that many consumers will see less than satisfactory results. **Consumer disappointment** then leads to a retreat in consumer demand, even if the products themselves were functioning properly. - While the "hype" cycle marketing and sales can fuel short-term growth, it also represents a threat to the industry's reputation and longevity.	1 . **Broad & Positive Public Perception** - Optimally, the public comes to regard Microbiome-addressing products as essential to their consumer habits. - If the public taboo on discussing **gastro-intestinal issues** recedes, and people feel like they can **share their G.I. experiences**, and treatments, more openly, public awareness and consumer demand could benefit from social network effects. - Citing similar studies in diet and lifestyle changes, **peer-to-peer advice and support** is seen as the most reliable form of creating long-term consumer awareness and demand. This can be facilitated by **educating NGOs**, and **pairing Microbiome-addressing products to overarching changes in lifestyle and diet.** - The development of **DIY Microbiome monitoring devices and analytics** could further fuel consumer demand. This would be facilitated by a set of clearly defined **validated biomarkers** (approved by EFSA, or another governing institution).

B	Factor und Current Situation	Future Assumption A	Future Assumption B	Future Assumption C
B6	**Commercialization & New Product Category** - Currently the R&D, production and sales costs for new Microbiome products are significant, making it difficult for industry leaders to diversify their products offerings and setting harsh conditions for SMEs to enter the market. - This difficulty is compounded by the lack of a clearly defined new product category that could streamline the process for classifying and regulating Microbiome products.	3 . **With the establishment of a "For Specific Medical Purposes" category by a governing institution (EFSA/EHA), R&D&I efforts (and costs) can be more streamlined**. - This would lead to a greater diversity of Microbiome products, and open the market to focused SMEs. - This new category helped move increases in insurance coverage for certain Microbiome products, and established a more legitimized position for these products as a part of a therapeutic/treatment regime.	2 **Persistence of no new product category** - Due to disagreements among governing institutions, no new category that can encompass Microbiome-addressing products. - This has continued to discourage any increase to investment in R&D, but has also set the conditions in which broad ranging research has led to some surprising discoveries.	1 . **Development of multiple new regulatory categories could evolve in different ways.** - It is possible that governing institutions establish multiple new categories that apply to Microbiome R&D&I. (For instance, topical treatments, preventative products, or "medical devices" for non-metabolizing organisms.) Such a development leads to multiple opportunities for SMEs, startups, and established industry leaders. - Alternatively, if a single new category is established, but differentiates along national or regional governance, the industry could be faced with higher market uncertainty due to regulatory nuances. This could lead to radically uneven development of the industry, and would work against single market economic policies.

7.6.3 Policy

	Factor	Future Assumptions	Future Assumptions	Future Assumptions
P1	**R&D&I Policy** - Considerable funding for microbiome R&D&I available	3 . **Status Quo: Funding opportunities for R&D&I remain at a comparable level**.	2 1 . **Extensive public funding made available**	**Less public financial support available**
P2	**EU Regulation for Nutrition and Health Claims** - Claims only allowed when listed on a so-called positive list - Terminology and categories not sufficiently clarified - Health claims that modulate the gut microbiome have had little success in obtaining approval in Europe	2 **Status-Quo development Limited clarifications**	3 . 1 . Improved clarification of terminology and categories - Food regime retains some differences to pharma - Some claims possible without intensive efficacy proving	High adaption to pharma regulatory regime - Usually clinical testing on to demonstrate the health claims needed - More extensive post-marketing surveillance
P3	**Global Harmonization of Health Claim Regulations** - Differences in terminologies between countries (e.g. probiotic has health claim in EU, but not in the US)	2 Differences in terminologies prevail	Rather high harmonization of terms; related health claims are limited	1 . High harmonization of terms; Key terms are linked to strong health claims

P4	**Safety and Ethical Issues** - Legal status of microbiome data is not defined - Scientific discussion about the importance of protection of microbiome data	3 . Microbiome data is treated equal to patient data A Strict regulatory framework to protect these data is established	2 1 . Microbiome data is not considered personal data therefore no further regulations are implemented	

Participants gave comments to the policy factors. They can be summarised as follows:

R&D&I Policy: Participants felt that considerable public funding is only available for basic science whereas for future R&D&I funding, a shift of focus is suggested: suggestions comprise funding of smaller projects and programs, funding of explorative industrial R&D, sufficient (=extensive) funding of clinical trials, linking public R&D&I funding to health benefits and business development. Standardization/harmonisation of diagnostics, protocols and microbiome profiles in R&D&I is needed. R&D&I funding should take the very fast progress in technological development into account. Bioinformatics, access to data and open source software are important.

- EU Regulation for Nutrition and Health Claims: Participants favour a new product category between pharma and food. Several comments stress the importance of impacts on microbiomes, health and health outcomes rather than on biomarkers. It cannot be deduced from the comments whether this is compatible with the suggested new product category between food and pharma. In other comments it is expected that a pharmaceutical-like regime will be implemented because this is seen as the only option to convince users and guarantee safety. Postmarketing surveillance are seen as important.
- Global harmonisation of health claim regulation: Comments point out that economic benefits are a prerequesite for global harmonisation, otherwise differences will remain. Moreover, it should be kept in mind that there are geographical differences in microbiomes which must be reflected in the harmonised claims.
- Safety and ethical issues: it is pointed out that science-based products and services and any personalisation of treatments, food/nutrition, products such as probiotics/prebiotics requires access to microbiome data sets/microbiome profiles from a large study population. However, a strict data protection regulation is seen as “most likely”.

7.7 Scenarios for biotech Flavours & Fragrances - Overview Factors and Future Assumptions

Scenario 1 (green): price driven scenario

Scenario 2a (yellow): non GMO scenario – alternative niches for the EU

Scenario 2b (turquoise): non GMO scenario – status quo development

Scenario 3 (red): Carbon footprint scenario

Scenario 1:

Prices drive market developments. While regulations stay mostly unchanged, technology is optimized mainly regarding cost reduction.

Scenario 2:a

GMO produced flavors are either not accepted as natural by the consumers or are not allowed to use this claim due to an amended regulation. While this hampers the diffusion of biotech in the F&F markets there are quite some successful attempts of European actors in advances in non-GMO biotech fields.

Scenario 2b:

GMO produced flavors are either not accepted as natural by the consumers or are not allowed to use this claim due to an amended regulation. This leads to a continuation of incremental advances of biotech in F&F markets, but rather slow growth.

Scenario 3:

Environmental concerns will gain significant importance as a driver of changes and rules in the market (T1A, B2A). Environmental footprint of F&F will become a major issue, which is usually favourable for biotech (at least compared to natural extraction from plants, but also to chemical synthesis). The trend to valorize waste may lead to new feedstock possibilities for biotech F&Fs.

7.7.1 Technology

T	Factor und Current Situation	Future Assumption A	Future Assumption B	Future Assumption C
1	**Drivers and Motivation** Biotech-driver for Flavors (90% natural) higher than for fragrances (90% cost reduction) For both segments environmental footprint is a driver for biotech F&F	3 **Environmental concerns** - Environmental footprint is major issue - Advantage for BioTech (compared to natural flavours obtained via extraction from plants) - Valorisation of side and waste streams (politically motivated) - more undefined raw material - more used for F&F - just for feedstock	2a 2b **Conventional Technologies dominate** - Combination of chemical synthesis + enzymes becomes more powerful - No GMO is allowed	1 **Low Price or new functionality** - Chiral compounds could be produced by Biotech (chemical synthesis expensive – even in China) - New products possible by Biotech for fragrances (is an option for high-value fragrances, but not for low price commodity fragrances))
2	**Scale up & Production** Key challenges: - Downstreamprocessing for volatile compounds - Scale-up capabilities not as advanced as microbe optimization capabilities - Suitable production capacity (for fermentation) often not available - Toxicity of ingredient for micro-organism -> Downstream processing technologies - Scale-up from research to production	2b **Research doesn't leave the lab** - no scale-up, no investment in Biotech, no customer - US-Biotech companies with focus on F&F fail - negative impact for use of biotech in the whole F&F sector - Loosing leading position in expertise of bio-process / downstream engineering in Europe to Asia	2a **Low hurdles to production, scale up of minor importance** - Small scale becomes economical - Increasing flexibility - Advanced technology is "easy to use" for everybody: "Fragrance brewery in the backyard" -	3 1 **Scale-up capabilities available** - Technical problems from lab to production are solved

T	Factor und Current Situation	Future Assumption A	Future Assumption B	Future Assumption C
3	**Knowledge & Research** - Focus on limited number of biosynthetic pathways - Knowledge for synthetic biology / enzymatic achievements has risen, but full potential remains to be unlocked - Cross sector cooperation important for exploiting additional pathways	2b **Focus kept on the known biosynthetic pathways and substance classes** - Not enough research for new pathways, e.g blocked by IP on basic methodology/ tools	3 1 **Many different pathways possible** - Synthetic Biology enables to produce desired products - More fundamental understanding of metabolic and regulatory processes thanks to more research	2a **Breed and growing plants with high content of F&F compounds as alternative for IB** - This development is enabled by knowledge accumulation

7.7.2 Business

B	Factor und Current Situation	Future Assumption A	Future Assumption B	Future Assumption C

1a	**Consumer Preferences for Flavors**
	
	User companies are willing to pay a premium for ingredients that allow them to market their products with "natural" claim. Regarding consumer trend one has to divide between organics, natural and natural identicals
	- Natural flavors market is growing faster (7% p.a.) than natural identiticals market (4 % p.a.)
	- Trend to organics in Food Flavouring (in particular in the US)
	
	For consumers it is often not clear what "natural claim" for products means. Moreover, there is confusion among consumers between biotechnology processes and GMO (e.g. whether end product contains GMO)
	
	Societal perception of synthetic biology and derived F&F products from it, is not clear yet
		2a 2b
		
		No demand for GMO produced flavors
		- GMO produced flavors are not accepted (by the consumer) or are not allowed (by regulation)
		- Key drivers:
		  - New technologies implemented that enable to check, whether the flavor compounds are natural (e.g. company Eurofins in France)
		  - Bloggers are disseminating the results
			3
			
			High diversification of markets
			- considerable markets will evolve for natural identicals, for natural ingredients and organic ingredients (not GMO)
				1
				
				High demand for GMO produced flavors
				- GMO methods are fully allowed and accepted to produce flavors
				- Main driver in the market is the price and sustainability
				- Consumer do not link the compound to the naturals fruits or plants, but the similar aroma is regarded as sufficient

B	Factor und Current Situation	Future Assumption A	Future Assumption B	Future Assumption C
1b	**Consumer Preferences for Fragrances** The main drivers for biotech fragrances are potential price or sustainability advantages. Natural claim is less important.	2a 2b **No demand for GMO produced fragrances** - Natural fragrances will be demanded similar to flavours → GMO produced fragrances are not accepted by the consumer	3 **High diversification of markets** - Natural fragrances will be demanded similar to flavors - Diversification into different markets: Markets for natural identicals and natural products and organic products	1 **Price and sustainability dominating drivers** - The market driver are not consumer preferences of naturality etc., but the price and sustainability issues dominate
2	**Environmental Impact** 1. Availability of feedstock for plant-derived ingredients is quite often limited 2. Carbon footprint of biotech F&F is potentially lower than for petrochemicals or plant extraction In those cases higher prices are payed in the markets → less cost sensitive	3 **High environmental awareness in demand** - Significant change from synthetic compounds to natural plants is not sustainable → for <u>many compounds</u> biotechnologically produced F&F are favourable - The technology is similar to which is used already today, as not breakthrough needed	2a 2b **Considerable environmental awareness in demand** - Significant change from synthetic compounds to natural plants is not sustainable → for <u>some compounds</u> biotechnological production is most favourable	

B	Factor und Current Situation	Future Assumption A	Future Assumption B	Future Assumption C
3	**Geographical distribution of activities** - Europe is strong in technology and possesses considerable production capacities, but activities are more fragmented compared to the US - Both the US and EU have several actors with capabilities and experiences in synthetic biology - The US has advantages in exploitation of synthetic biology advances due to more access to Venture Capital - In the EU, "organic" product-based growth prevails - China has some strong players in the F&F industry - Europe has strong F&F user industry	2a **Europe is improving its competiveness in certain segments** - One key driver is the establishment of a network (of academia, F&F producers from different countries) in the EU	1 **The US dominates in GMO biotech**	2b **China dominates in non GMO-biotech**

B	Factor und Current Situation	Future Assumption A	Future Assumption B	Future Assumption C
4	**Costs: Competitiveness and volatility** - High volatility for prices of natural resources => may lead to advantages (if plant derived flavors get more expensive) or disadvantages for biotech F&F (if biomass source prices get more expansive and /or unpredictable) - Markets are fragmented into many products as well as within the EU => R&D&I costs have to be covered by small product markets - Production cost for biotech conversion are often somewhat higher than for plant-derived ingredients and often significantly higher compared to chemical synthesis of F&F - Synthetic biology offers significant potential for cost reduction and may lead to lower costs compared to plant-derived ingredients	3 1 **Higher cost competiveness via synthetic biology** - Advances in synthetic biology leads to higher cost competitiveness - Costs for plant-derived ingredients are increasing - Increased cross-sector collaboration (e.g. transfer of methods for the pharmaceuticals to F&F) and common target selection	2a 2b **Limited cost competitiveness** - Synthetic Biology is not sufficiently competitive - Costs for biotech produced F&F remain higher compared to plant-derived ingredients and synthetic compounds	

7.7.3 Policy

P	Factor und Current Situation	Future Assumption A	Future Assumption B	Future Assumption C
1	**R&D&I Policy**	2b **Status Quo: Funding opportunities for R&D&I remain at a comparable level.**	3 1 **Extensive public funding made available** - More PPP's	2a **Less public financial support available for synthetic biology, but more for other methods**
2	**EU regulation for "Natural Products" claims for flavors in food** - EFSA regulation concentrates on process, accepting a limited list of procedures - Regulation on flavors is already uniform in all European countries (EC1334/2008), but implementation still differs between EU Member States - Natural label for GMO produced F&F challenged by NGOs	2a 3 **Explicit declaration of use of biotechnology** - New regulation on adding the prefix "bio-" to the name of the flavor compound to inform that biotechnological approaches have been used	1 **Status Quo-Regulation** - Regulations principally allowing modern biotechnological produced flavors claimed to be natural	2b **Stricter regulations regarding use of advanced technologies** - Products with advanced process methods (e.g. from synthetic biology) not accepted as natural products

8 ANNEX II: Final Conference Programme

Final Conference of the H2020 project PROGRESS

27 September 2017

Programme

08:30

Welcome Coffee and Registration

09:30-09:40

Opening Address

Jürgen Tiedje (Head of Unit D2, DG RTD, European Commission)

09:40-10:00

General Overview of Project and Approach

Sven Wydra (Fraunhofer ISI)

10:00-10:30

Setting the Scene: Importance, Current Status, Policy Issues of Industrial Biotechnology in Europe

Sven Wydra (Fraunhofer ISI)

Joanna Dupont Inglis (EuropaBio)

Jim Philp (OECD)

Future Paths for Europe: Scenarios for Value Chains

10:30-10:45

Value Chain Selection and the Scenario Methodology

Sven Wydra (Fraunhofer ISI)

Aaron Rosa (Fraunhofer ISI)

10:45-11:00

In-depth Analysis and Scenarios for Enzymes

Bärbel Hüsing (Fraunhofer ISI)

11:00-11:10

Views from the Enzyme Value Chain

Simon Charnock (Prozomix)

11:15-11:30

In-depth Analysis and Scenarios for Bio-based Plastics

Bärbel Hüsing (Fraunhofer ISI)

11:30-11:40

Views from the Bio-based Plastics Value Chain

Kristy-Barbara Lange (European Bioplastics)

11:45-12:00

Presentation of Other Value Chains and Overall Conclusion

Sven Wydra (Fraunhofer ISI)

12:00-12:30

General Discussion

All

12:30-13:30

Lunch

13:30-13:50

Future Aims for Europe, R&D&I Needs & Actions

Bärbel Hüsing (Fraunhofer ISI)

13:50-14:45

Panel Discussion Regarding R&D&I Needs/Actions

Moderator: Aaron Rosa (Fraunhofer ISI)

Joanna Dupont Inglis (EuropaBio)

Jim Philp (OECD)

Simon Charnock (Prozomix)

Kristy-Barbara Lange (European Bioplastics)

Sven Wydra (Fraunhofer ISI)

Bärbel Hüsing (Fraunhofer ISI)

14:45-15:00

Coffee Break

15:00-15:10

Role of Member States and Cooperation Between them

Liliya Pullmann (Fraunhofer ISI)

15:10-16:20

Panel Discussion: Role of Member States and Cooperation Between them

Moderator: Aaron Rosa (Fraunhofer ISI)

Milan Polakovic (Slovak University of Technology), Slovakia

Maeve Henchion (Teagasc), Ireland

Haralabos Zorbas (IBB Netzwerk GmbH), Germany

Sven Wydra (Fraunhofer ISI)

16:20-16:30

Conclusions and Final Remarks

Sven Wydra (Fraunhofer ISI)

16:30

End of the Conference