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Successful Scale-Up Support for Start-Ups in Industrial Biotechnology: A Multiple Case Study on Scale-Up Support Ecosystems

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Abstract

Industrial biotechnology is labelled by the European Commission as one of the six key enabling technologies to fight climate change. Industrial biotechnology is a sector where biocatalysts (cells or enzymes) are used to convert renewable feedstocks (e.g. sugars) or even waste into valuable compounds such as renewable chemicals or food (ingredients). Unfortunately, the road from invention to commercial production is long in industrial biotechnology, and most biotechnologies that look promising after laboratory development fail to cross the Valley of Death and reach industrial scale. Industrial biotechnology has a long technology development time before being commercialised, is capital intensive, has economies of scale, and usually produces bulk products with low profit margins requiring large industrial-scale production for economic viability. Scale-up support can facilitate scale-up towards industrial scale. Scale-up support was, for example, offered with the Bioprocess Pilot Facility at the Biotech Campus Delft, before its bankruptcy in November 2022. This bankruptcy occurred while being fully booked. This has left the Planet B.io - Biotech Campus Delft scale-up support ecosystem with a lot of potential. In an attempt to scientifically address this scale-up support problem, a knowledge gap was found on the verge of technical scale-up, industrial biotechnology, and scale-up support ecosystems. This led to the main research question: How can a scale-up support ecosystem for industrial biotechnology be best organised and operated?

To answer this, a multiple case study was conducted on the scale-up support ecosystems of Planet B.io - Biotech Campus Delft, Copenhagen, and Brightlands Chemelot. This case study was performed through desk research and semi-structured expert interviews with 3 different types of experts (ecosystem, technical scale-up and start-up expert) per ecosystem, resulting in 9 interviewees. This case study applies the Technological Innovation System (TIS) framework to a novel context and integrates it with the four identified scale-up support elements (technical facilities & services, funding & business services, network formation & coordination, and knowledge & talent) offering a framework to study scale-up support ecosystems. This study identified the scale-up support requirements for industrial biotechnology. These scale-up support requirements are, among others, a flexible and fully-serviced shared piloting facility up until TRL 6 ($\approx$ 2000 L bioreactor), a lab- to pilot- and industrial-scale technical support service, investment planning service and help with raising funding. These should be offered within a scale-up support ecosystem using milestone-based billing as a preferred revenue model, whereas a government voucher system should be set up to pay for the lab- to pilot- and industrial-scale technical support service. Also, the most important stakeholders for a scale-up support ecosystem were identified, including multiple large corporations, government institutions, universities (and other types of education), suppliers, and service providers. Based on the findings, a roadmap for the development of the Planet B.io - Biotech Campus Delft scale-up support ecosystem was proposed, focusing on strengthening the network, knowledge, talent, and funding before offering a piloting facility and business services. This study contributes to the field with a framework to study scale-up support ecosystems as well as with practical recommendations for scale-up support ecosystems in industrial biotechnology and similar industries, identifying the scale-up support requirements, its business models and required stakeholders.

Keywords

Scale-up Support Ecosystem - Industrial Biotechnology - Valley of Death - Piloting - Technological Innovation System (TIS) - Business Models - Stakeholders - Roadmap

Contents

Glossary

Biotechnology Term	Description
Alternative Feedstocks	Utilization of non-traditional biomass sources, such as agricultural residues, algae, waste streams, and non-sugar based feedstocks (e.g., CO_2 or carbon monooxide) as a feedstock for bioprocessing.
(Bio)reactor/ fermentor	Vessel which has been designed for fermentation processes.
Bulk chemicals	Commodities, usually building blocks for other chemicals, plastics, materials or fuels.
Cell	The basic structural and functional unit of all living organisms. Cells are the smallest entities that can carry out all the processes necessary for life.
Centrifuge	Equipment used for phase separation based on density through rotation, usually used in biotechnology to separate the cells from the liquid phase.
Chromatography	A technique used for separating and analyzing mixtures of molecules based on their different properties, such as size, charge, or affinity for certain substances.
Cultivated meat	Meat produced using tissue engineering techniques and grown in bioreactors. Offers a sustainable and ethical alternative to traditional animal farming.
Downstream processing	The subsequent stages of bioprocessing that involve the isolation, purification, and recovery of the desired product from the cell culture or fermentation broth.
Enzyme	A protein that acts as a catalyst, speeding up chemical reactions in living organisms.
Feedstock or substrate	The raw material or substance used in a biotechnological process. It serves as the starting material for the production of desired products through fermentation.
Fermentation	Process that uses cells or microorganisms to convert a substrate into a product. This process takes place in a bioreactor (also called a fermentor).
Food grade	Licensed to produce food products for human consumption.
Gas Fermentation	Utilizes microorganisms to convert gases (e.g., CO_2, methane) into valuable products such as biofuels, chemicals, and pharmaceuticals. Enables waste gas utilization and reduces greenhouse gas emissions.
Microorganism	A microscopic organism, such as bacteria, yeast, or fungi.
Microfiltration	Equipment with a microporous filter used to separate based on size, usually used to separate cells from proteins and liquid.
Operator	Someone operating a (pilot) manufacturing plant.
Piloting facility	A piloting facility is a scaled-down version of a production plant used to test and optimize (bio)processing operations before full-scale implementation.
Precipitation	A process in which solid particles are separated from a liquid solution by forming insoluble particles, which settle to the bottom of a vessel or are removed by filtration.
Recombinant proteins	Proteins that are artificially engineered by introducing specific DNA sequences into host organisms, such as bacteria or yeast, to produce proteins with desired characteristics.
Ultrafiltration	Equipment with a nanoporous filter used to separate based on size, usually used to separate cell components or proteins from liquid.
Upstream processing	The initial stages of bioprocessing that involve the preparation and cultivation of cells or microorganisms, including media formulation, sterilization, inoculation, and optimization of growth conditions.

Technology Management Term (Abbreviation)	**Description**
Accelerator	Programs that provide resources, mentorship, and support to accelerate the growth and commercialization of start-up companies and their innovative technologies.
Accidents and events	Unforeseen incidents, accidents, or events that can disrupt or influence the development, deployment, or public perception of technologies or innovations.
Business scale-up	The processes related to expanding and growing a company, human capital growth, organizational growth, and coordination. However, business scale-up does not require a company already has a product on the market.
Complementary products and services	Additional products, services, or technologies that complement and enhance the value, functionality, or application of a core product or technology.
Economies of scale	The cost advantages achieved through increased production volume, which leads to a reduction in the average cost per unit, making the production more efficient and cost-effective.
Ecosystem	A network of actors and organizations that interact and collaborate, often in physical proximity, to facilitate innovation and economic activities within a specific industry or area.
Ecosystem map	A visual representation or depiction of the interconnected network of actors and organizations, and their role (technical facilities & services, funding & business services, network formation & coordination, and knowledge & talent) and importance within an innovation ecosystem.
Financial resources	The capital, funding, and financial assets available to support the development, scaling, and commercialization of technologies and businesses.
Funding & business services	Services and resources related to funding, financing, business planning, market analysis, and other financial and business aspects necessary for the successful commercialization and scaling of technologies.
Good Manufacturing Practices (GMP)	A set of quality management practices and guidelines ensuring that pharmaceutical and biotechnological products are consistently produced and controlled to meet regulatory standards and requirements.
Growth Chasm	The phase in a company or technology's development where there is a significant shift in product requirements and market needs as its customer group changes (e.g., from early adopters to the early majority), often causing challenges and adjustments.
Hub	A physical (or virtual) space that serves as a central point bringing together entrepreneurs, investors, and other stakeholders to foster innovation, collaboration, and knowledge exchange.
Human resources	The people, skills, knowledge, and expertise within an organization or industry, crucial for the successful implementation and management of technology and innovation.
Incubator	Organizations that offer resources, mentorship, and support to nurture the development and growth of early-stage start-ups and their innovative ideas or technologies.

Industrial Biotechnology	Also known as White Biotechnology, it refers to the use of biological systems and processes for industrial applications, such as manufacturing chemicals, materials, and fuels in an environmentally sustainable manner.
Innovation-specific institutions	Regulations and policy affecting specifically designed to support and promote innovation, technology development, and the commercialization of innovative products or technologies.
Innovation System	A network of actors, institutions, and organizations interacting within a specific domain to generate, diffuse, and exploit knowledge, fostering innovation and economic growth.
Intellectual property (IP)	Legal rights protecting intangible creations, such as inventions, designs, or artistic works, providing exclusive rights and ownership to the creator or innovator, e.g., patents.
Knowledge and awareness of application and market	Understanding and awareness of how a technology or innovation can be applied, its potential market opportunities, and the needs of potential users or customers.
Knowledge and awareness of technology	Understanding and familiarity with the technical aspects, features, and capabilities of a particular technology or innovation.
Start-up	A newly established business or company, typically with innovative ideas or technology, aiming for growth and scalability.
Scale-up company in industrial biotechnology	A scale-up in industrial biotechnology has been defined as a company in the “growth-phase” life cycle (Miller & Friesen, 1984) also including technical scale-up, not necessarily already having a product on the market.
Triple-helix	An organizational model formed by the collaboration of three entities: corporation, university, and government.
Macro-economic and strategic aspects	The broader economic and strategic factors and conditions that impact the development, adoption, and diffusion of technologies, including government policies, market dynamics, and global trends.
Natural resources	The resources provided by nature, such as minerals, water, energy sources, and raw materials, that are used in various production processes.
Network formation and coordination	The development and coordination of networks, partnerships, collaborations, and relationships among different actors, organizations, and stakeholders involved in technology development and innovation.
Pharmaceutical biotechnology	Also known as Red Biotechnology, it refers to the application of biotechnology in the development and production of pharmaceuticals, including the use of cells, enzymes, or microorganisms to produce therapeutic drugs or other products that could be applied for medical purposes.
Product performance and quality	The attributes, characteristics, and overall quality of a product or technology, including its functionality, reliability, safety, and compliance with regulatory standards.
Production system	The system or set of processes, equipment, and resources involved in the production of goods or services, including the integration of technology and human labor.
R&I ecosystem	Research and Innovation ecosystem, comprising the various actors and organizations involved in research and innovation activities within a specific field or region.
Scale-up support ecosystem	An research & innovation (R&I) ecosystem that provides both technical (e.g., piloting facility) and business (e.g., funding, subsidies, investment planning) support for scaling up technologies.

SDG (Sustainable Development Goal)	Goals established by the United Nations to address global challenges and promote sustainable development across various areas, including poverty, climate change, education, and health.
Socio-cultural aspects	The social and cultural factors, norms, values, and attitudes that influence the acceptance, adoption, and impact of technologies within society.
Sustainable Chemistry	An umbrella term encompassing the use of biobased materials, sustainable/renewable materials, recycling of materials, and environmentally friendly chemical processes.
Technical facilities & services	All the technical infrastructure, facilities, equipment, and services that support and facilitate the development, testing, and scale-up of technologies.
Technical scale-up	The processes involved in transitioning a technology or process from small-scale (lab-scale) to large-scale (commercial/industrial-scale) production.
Technology Readiness Level (TRL)	A scale ranging from 1 to 9 that assesses the maturity level of a technology and its readiness for large-scale production and market deployment.
TIS building block	Technological Innovation System building block assesses the status and development of specific elements or components within a Technological Innovation System that influence its readiness for large-scale deployment of a technology.
Knowledge and awareness of technology	Understanding and familiarity with the technical aspects, features, and capabilities of a particular technology or innovation.
TIS influencing condition	Technological Innovation System influencing condition refers to specific factors or conditions that can hinder or promote the development of building blocks within a Technological Innovation System, affecting its readiness for large-scale technology deployment.
Valley of Death	The challenging phase in a technology or company's development where it faces difficulty in securing public funding and is not yet attractive to private funding due to its intermediate technology maturity level.
Venture Capital (VC)	Private investment capital provided to start-up companies or small businesses with high growth potential, typically in exchange for equity or ownership in the company.

Organisation (Abbreviation)	**Description**
Aachen-Maastricht Institute for Biobased Materials (AMIBM)	A collaborative institute between Aachen University and Maastricht University, focusing on sustainable and economically viable production of advanced bio-based materials through interdisciplinary research and knowledge transfer.
BioInnovation Institute (BII)	An accelerator for biotech start-ups in Denmark, providing funding, mentorship, and infrastructure to support the translation of innovative ideas into viable commercial ventures.
Bioprocess Pilot Facility (BPF)	Formerly a piloting facility at the Biotech Campus Delft, providing technical support and infrastructure for scaling up bioprocesses, but declared bankrupt since November 2022.
Brightlands Chemelot ecosystem	Chemelot campus and industrial production site in Geleen, Limburg, The Netherlands, comprising offices, labs, education facilities, and a piloting facility focused on the chemical industry and sustainable chemistry & materials, fostering collaboration and innovation.
CHemelot Innovation and Learning Labs (CHILL)	A research facility at the Chemelot campus that conducts contract research for companies, while also providing educational and training opportunities for student interns.
Copenhagen industrial biotechnology ecosystem	Ecosystem in Copenhagen, Denmark, supporting industrial biotechnology ventures and fostering innovation and growth in the sector.
European Molecular Biology Laboratory (EMBL)	An international research institution that conducts cutting-edge molecular biology research and offers advanced training and services to scientists across Europe.
Lägemiddelindustriforeningen (LIF)	The Danish association of the pharmaceutical industry, representing and advocating for pharmaceutical companies in Denmark.
LImburg Ontwikkelings Fonds (LIOF)	An organization in Limburg, The Netherlands, supporting economic development in the region through investment, funding, and business support services.
Planet B.io	Scale-up support hub at the Biotech Campus Delft, providing labs, offices and a network for industrial biotechnology start-ups to accelerate their growth and development.
Technical University of Denmark (DTU)	A university based in Copenhagen, offering world-class education and research in various scientific and engineering disciplines, including biotechnology.
Toulouse White Biotechnology (TWB)	A French scale-up support ecosystem focused on industrial/white biotechnology, providing resources, expertise, and networking opportunities for companies in the sector.

1 Introduction

The environmental impact of our use of resources and fossil fuels can no longer be denied. Drastic changes are needed to restrict climate change and prevent the earth from becoming inhabitable. This requires reducing our carbon footprint by adapting our lifestyle (e.g., no meat, no flying) and to lower our environmental impact through innovations in our current value chains. Industrial biotechnology can contribute to such innovations and is labelled by the European Commission as one of the six key enabling technologies to fight climate change (European Commission, 2017). Industrial biotechnology is a sector where biocatalysts (cells or enzymes) are used to convert renewable feedstocks (e.g., sugars) or even waste into valuable compounds. Therefore, fossil fuel derived products can be replaced by sustainable alternatives produced with biotechnology. This makes industrial biotechnology essential to reach net zero CO_2 emissions by 2050 as posed by the sustainability goals of the Paris Agreement (Horowitz, 2016). The conversion of renewable feedstocks or waste into a product by a cell or enzyme is called fermentation and its products range from commodity compounds to pharmaceuticals. The products of industrial biotechnology are, for example, bioplastics, biofuels, renewable chemicals, food (ingredients), and cultivated meat (Nielsen, Tillegreen, & Petranovic, 2022). A successful industrial-scale industrial biotechnology process is the production of the cheese production enzyme called chymosin. This enzyme used to be extracted as Rennet from the stomachs of calves after slaughter, but is currently produced on a global scale through fermentation. Nowadays, fermentation-produced chymosin is used for about 80- 90% of global cheese production, demonstrating the successful introduction and acceptance of industrial biotechnology into the market.

1.1 Commercialisation in Industrial Biotechnology

Unfortunately, the road from invention to commercial production is long in industrial biotechnology, and most biotechnologies that look promising after laboratory development fail to cross the Valley of Death and reach industrial scale or do so under unviable economic conditions (Efara, Marquis, & Tremblay, 2019; Kampers, Asin-Garcia, Schaap, Wagemakers, & dos Santos, 2021; Linton & Xu, 2021). Before a company becomes a scale-up, it is a start-up and Blank and Dorf (2012) characterises a start-up by its search for a business model, which should be scaleable and geographically orientated at a broad scope of customers. They developed a methodology for developing a successful, scaleable start-up. When a repeatable and scaleable business model is found, only the requirement for external venture-capital is in the way of rapid expansion (Blank & Dorf, 2012). Moreover, Blank and Dorf (2012) divide early-stage ventures, i.e. start-ups, into two types.

1. Start-ups with customer/ market risk, where it is unsure if there is a market for the technology.
2. Start-ups with invention risk, where it is unsure if the technology will work commercially.

Also mentioned is that there are markets where the risk is truly invention. "These are markets where it may take five or even 10 years to get a product out of the lab and into production (e.g., biotech)" (Blank & Dorf, 2012, p.20). As Blank and Dorf (2012, p.20) described, "for start-ups in these invention markets, the start-up manual is not applicable". Therefore, biotechnology start-ups cannot use this manual and have to be treated differently from start-ups in other industries which do not have this long technology development time and invention risk. One of the reasons start-ups in industrial biotechnology fail is that for industrial biotechnology it is not possible to produce a Minimal Viable Product (MVP), bring this to market early, and have paying customers early and then through continuous iterations with customer feedback continuously improve the product as described for the concept of lean start-ups (Ries, 2011).

1.1.1 Different types of biotechnology and their correlation between product price and production scale

Biotechnology encompasses a broad range of techniques and applications, including red, white, and green biotechnology. Red biotechnology, also known as pharmaceutical biotechnology, involves the use of genetically modified organisms for medical purposes, such as the production of recombinant proteins and antibodies. Examples of red biotechnology products are insulin, human growth hormone, and vaccines. Moreover, red biotechnology also includes diagnostics and regenerative medicine, thus not only pharmaceuticals production. White biotechnology, also known as industrial biotechnology, is focused on the use of enzymes and microorganisms to produce industrial chemicals, biofuels, bioplastics, enzymes, and food additives. Whereas, green biotechnology, also known as agricultural biotechnology, involves the use of genetically modified plants for agricultural and environmental purposes, such as the production of drought-resistant crops, bioremediation, biodegradable plastics, and biopesticides. The production scale and price of these biotechnology products are highly dependent on the specific type of biotechnology used. The price and scale of production tend to be positively correlated, with high-priced products typically requiring smaller production scale, and low-priced products requiring larger production scale (Figure 1). The relationship between price and scale of production is an essential consideration when developing biotechnology products for industrial or commercial use. Due to the bulk products with low profit margins produced within industrial biotechnology, there is a much larger scale required for industrial biotechnology than for pharmaceutical biotechnology which have a higher price and product margin per amount of product produced (see Figure 1). Therefore, I specifically focused on industrial biotechnology during this study since scale-up is of a greater importance and magnitude for an economically viable process.

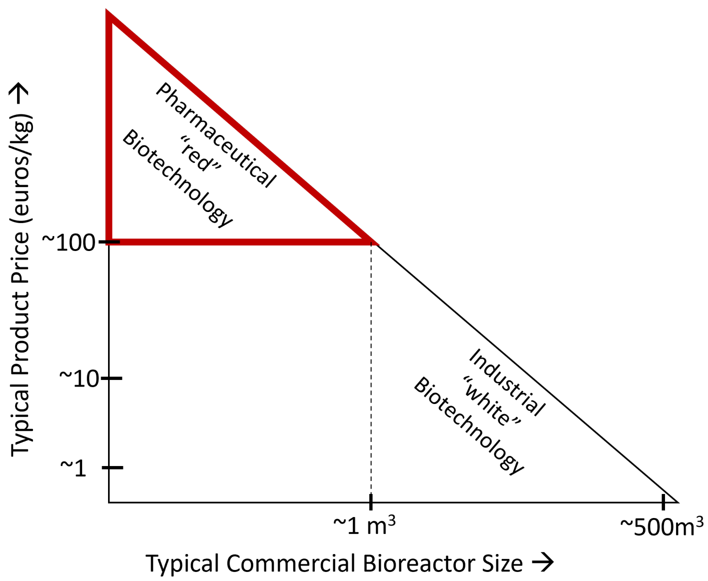

Figure 1: This figure illustrates the comparison between pharmaceutical "red" biotechnology and industrial "white" biotechnology in terms of commercial bioreactor size (x-axis) and product price (y-axis). It shows a clear negative correlation between product price and commercial-scale bioreactor size. The figure highlights the difference between red and white biotechnology, as the higher price of red biotechnology products alleviate the need of producing on a really large scale. This means that scaling up in industrial biotechnology is of greater importance and magnitude to achieve an economically viable process.

1.1.2 Four characteristics defining industrial biotechnology

Industrial biotechnology is characterised by the need for efficient large-scale production to be competitive and have market potential (Efara et al., 2019). This is especially the case for products that are replacements for oil-derived chemicals (Sanford, Chotani, Danielson, & Zahn, 2016). For new chemicals this price restriction is less, which results in less severe scale-up challenges (Sanford et al., 2016). However, technical scale-up is required to be able to make these technologies and their products cost effective and available on a large scale. Before actual product is produced on a large scale and at a competitive price, the process has to be piloted and scaled up in several steps, this requires a lot of time and capital investments into different scales of equipment and facilities, only to test the process. This is all done before an industrial-scale plant can be build. Therefore, for this study it was hypothesised that, industrial biotechnology has the following four characteristics:

1. Long technology development time before first to market ($\approx$ 10 years or more)
2. Capital intensive (high capital expenses for equipment and facilities)
3. Economies of scale (large-scale production reduces the costs per amount of product (Obloj, Grosse-Holz, Bergmann, & Davies, 2023))
4. The product is a bulk product with low profit margins (requiring large industrial-scale production for economic viability)

1.1.3 Scaling up in industrial biotechnology

Scaling up from laboratory-scale to industrial-scale production in industrial biotechnology is a challenging task. A variety of risks and unknowns exist, and factors such as volume of the fermentation process can significantly impact strain and overall process performance (Delvigne, Takors, Mudde, van Gulik, & Noorman, 2017; Wang, Haringa, Noorman, Chu, & Zhuang, 2020). Downstream processing to purify the product poses unique challenges, with expensive and time-consuming separation processes often necessary to purify molecular intermediates and products (Smanski et al., 2022). For protein-based products, the three-dimensional structure and activity must be maintained (Hearn, 2017). Moreover, the genetic stability of the cells used must also be maintained to ensure consistent production quality (Smanski et al., 2022). While process-guided approaches to strain engineering and downstream process modelling can help mitigate such issues, bioindustrial manufacturing faces several challenges that require careful consideration and planning. Therefore, **piloting of the process on intermediate scales is essential to ensure process performance before building a plant for industrial-scale production**. Piloting at intermediate scales is needed to fill gaps in understanding that are critical to industrial-scale, gather data for successful scale-up, demonstrate ability to produce high-quality product and test with customers (Biggs et al., 2021; Sanford et al., 2016). All of this to reduce the risk of nonperformance when commercialising on an industrial scale (Biggs et al., 2021; Davison & Lievense, 2016; Sanford et al., 2016). The importance of scale-ups is that, although not all start-ups get there, the ones that do impact society greatly by means of new technology, services, and increased employment. As Isenberg (2012) put it:

> ”extraordinary value creation cannot occur without growth, and entrepreneurial growth post start-up has numerous challenges, which can be an order of magnitude more difficult than simply starting a venture.”

1.2 Scale-Up

1.2.1 Business Scale-Up

There are different types of scale-up. On the one hand, scale-up is defined as a company in the ”growth-phase” life cycle with a tested and scaleable business model and already gained market traction and expanding in terms of organisation and customer base (Blank & Dorf, 2012; Miller & Friesen, 1984)). Moreover, according to the definition of the OECD a scale-up is a company who has an average annualized return of at least 20% in the past 3 years with at least 10 employees in the beginning of the period (OECD, 2007). Since, for already growing companies within industrial biotechnology there is no revenue yet these scale-ups would be referred to as a start-up according to the definition of the OECD. The transition of a small start-up to a more mature scale-up company is not easy and has been previously described as the Growth Chasm (Moore, 2014). In addition, before industrial biotechnology products are on the market, regulatory approval is another hurdle that requires elaborate documentation and testing of the process and product that require production under conditions representative of industrial-scale production. That is another reason for scale-up and piloting of industrial biotechnology before having a product on the market.

1.2.2 Technical Scale-Up

On the other hand, the word scale-up is used when discussing the process of technical scale-up in terms of size of production or amount of users. Sanford et al. (2016, p.112) discusses the scale-up of renewable chemicals and states that the "details involved in all aspects of manufacturing, such as utilities, sterility, product recovery and purification, regulatory requirements, and emissions, must be managed successfully". This technological scale-up is a crucial aspect of scaling up a business. However, for certain fields such as industrial biotechnology, technological scale-up is already required, from lab-scale (litre scale) to industrial scale (100 m^3 scale), to enable competitive production (Sanford et al., 2016). This places technological scale-up of industrial biotechnology on the border of birth- to growth-phase of the corporate life-cycle (Miller & Friesen, 1984), and successful technological scale-up is a key requirement enabling business scale-up (i.e., number of employees, customer base). Therefore, the commonly used definition of scale-up does not hold for industrial biotechnology, since for industrial biotechnology, there is no market traction yet while the business is already scaling. Therefore, **a scale-up in industrial biotechnology** has been defined as **a company in the 'growth phase' life cycle** (Miller & Friesen, 1984) **also including technical scale-up, not necessarily already having a product on the market**.

1.3 Technology Readiness Levels and the Valley of Death

The progress of technological scale-up is commonly tracked using Technology Readiness Levels (TRL), which range from 1 to 9, with TRLs typically 1–3 in academia and TRLs 8 and 9 in industry (Mankins, 1995). At TRL 4–7 the discovery process is generally considered too applied for further scientific funding but too risky to fund for industrial market implementation (Kampers et al., 2021) (see Figure 2). This essentially makes TRLs 4-7 the Valley of Death (see Figure 2). This stresses the need for alternatives to start-ups performing their own pilots and building their own capital intensive and time-consuming piloting facilities to scale up.

1.4 Scale-up support

One way that scale-up can be made easier is through scale-up support. Scale-up support could for example provide a shared piloting facility to reduce the time and costs of piloting. Everything that is provided to aid scaling up and help overcome the Valley of Death is seen as scale-up support (see Figure 3). Especially for production and testing of the first kilogram of product, Scale-up support can be very beneficial (Smanski et al., 2022, p. 7). There are possibilities to use pilot facilities from other companies or other institutions, however, there is a shortage of available piloting and manufacturing facilities for process scale-up in industrial biotechnology

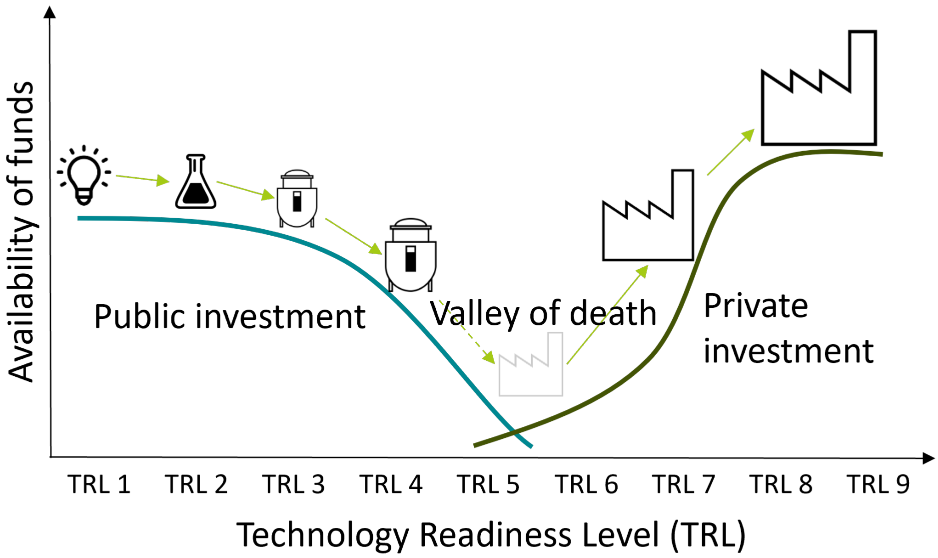

Figure 2: Technology Readiness Levels linked to the availability of funds showing the Valley of Death for industrial biotechnology between TRL 4 and TRL 7. The phase of technology development starts at invention (TRL 1) and goes from the research phase (until TRL 3) to the piloting phase (TRL 4 to TRL 6) and demonstration (TRL 7-8) until industrial-scale production is reached (TRL 9).

(Biggs et al., 2021; Obloj et al., 2023). Increased access to shared facilities could alleviate this hurdle (see Figure 3).

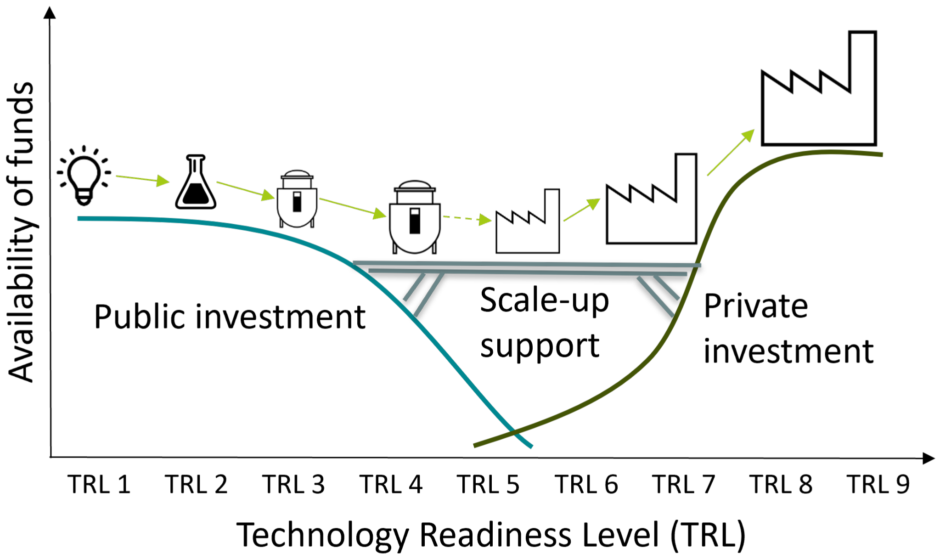

Figure 3: Technology Readiness Levels linked to the availability of funds showing the Valley of Death for industrial biotechnology between TRL 4 and TRL 7 and the role of scale-up support in bridging the Valley of Death. The phase of technology development starts at invention (TRL 1) and goes from the research phase (until TRL 3) to the piloting phase (TRL 4 to TRL 6) and demonstration (TRL 7-8) until industrial-scale production is reached (TRL 9).

There are three types of organisations/ programs that support start-ups and entrepreneurs: accelerator programs, incubators and hubs. These offer access to resources, mentorship, and networking opportunities, and they aim to create a supportive ecosystem where start-ups can thrive. The definitions and main differences between accelerators, incubators, and hubs are

Table 1: Comparison of Accelerators, Incubators, and Hubs

Type	Definition	Target Start-Up Phase	Characteristics
Accelerator	Programs that help 'accelerate' the trajectory of start-ups from commercial idea or technology to successful commercialization.	Later stages, from prototype to commercialization.	Accelerators provide time-bound support, education and mentoring focused on business and product advice, and networking programs, among other benefits. They act as entrepreneurial matchmakers, providing start-ups with feedback, technical know-how, and relevant networks and investments.
Incubator	Organizations that support the development and growth of early-stage start-ups by providing resources, mentorship, and sometimes funding.	Early stages, from ideation to prototype.	Incubators provide office space, administrative and logistical support, access to mentorship and funding, and networking opportunities. They act as a safe and nurturing environment for start-ups to grow and develop.
Hub	A physical or virtual space that brings together entrepreneurs, investors, and other stakeholders to facilitate innovation and collaboration.	All stages of the start-up process.	Hubs provide co-working spaces, networking opportunities, mentorship and training programs, access to funding and investors, and other resources. They act as a central hub for the start-up ecosystem, bringing together people and resources to drive innovation and collaboration.

given in Table 1. When discussing the Valley of Death of industrial biotechnology and scale-up support to help cross the Valley of Death only an accelerator or hub can be relevant according to the definitions (see Table 1).

1.5 Scale-up support ecosystem

These supporting organisations are usually part of a larger Research & Innovation (R&I) ecosystem which provides several of the success factors required for scale-up. A R&I ecosystem has been defined as a network of individuals, organisations, institutions, and resources working together to create and commercialise new ideas, products, and services (Vankan, den Hertog, Janssen, de Boer, & Smeitink, 2020). It includes academic and research institutions, start-ups, corporations, government agencies, and resources like funding, mentorship, and infrastructure. For this study, a **scale-up support ecosystem** has been defined as a **R&I ecosystem focused on both technical and business scale-up support**, thus offering services, a network of relevant actors, and most likely piloting facilities. An example of a hub focusing on the scale-up support of industrial biotechnology and offering a scale-up support ecosystem is Planet B.io at the Biotech Campus Delft.

1.6 Planet B.io at the Biotech Campus Delft

The non-profit organisation Planet B.io, a hub for industrial biotechnology, was founded in 2019 at the Biotech Campus Delft (BCD) as a triple-helix organisation (Etzkowitz & Leydesdorff,

2000) of corporate (DSM), university (Delft University of Technology, TU Delft) and government (municipality of Delft, province South-Holland and InnovationQuarter). The Biotech Campus Delft is a campus for open innovation in industrial biotechnology. Planet B.io has the vision to support industrial (white) biotechnology start-ups through their technology development amongst all TRLs until successful commercialisation by offering facilities, services and a network. Planet B.io started off renting one building with offices and labs to start-ups, including some shared facilities. Besides Planet B.io there are other actors present at the Biotech Campus Delft offering a part of the scale-up support present at the campus. One of the actors is DSM which is the owner of the Biotech Campus Delft and among others facilitates the use of the utilities, wastewater treatment plant and permits. Currently, Planet B.io is renovating a second building with additional labs and offices to strengthen the ecosystem. The planned open-access lab with shared equipment will enable the education of students and be available for start-ups to perform experiments, thus fostering innovation and collaboration. Besides, there was a piloting facility present at the BCD, called the Bioprocess Pilot Facility (BPF) which offered fully-serviced piloting, including equipment and operators, to help start-ups scale-up their process beyond the lab-scale offered at Planet B.io. However, despite the growing demand for technical scale-up and piloting, there are no longer any piloting facilities available at the BCD due to the bankruptcy of the BPF in December 2022, despite being fully booked. It is hard to run a sustainable business model for a piloting facility, as pilot plants do not make money (Sanford et al., 2016). While the need for additional scale-up facilities was already apparent, the lack of options has only increased this demand. Therefore, the industrial biotechnology support ecosystem offered by Planet B.io at the BCD has a lot of potential for growth and development in terms of technical scale-up facilities as well as other parts of scale-up support. This brought forward the following research question: **what are the factors affecting successful scale-up in industrial biotechnology and how should scale-ups be supported?**

Therefore, it might offer valuable insights to look at scale-up support ecosystems elsewhere in industrial biotechnology or other industries with similar characteristics. These are used, among others, as industry selection criteria to be relevant for translation to industrial biotechnology. The support of scale-ups also needs to be sustaining and requires a business model that ensures it to be viable (in the long-term). The financing and business model of these types of scale-up support should be investigated. As well as which stakeholders should be involved and what role these stakeholders should play in providing and developing scale-up supporting facilities.

Therefore, this thesis project will focus on understanding the factors affecting successful scale-up and what role scale-up supporting ecosystems should play and how these can best be organised. To limit the scope of this project only ecosystems within the European Union were considered, since policy and regulation also affects technology development (Biggs et al., 2021; Kampers et al., 2021; Linton & Xu, 2021). Additionally, support ecosystems were only considered when containing both business support and technical scale-up support within its ecosystem. The insights generated by the multiple case-study will provide start-up/ scale-up supporting ecosystems, industry, policy makers and academia with insights and best practices on offering technical scale-up support and how to organise this in terms of business model and stakeholders. Moreover, these insights will be applied to the context of Planet B.io at the Biotech Campus Delft for strategic decision making and organisation of its scale-up support ecosystem.

1.7 Thesis Overview

In this thesis, a multiple case study will be performed on scale-up supporting ecosystems in industrial biotechnology or industries with similar characteristics (see section 1.1.2). The insights generated by the multiple case-study will provide start-up/ scale-up supporting ecosystems, industry, policy makers and academia with insights and best practices on offering technical scale-up support and how to organise this in terms of business model and stakeholders. Moreover, these insights will be applied to the context of Planet B.io at the Biotech Campus Delft for strategic decision making and organisation of its scale-up support ecosystem. Firstly, the findings of the literature review are discussed, leading to the identified research gap and posed research questions (section 2). Then the research methodology for the multiple case study is described (section 3), including the timeline for the thesis. In section 4, the results of the conducted multiple case study are presented and discussed leading to theory on the ideal scale-up support ecosystem and advice for the development of the scale-up support ecosystem of Planet B.io - Biotech Campus Delft. These results are discussed (section 5) and lastly the conclusions as well as recommendations for further research are given (section 6).

2 Literature Review

2.1 Literature Findings

In this section, the relevant literature on the topic of factors affecting successful scale-up and the support of technical and business scale-up in industrial biotechnology is discussed. First of all, the highly regarded "general" business literature is elaborated and discussed in relation to its relevance for industrial biotechnology. Then the literature on the scale-up of industrial biotechnology is reviewed. Moreover, the literature on scale-up support, its ecosystem, stakeholders, and business models has been reviewed.

2.1.1 Business vs. Technical Scale-Up

Looking into relevant literature on scale-ups, Harnish (2014) is repeatedly cited. This book focuses on the four major decision areas in the company scaling-up process (people, strategy, execution, and cash) (Harnish, 2014).

Three general barriers to scaling up are identified from business literature (Harnish, 2014):

1. Leadership: the inability to staff or grow enough leaders throughout the organisation who have the capabilities to delegate and predict.
2. Scalable infrastructure: the lack of systems and structures (physical and organisational) to handle the complexities in communication and decisions that come with growth.
3. Market dynamics: the failure to address the increased competitive pressures that build (and erode margins) as you scale the business.

In addition, according to Harnish (2014) the key to scaling is:

1. Attracting and keeping the right people
2. Creating a truly differentiated Strategy
3. Driving flawless Execution
4. Having plenty of Cash to weather the storms

Though Harnish (2014) is a practical guide book, it does not generate any insight whatsoever into how scientifically justified these claims are and does not include specific needs or requirements for industrial biotechnology or other specific markets or industries, since this would differ drastically between and even within industries. Therefore, it also misses the in-depth challenges of technical scale-up in different industries, or at least in biotechnology.

On the one hand, general theory upon successful start-up and scale-up includes the start-up manual (Blank and Dorf (2012)) and the Rockefeller habits 2.0 (Harnish (2014)) respectively. This literature is only focused on the business aspect of scale-up and is not applicable for the complex characteristics of scale-up in industrial biotechnology as stated by Blank and Dorf (2012). Where for industrial biotechnology both technical and business scale-up occur simultaneously before commercialisation of the product, resulting in the Valley of Death.

On the other hand, there is literature on the technical challenges of industrial biotechnology. This literature touches upon the requirements on the technical scale-up side as well as the commercialisation of renewable chemicals, technology challenges and opportunities, and proposes a new approach to scale-up, respectively Davison and Lievense (2016); Efara et al. (2019); Sanford et al. (2016). There is no literature discussing both the technical and business sides of the scale-up of industrial biotechnology and relating it to factors affecting the successful scale-up of industrial biotechnology.

2.1.2 The Valley of Death of (Industrial) Biotechnology

The Valley of Death refers to the transition of a technology from lab to market, which is extremely difficult (Kampers et al., 2021; Linton & Xu, 2021). As Ellwood, Williams, and Egan

(2022) describes, there is no consensus (yet) on why it is so difficult to cross the Valley of Death. Therefore, Ellwood et al. (2022) has built a conceptual framework of the five innovation processes that are required to cross the Valley of Death for biotechnology. There is no set order found for successful commercialisation, but these processes are:

1. Refinement of narrative for the technology concept
2. Technical evaluation of lab-scale models (e.g., pilot-scale testing)
3. Refinement of understanding of how the technology will be used
4. Comparative value assessment
5. Integration of innovator actor inputs

However, Ellwood et al. (2022) is specifically focused on biopharmaceuticals, which are high-end products that do not have the same scale-up requirements and industry characteristics as industrial biotechnology (see Figure 1). Therefore, it is not completely representative of industrial biotechnology. Crossing biotechnology's Valley of Death is not a simple trade-off between encouraging and regulating (Linton & Xu, 2021). Product validation for industrial biotechnology is a trade-off between cost, time, and quality. However, these trade-offs should be prevented by obtaining resources elsewhere (Kampers et al., 2021; Linton & Xu, 2021). Normally, the choices to ease crossing the Valley of Death are to reduce requirements or increase the magnitude of the reward of successful commercialisation (Linton & Xu, 2021). However, this does not work as easily for industrial biotechnology since they have to compete with traditional (petro)chemical or food products. Especially the product requirements in terms of quality, price, safety, and capacity are really high (Sanford et al., 2016). Besides the high technology requirements, Kampers et al. (2021) mentions that reasons why new technology often does not bridge the Valley of Death include cumbersome contracting or procurement of technology requirements, lack of exposure, lack of entrepreneurial management, lack of adequate funding for further development, and a lack of a strong link between technology development efforts and industrial deployment (see Table 3). Linton and Xu (2021) has visualised the biotechnology's Valley of Death, analogous to Arrhenius's model of chemical transformation, to enable better strategy selection to cross the Valley of Death (Figure 4). This shows that the Valley of Death is divided into two stages:

1. Failure to qualify (trade-off between quality, time, and cost)
2. Failure to industrialise (scaling up qualifying technology)

The Valley of Death is also partly a function of government (regulation) (see Table 3, Biggs et al. (2021); Kampers et al. (2021); Linton and Xu (2021)). A key takeaway of Kampers et al. (2021) is that grant applications should include commercialisation, leading to more attention on industrialisation (see Table 3).

2.1.3 The Growth Chasm is not relevant for scale-up (support) of industrial biotechnology

Another phenomena that occurs during the transition from a start-up to scale-up in terms of business scaling, there is a transformation needed to successfully enter the scale-up phase. This transformation from start-up to scale-up is commonly referred to as the growth chasm (Moore, 2014). Crossing the Chasm is a theory that seeks to explain how, why, and at what rate discontinuous ideas and technologies are adopted (Moore, 2014). According to this theory, crossing the growth chasm is a crucial aspect of scaling up in the technology adoption life cycle. This theory gives insight into the product-market fit aspect of scaling, which changes due to the differences in customer groups. However, this requires a product on the market already before scaling up as a company, which is not the case when scaling up in industrial biotechnology. Therefore, the growth chasm phenomenon is not deemed relevant for this study on technical scale-up problems in industrial biotechnology.

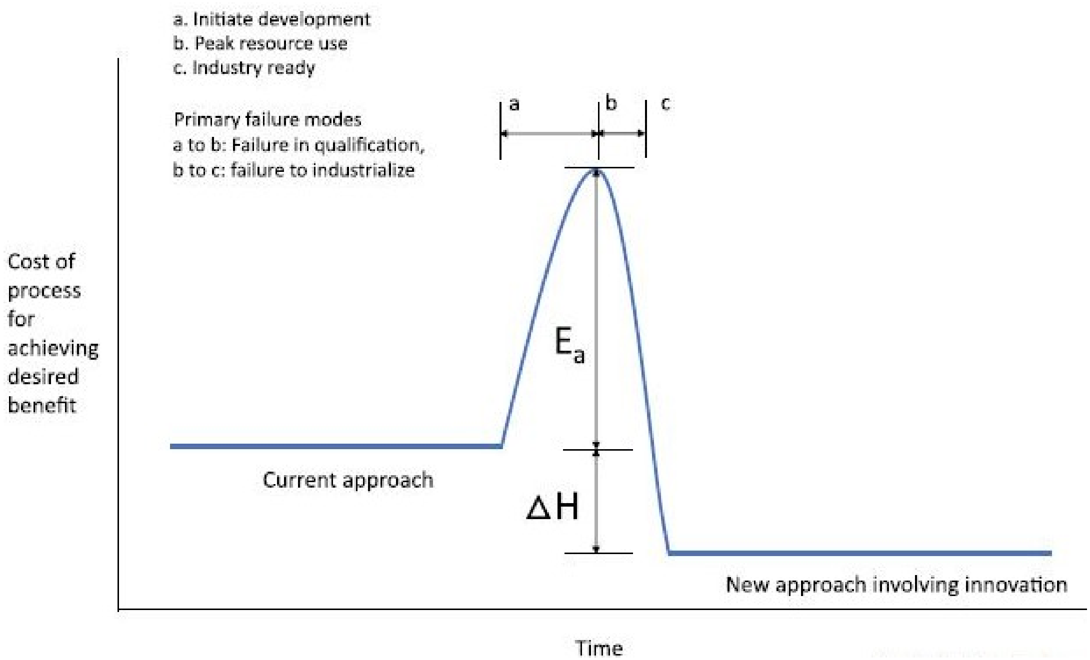

Figure 4: Biotechnology's Valley of Death adapted from Linton and Xu (2021). This model is an analogue to Arrhenius's model of chemical transformation. The resource requirement to traverse the Valley of Death is the blue curve. The resources required to reach qualification in biotechnology commercialization (a to b) are represented by the activation energy (Ea), while the requirements after the peak of costs are the industrialization process (b to c). As resource requirements using a new approach decrease, the attractiveness of using resources to transform from the current to a new approach increases. The relative attractiveness of crossing the Valley of Death depends on the resources required in comparison to the surplus that is provided by the new approach over the old approach (ΔH).

2.1.4 Technical Scale-Up Requirements

Technical scale-up in industrial biotechnology has very specific requirements. Sanford et al. (2016) elaborates on the concrete technical scale-up requirements for renewable chemicals, such as extreme productivity, feedstock availability, affordable costs, and an efficient and effective biocatalyst (see Table 3). **One scale-up success factor that stands out is piloting where you operate** (Sanford et al., 2016). This demonstrates the relevance of ecosystems like Planet B.io - Biotech Campus Delft with their facilities on one campus.

Besides, Takors (2012) gives an overview of the technical requirements for scale-up of microbial processes to maintain constant at lab- and production-scale. All of these criteria share a common motivation based on physical constraints rather than biological properties. To support successful scale-up, better simulators are needed requiring increased holistic understanding of cellular activities and responses will generate new scale-up criteria that are not solely based on physical constraints, but also account for intrinsic biological properties (Noorman, 2011). By using these criteria in process design, improvements can be made to successfully transfer from lab to production without any surprises on a large-scale (Noorman, 2011). This has been interpreted as a scale-up influencing factor related to technical knowledge (see Table 3).

Pilot and Manufacturing Facilities for Industrial Biotechnology

A key requirement for technical scale-up is a pilot plant, which should be designed specifically to represent the large-scale conditions (Davison & Lievense, 2016; Sanford et al., 2016). Which also confirms the view of Efara et al. (2019) to already think scale-up from the start. Piloting is needed to fill gaps in understanding that are critical to commercial scale, gather data for successful scale-up, demonstrate ability to produce high-quality product, and test with customers

(Biggs et al., 2021; Sanford et al., 2016). This all aims to reduce the risk of non-performance at commercial scale (Biggs et al., 2021; Davison & Lievense, 2016; Sanford et al., 2016). However, there is a limited capacity at pilot plants, which restricts the possibility to actually pilot toward a commercial-like scale Biggs et al. (2021). Also, there is still a clear knowledge gap in defining predictive metrics for effective scale-up with appropriate project management skills, which Sanford et al. (2016) describes as essential in scale-up activities. Biggs et al. (2021) mentions the deficit of pilot and production facilities, as well as the insufficient capacity of pilot facilities for industrial biotechnology. Besides, high capital investments and a long timeline (at least 18 months) for building an own facility can cause huge scale-up problems (Davison & Lievense, 2016). A complete overview of the factor affecting scale-up found has been given in Table 3. Furthermore, there was no other literature found on the manufacturing requirements of industrial biotechnology.

Scale-Up Approach: Already Think Scale-Up from the Beginning
Davison and Lievense (2016) stated that process scaling should follow a structured, stage-gate approach that defines the full-scale fermentation process early and employs rigorous project-management techniques throughout, which is really similar to the already think scale-up from the beginning proposed by Efara et al. (2019) (see Table 3). This approach to preventing scale-up problems is also formulated slightly different by respectively.(Obloj et al., 2023) which describes three main challenges for scaling the bioeconomy and how to resolve these:

1. defining a go-to-market strategy can be done by considering the maximum acceptable Cost Of Goods Sold (CoGS)

2. Developing a scaleable process can be done by choosing the microorganism and developing the process with scale in mind

3. Financing biomanufacturing capacity can be done by building the business with credit-worthiness in mind

Therefore, **starting the process development with the end-in-mind is considered a scale-up success factor for industrial biotechnology** (see Table 3).

Scale-up Approach: Acquiring Funding for Biomanufacturing Capacity
Financing of biomanufacturing capacity is highlighted as one of the three challenges of scaling the bioeconomy where industrial biotechnology is a part of (Obloj et al., 2023), this acknowledges the need for flexible open facilities to perform technical scale-up, lowering costs, time, as well as knowledge and people required for technical scale-up. Thus, highlighting the need for technical scale-up support facilities. The approach to scaling up biomanufacturing capacity by acquiring funding is discussed in Obloj et al. (2023). A potential capital sourcing approach is from VC equity (the parent company) → subsidies → venture debt → Private equity → Institutional capital. To bridge the lack of funding **government, off-takers, or industry partners can act as guarantors to enable lower-cost debt capital. Additionally, corporate partnerships in the bioeconomy are crucial for success**, also a scale-up success factor (Table 3).

2.1.5 Emerging Technologies in Industrial Biotechnology

According to Nielsen et al. (2022), an academic review consisting of two case studies, emerging innovation trends in industrial biotechnology lie with the utilization of machine learning and artificial intelligence, advancements in agricultural biotechnology and novel food development, and the application of precision fermentation techniques, specifically in the production of alternative meat and dairy products. Moreover, the development of fermentation processes utilising

Table 2: Comparison of Emerging Technologies in Industrial Biotechnology

Technology	**Main Characteristics**	**Key Aspects in Their Innovation**
Cultivated Meat	Meat produced using tissue engineering techniques and grown in bioreactors. Offers a sustainable and ethical alternative to traditional animal farming (Guan et al., 2021).	Scaling up production, reducing production costs, improving taste and texture, addressing regulatory challenges, and consumer acceptance (Allan, Bank, & Ellis, 2019; Chen et al., 2022; Guan et al., 2021; Humbird, 2021).
Gas Fermentation	Utilizes microorganisms to convert gases (e.g., CO_2, methane) into valuable products such as biofuels, chemicals, and pharmaceuticals. Enables waste gas utilization and reduces greenhouse gas emissions.	Identifying and engineering suitable microorganisms, optimizing gas conversion efficiency, developing cost-effective fermentation processes, and integrating with existing industrial infrastructure (Caillat, 2017; Köpke & Simpson, 2020; Liew et al., 2022).
Alternative Feedstocks	Utilization of non-traditional biomass sources, such as agricultural residues, algae, and waste streams, as feedstock for bioprocessing. Reduces reliance on food crops and opens up new feedstock options for conversion into valuable products such as sustainable chemicals, bioplastics or biofuels.	Pre-treatment and conversion technologies to make feedstocks more amenable to bioprocessing (Benalcázar, Deynoot, Noorman, Osseweijer, & Posada, 2017), improving feedstock availability and quality, optimizing process efficiency and yield, and ensuring sustainability and environmental benefits.

alternative feedstocks (e.g., agricultural waste) or waste gasses are also emerging within industrial biotechnology. Furthermore, Nielsen et al. (2022) offers a comprehensive assessment of opportunities within industrial biotechnology, focusing primarily on the technical scale-up of these emerging technologies. Cultivated meat, gas fermentation and alternative feedstocks are emerging technologies that are currently reaching scale-up phase and have been compared in terms of main characteristics and key aspects in their innovation (see Table 2). A lot of literature was found on the challenges of cultivated meat. All found scale-up challenges or success factors are also listed in Table 3.

2.1.6 Factors affecting the success or failure of scale-up in Biotechnology

The relevant literature that could be linked to a specific factor influencing the success of technical or business scale-up of (industrial) biotechnology or similar industries has been listed (Table 3). Moreover, the main findings and scientific relevance to answering the research question have been discussed. This shows that there is a lack of literature looking at the overarching scale-up factors causing problems in industrial biotechnology. Not only the technical issues but also the business side of scaling up. For specifically renewable chemicals or cultivated meat there are some specific challenges mentioned, e.g., regulatory and consumer acceptance challenges (Table 2).

Table 3: Factors influencing (technical or business) scale-up in industrial biotechnology found in literature, its main findings and relevance for the research question.

Factor	Source	Main Findings	Relevance
Technical Knowledge	Noorman (2011)	Increased holistic understanding (physical and biological) for process design will help successfully transfer from lab- to large-scale	Relevant for industrial biotechnology, highly cited
Pricing	Davison and Lievense (2016)	New bioprocesses for existing products must have at least a 30% cash cost advantage compared with the best available commercial technology.	High, specifically on the commercialisation of industrial biotechnology, 7 citations to date.
	Sanford et al. (2016)	Drop-in replacements for petroleum derived chemicals price is incredibly important. For new chemicals/ materials this is less of a scale-up challenge since higher prices can be asked.	High, but only focused on renewable chemical production which is only a part of industrial biotechnology. 58 citations to date.
	Nielsen et al. (2022)	Price should be competitive with the price of oil-based products	Relevant, on the emerging technologies in industrial biotechnology
	Humbird (2021)	Capital and operating costs analyses likely preclude the affordability of their product as food even with metabolic efficiency enhancement and low-cost media.	Relevant, techno-economic analysis on cultured meat, 6 citations within a year
	Obloj et al. (2023)	Product price. Determine the maximum acceptable Cost of Goods Sold (CoGS) at the beginning	White paper on the bioeconomy, its challenges and possible solutions. Not peer-reviewed paper.
Product Quality	Davison and Lievense (2016)	Novel bioproducts must provide at least a threefold improvement in properties over the existing commercial alternatives.	High, specifically on the commercialisation of industrial biotechnology, 7 citations to date.
	Chen et al. (2022)	For cultured meat a public health benefit would help the adoption of the product	High, on technical scale-up of cultured meat. 6 citations within 6 months, but a review paper
Process scaling	Davison and Lievense (2016)	Structured stage-gate approach with early full-scale process definement is required for scaling. Pilot plant representing commercial scale production required. **Commercial-scale thinking from the start.**	High, specifically on the commercialisation of industrial biotechnology, 7 citations to date.
	Sanford et al. (2016)	Technical scale-up requirements for renewable chemicals, such as extreme productivity, feedstock availability and affordable costs, and an efficient and effective biocatalyst. Also success factors for scale-up are mentioned (e.g., piloting where you operate).	High, but only focused on renewable chemical production which is only a part of industrial biotechnology. 58 citations to date.
	Efara et al. (2019)	**Already think scale-up from the beginning**. New approach to the Develop-then-Scale model.	Relevant, but only on the method of technical scale-up of biotechnological chemical processes. 2 citations to date.
	Allan et al. (2019)	identified as key factors for cultured meat production an animal component-free medium, high-volume bioreactor, edible scaffolds, final product formulation, waste treatment and recycling and a reduction of production cost.	High, but only focused on technical challenges of cultivated meat production.
	Guan et al. (2021)	identified the requirements for an animal component-free medium, high-volume bioreactor, edible scaffolds, and a reduction of production cost among others.	High, but only focused on technical (regulatory and social) challenges of cultivated meat production. 16 citations in one year.
	Biggs et al. (2021)	Pilot-scale facilities are essential for the risk-reduction process and The shortage of facilities and inability to reduce risks are major contributions to the Valley of Death between demonstration and commercial-scale production	High, published in Science (1 citation in 6 months), a literature review paper so not a primary source.
	Chen et al. (2022)	Starting cell lines, serum-free media, seed train proliferation bioreactors, large-scale bioreactors are required, as well as food safe scaffolds	High, on technical scale-up of cultured meat. 6 citations within 6 months, but a review paper
	Ducrée (2018)	High TRLs in microfluidics will be accomplished by using a platform approach, virtual prototyping / digital twin, and quality-by-design.	Conference paper on microfluidics, but can be relevant for ind. biotech.
Business scaling	Coad, Frankish, and Storey (2020)	Effects of growth on survival across the growth distribution. Growing in short intense bursts seems to be harmful and growth should not be too high ("too fast to live" effect).	Not specifically focused on industrial biotechnology, so only relevent as a starting point for further research into growth of start-ups in industrial biotechnology. Looked into 6578 new ventures.
Workforce	Biggs et al. (2021)	Prioritization of biomanufacturing work force training and education required for commercial success of industrial biotechnology	High, published in Science (1 citation in 6 months), a literature review paper so not a primary source.
Policy/ Regulation	Davison and Lievense (2016)	Mitigate regulatory-related risks by hiring a regulatory expert in the country of fermentation manufacturing.	High, specifically on the commercialisation of industrial biotechnology, 7 citations to date.
	Guan et al. (2021)	Regulatory policy on the whole process of production, and especially the use of gene-editing technologies should be formulated.	High, but only focused on technical (regulatory and social) challenges of cultivated meat production. 16 citations in one year.
	Biggs et al. (2021)	Policy should promote translational science and sustainability and investment in technology and infrastructure to enable translational research and education	High, published in Science (1 citation in 6 months), a literature review paper so not a primary source.
	Chen et al. (2022)	Factors that may impact the ability to succesfully scale and market cultured meat: social acceptance, environmental trade-offs, regulatory guidance, and public health benefit	High, on technical scale-up of cultured meat. 6 citations within 6 months, but a review paper
	Kampers et al. (2021)	The Valley of Death of Ind. biotech. is partly a function of government (regulation).	Peer-reviewed short survey, 10 citations to date.
	Hughes and Meckling (2018)	Governments are crucial in driving innovation, particularly in the development of clean technology	Focused on clean, low-carbon technology, thus relevant for industrial bitoechnology.
Social Acceptance	Chen et al. (2022)	Factors that may impact the ability to succesfully scale and market cultured meat: social acceptance, environmental trade-offs, regulatory guidance, and public health benefit	High, on technical scale-up of cultured meat. 6 citations within 6 months, but a review paper
Stakeholders	Obloj et al. (2023)	Every party can contribute to unlocking bioeconomy scale- up: researchers, founders, governments, investors, and lenders.	White paper on the bioeconomy, its challenges and possible solutions. Not peer-reviewed paper.
Funding	Strömsten and Waluszewski (2012)	Governance and resource interaction in networks. The role of venture capital in a biotechnology start-up.	Relevant, to gain insight into the role of venture capital in biotechnology. Is a case study with 33 citations, however it is not an industrial biotechnology case study which limits complete relevance.
	Bains, Wooder, and Guzman (2014)	Funding for early stage biotechnology companies has declined very substantially since 2006. Companies are adapting by adopting financial modes based on angel investment, grants and revenue as well as crowdfunding.	Relevant, but not specific to industrial biotechnology. And may be already outdated in terms of publication, since the investment landscape changes rapidly.
	Duruflé, Hellmann, Bruegel, and Fellow (2017)	Main requirements for scale-up investors: 1. Deep pockets, 2. Smart money, 3. Networks, 4. Patient money.	Relevant, but not specific to industrial biotechnology. Database research.
	Biggs et al. (2021)	Early-stage research translation should be funded through targeted grants and multidisciplinary solutions that aim to reduce risk or solve complex problems should be funded through policy	High, published in Science (1 citation in 6 months), a literature review paper so not a primary source.
	Obloj et al. (2023)	Funding biomanufacturing capacity by building the business with credit worthiness in mind	White paper on the bioeconomy, its challenges and possible solutions. Not peer-reviewed paper.
Third-parties	Davison and Lievense (2016)	Industrial biotechnology needs a proponent analogous to the U.S. National Institutes of Health (NIH).	High, specifically on the commercialisation of industrial biotechnology, 7 citations to date.
	Kampers et al. (2021)	There is a third-party needed to act as a bridge between academia and industry, both in communication as in TRLs.	Peer-reviewed short survey, 10 citations March 2023.

Factor	Source	Main Findings	Relevance
Partnerships	Davison and Lievense (2016)	Gain advantages through partnerships across the value-chain. Sharing insights and formation of partnerships helps to improve the commercialization process (across the Valley of Death).	High, specifically on the commercialisation of industrial biotechnology, 7 citations to date.
	Chen et al. (2022)	Partnerships required to get to commercial scale production	High, on technical scale-up of cultured meat. 6 citations within 6 months, but a review paper
Business Model	Hatvani, van den Oever, Mateffy, and Koos (2022)	Additional business model canvas requirements for bio-based business models: drivers and stakeholder involvement tools and sustainability requirements	not hugely relevant for scale-up support, 1 citation in a year.
	Bocken, Short, Rana, and Evans (2014)	Identified eight archetypes to de-risk the innovation process of sustainability business models.	Field-weighted citation impact of 16 (1737 citations to date.).
Marketing	Schoonmaker and Rau (2014)	The nature of and the extent to which the type and level of marketing efforts help with the continuation of early-stage innovations.	Medical Biotech (NIH as a database), likert-scale survey based on earlier qualitative study, 1 citation. So not directly relevant for industrial biotechnology, but illustrates the factor of marketing required for biotechnology

Table 7. Factors influencing (technical or business) scale-up in industrial biotechnology continued.

2.1.7 Scale-Up Support and Research & Innovation Ecosystems

Besides the factors influencing (technical or business) scale-up (see Table 3), there are also support organisations like accelerators, incubators, and hubs that can be a part of a Research & Innovation (R&I) ecosystem and provide several of the success factors required for scale-up.

Requirements of a successful Dutch start-up ecosystem

According to Henz, Hofstee, Jacobs, Ouass, and Smit (2022) to achieve more successful scaling of Dutch start-ups, the conditions for scaling a company in the Netherlands will need to improve and identified six prerequisites to help the Netherlands resolve its scaling challenges. From this the following scale-up success needs are identified: **a need for funding, network formation & coordination, and knowledge & talent as well as supportive policy and taxation benefits**. In addition, Vankan et al. (2020) presented some extra focus points, where also government should help with:

- Investments in research and testing facilities
- Strengthening knowledge transfer and valorisation processes for greater impact
- Giving earlier attention to regulations and legislation
- Enhancing the organizing capacity of ecosystems
- Taking a long-term perspective and coherence in investments in research and innovation

Moreover, engaging everyone from educators and legislators to VCs, founders, and even CXOs is said to help embed internationally scalable entrepreneurship in both the institutions and the culture of the Netherlands, which could help address barriers that hinder start-ups' ability to scale through incentives and guidance on how to succeed (Henz et al., 2022). However, these findings are presented in white papers, so should only be used as indicators. However, this does not describe the technical scale-up support and/ or focus on industrial biotechnology.

Role of accelerators

Bhatli, Borella, Jelassi, and Saillant (2015) conducted an exploratory qualitative research study using semi-structured interviews to examine the challenges facing successful start-up accelerator programmes. They closely examined two successful European start-up accelerators, Startup Sauna in Espoo, Finland, and Le Camping in Paris, France. However, according to Banc and Messeghem (2020), there is a lack of consistent criteria for measuring the performance of corporate accelerators.

Their study revealed that accelerator programmes act as entrepreneurial matchmakers, providing several benefits to participants, such as feedback and technical know-how, time-bound support, education and mentoring focused on business and product advice, and networking programmes (Bhatli et al., 2015). An in-depth analysis highlights the evolution of start-up resource needs and the matchmaking role of accelerators in fulfilling those needs, which change during the three stages of start-ups: the nascent (conception) stage, functional (prototype) stage, and operational (commercialization) stage. The latter two stages can be linked to technical scale-up in industries such as industrial biotechnology. The focus on resource needs shifts during these stages, from relevant feedback to relevant networks to relevant investments. At all stages, accelerators act as matchmakers (Bhatli et al., 2015).

Furthermore, Banc and Messeghem (2020) emphasizes the importance of strategic attributes of a corporate accelerator and its entrepreneurial micro-ecosystem, which include obtaining stakeholder approval, the need for coopetition to create sustainable relationships and pool resources, and creating a reliable business model adapted to the environment to support the creation of value and costs. This does show that an accelerator is focused on the business support and not on the technical support of scale-up.

Role of Incubators

Djordjević and Mihić (2022) investigated the impact of incubators in the post-COVID era. Incubators can reduce cost of information, administration and training through their functions and services that they offer, making entrepreneurship more widely accessible, and thus stimulating innovation and value generation. This resulted in the most important roles of business incubators (Djordjević & Mihić, 2022):

1. Help to set up businesses
2. Ensuring survival of start-ups
3. Helping start-ups in raising funds
4. Increase in employment
5. Positive impact on innovation
6. Increase productivity
7. Economic and social sustainability

However, this case study does not go discuss technical scale-up facilities, the business models of the supporting incubators, or stakeholders involved in supporting activities, it only focuses on business incubators and accelerators. Also, Djordjević and Mihić (2022) does not focus on industrial biotechnology.

2.2 Synthesis and Research Gap

Most biotechnologies that look promising after laboratory development fail to cross the Valley of Death and reach industrial scale, or do so at unviable economic conditions. To help start-ups in industrial biotechnology overcome these scale-up problems the following research questions were investigated:

1. What are the factors affecting successful scale-up of industrial biotechnology?

2. How can a (technical) scale-up support ecosystem for industrial biotechnology best be organised and operated?

The definition of scale-up for industrial biotechnology has on the one hand the technical scale-up, with crossing the Valley of Death to commercialisation. On the other hand, the business scale-up, with organisational growth in terms of personnel, facilities, costs and funding requirements. For industrial biotechnology this technical and business scale-up occurs simultaneously, before commercialisation, causing most start-ups to fail. The Valley of Death for biotechnology has two stages. Firstly, the resources required to reach qualification in biotechnology commercialization. Secondly, after the peak the requirements of the industrialization process.

2.2.1 Most Important Factors Affecting Successful Scale-Up in Industrial Biotechnology

Looking at the findings, the most important factors affecting scale-up in industrial biotechnology found in literature are almost only factors related to technical scale-up. Factors that stood out in terms of importance and in-depth discussion of literature are:

- Pilot and manufacturing facilities, which should be available at a sufficient scale and capacity and pilots should represent commercial-scale conditions.
- Process scaling approach, where the "already think scale-up from the beginning" model emerged (Davison & Lievense, 2016; Efara et al., 2019; Obloj et al., 2023). Which also means the go-to-market strategy should be determined beforehand.

The other factors affecting scale-up in industrial biotechnology are (see Table 3):

- Pricing (competitiveness, costs of production)
- Product Quality
- Business Scaling
- Workforce (and education)
- Policy & Regulation
- Social Acceptance
- Third-parties
- Partnerships
- Funding
- Marketing

Looking at emerging technologies in industrial biotechnology, literature has been found regarding technical, regulatory and social challenges for cultured meat. Its technical requirements found in literature are lower operating costs (cheaper medium) and higher productivity, final product formulation, waste treatment and recycling as well as partnerships for scaling. In terms of regulatory and social challenges regulatory policy on the whole process of production, and especially whether gene-editing technologies can be applied is needed. Furthermore, there is a need for social acceptance.

There is insufficient scale and capacity of pilot and manufacturing facilities (Obloj et al., 2023). Moreover, due to the long technology development and high capital expenses for building and piloting yourself as a scale-up in industrial biotechnology, there is a direct need for scale-up support(ing ecosystems) in industrial biotechnology.

2.2.2 Scale-up elements

All scale-up success factors found (see Table 3, section 2.2.1) and all five innovation processes required to cross the Valley of Death for industrial biotechnology (Ellwood et al., 2022) can be grouped into one of these four scale-up categories:

1. Technical
2. Funding & business
3. Network formation & coordination
4. Knowledge & talent

The aspects of funding & business, network formation & coordination, and knowledge & talent also came back in the literature on start-up and R&I ecosystems and factors required for successful scale-up (see 2.1.7).

2.2.3 Scale-Up Supporting Ecosystems in Industrial Biotechnology

Based on the literature on scale-up support and ecosystems **a scale-up supporting ecosystem has been defined for this study as a distinct type of (R&I) ecosystem that focuses on supporting the scaling of start-ups through a combination of business support** (e.g. accelerator, incubator or hub) **and technical support services** (e.g. pilot facilities), which may or may not be physically located in close proximity to each other. As a recap, an R&I ecosystem was defined as a network of individuals, organisations, institutions, and resources working together to create and commercialise new ideas, products, and services. It includes academic and research institutions, start-ups, corporations, government agencies, and resources like funding, mentorship, and infrastructure (Vankan et al., 2020). Therefore, interaction is required for actors/ stakeholders to be part of the scale-up support ecosystem.

one scale-up supporting ecosystem for industrial biotechnology was found in literature. This is the IAR cluster in France (Stadler & Chauvet, 2018), which supports technical scale-up from TRL 5 to 9. This scale-up supporting ecosystem(s) could be used as a source for further study, since these did not describe the specific technical scale-up facilities, their financing, business models and stakeholder roles (see Appendix B.7.3).

2.2.4 Stakeholders and Roles in Scale-Up Supporting Ecosystems

The roles of stakeholders in the scale-up supporting ecosystem are very important. According to Stadler and Chauvet (2018) the alignment of regional, national and European policy is required to have a strong leverage effect. Moreover, Hatvani et al. (2022) discussed bio-based business models and described the stakeholders with cross-cutting activities for the bio-based value chain.

- Educational and R&D organisations (e.g., universities)
- Investors
- Business support organisations (e.g. clusters/ ecosystems, consultancy services)
- Policy makers (e.g., in the field of waste management, climate issues, circular economy)

2.2.5 Identified Research Gap

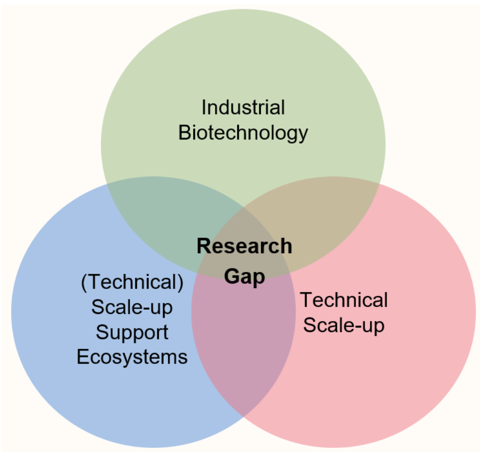

Figure 5: Venn diagram of the identified research gap in the field where technical scale-up, scale-up support ecosystems and industrial biotechnology overlap. This identified research gap illustrates the need for further research upon how to organise scale-up support ecosystems for successful commercialisation, across the Valley of Death, of start-ups in industrial biotechnology.

After conducting a comprehensive literature review, it is evident that there is still a significant research gap in understanding the intersection of technical scale-up support, effective scale-up support ecosystems, and industrial biotechnology (Figure 5). This identified research gap illustrates the need for further research upon the technical and business scale-up support ecosystems, what should be offered in terms of scale-up support for industrial biotechnology (e.g. type of support/ facilities), and how a scale-up support ecosystem can thrive while offering this scale-up support (business model of scale-up support, stakeholders and their roles).

The different types of scale-up support possible for industrial biotechnology and their respective business models remain unclear. Therefore, the following research question arose:

RQ1. ***What are the types of technical scale-up support for industrial biotechnology and what are their associated business models?***

This research question highlights the need to explore the various forms of technical support available to scale-up businesses, as well as the business models that enable their successful operation. In addition, some stakeholders of the R&I ecosystem are mentioned, in different contexts, but not specifically aimed at the technical scale-up supporting part of the ecosystem and what their roles should be for successful (technical) scale-up support. This presents the second research question being:

RQ2. ***Which types of stakeholders should be involved in a (technical) scale-up support ecosystem for industrial biotechnology?***

Research question 1 and 2 need to be answered in order to be able to translate the context dependent and independent factors and see what should be applied to the specific scenario of Planet B.io at the Biotech Campus Delft and answer the last research question:

RQ3. ***How should the (technical) scale-up support ecosystem supplied by Planet B.io and the Biotech Campus Delft be organised and operated?***

2.2.6 Research Questions

Based upon this identified research gap this study offers the following research questions to be able to answer:

> How can a (technical) scale-up support ecosystem for industrial biotechnology best be organised and operated?

Therefore, this study focuses on the following research questions, which can be subdivided in three parts:

RQ1. ***What are the types of technical scale-up support for industrial biotechnology and what are their associated business models?***

a. In industrial biotechnology?
b. In other relevant markets according to the above-mentioned criteria (long technology development, high capital expenses, economies of scale, the product is a bulk product with low profit margins)?
c. On which Technology Readiness Levels (TRLs) do these different types of scale-up support focus?

RQ2. ***Which types of stakeholders should be involved in a (technical) scale-up support ecosystem for industrial biotechnology?***

a. What are inevitable stakeholders?
b. What are other possible stakeholders?

c. What should be the roles of the different stakeholders?

RQ3. ***How should the (technical) scale-up support ecosystem supplied by Planet B.io and the Biotech Campus Delft be organised and operated?***

a. On which Technology Readiness Levels (TRLs) should be focused?

b. What are the possible business models?

c. What are the possible stakeholders and how should these be involved?

d. What are the differences when comparing a theoretical (best practices) scale-up support ecosystem stakeholder map with the Planet B.io - Biotech Campus Delft case?

e. What would be the road-map for the development of scale-up facilities?

f. Which business model would be attractive for the start-/ scale-ups of interest?

Besides, an implicit goal of this study was to find out how scale-up support ecosystems can be studied and described, resulting in answers to the posed research questions. This required some further literature review and theory selection (see section 2.3)

2.3 Theoretical frameworks to study innovation systems

Ecosystems are interconnected, subjective and context-dependent, to enable comparison of the different scale-up support ecosystems studied and translate these findings to the case of Planet B.io - Biotech Campus Delft a framework was required.

2.3.1 Innovation systems

Innovations were seen as the product of an individual's behaviour via the innovator-entrepreneur view of Schumpeter. However, currently the innovation process is seen as the outcome of a collective process (Coenen & López, 2010; Dosi & Nelson, 2013; Fagerberg, 2006). Resulting in the complex interactions that lead to an innovation is described as an "innovation system". Which has been defined by Edquist and Chaminade (2006, p. 1): "all factors that influence the development, diffusion and use of innovations". An Innovation System consists of actors, networks, institutions, and technology. Actors influence the innovation, while networks are social connections between them. Institutions are the formal and informal rules governing social interactions.

A scale-up support ecosystem also consists of a network of actors, institutions, and technology. But focuses on a specific phase and part of a technology/ industry and its development in supporting the start-ups. Therefore, the innovation system can be used to describe scale-up support ecosystems and the status of its technology/ industry focus. For this study comparison of the different scale-up support ecosystems was required. Therefore, different types of Innovation System frameworks were considered for this study.

2.3.2 System dynamics model not useful for this study

System dynamics models are also commonly used to describe and gain insight into complex systems and networks, which is well-suited when looking into ecosystems which are really complex systems with a dense network. However, system dynamics models were not considered for this study, since the comparison of the scale-up support ecosystems requires a static framework which enables describing the status of the ecosystem and industry itself in general terms at one moment in time.

2.3.3 Innovation System frameworks

There are several frameworks to describe and study innovation systems. One can differentiate focused IS frameworks by geographical focus and by technological focus. However, in reality, all IS, be it scoped by geography or technology, interact and overlap (Hekkert, Suurs, Negro, Kuhlmann, & Smits, 2007).

Socio-technical systems framework

The socio-technical systems framework framework focuses on the interdependence between social and technical systems (Geels, 2004). It emphasizes the role of both technical and social aspects in innovation processes and recognizes the importance of social structures and values in shaping technological change. The socio-technical systems framework places emphasis on the social and cultural dimensions of technological innovation, rather than just focusing on the technological system. It acknowledges that technology is not just a technical matter, but is also influenced by social factors.

Diffusion of innovation framework

The diffusion of innovation framework focuses on how innovations are adopted and diffused throughout society (Rogers, 2010). It looks at the factors that influence the rate of adoption of innovations, such as the characteristics of the innovation, the characteristics of the adopters, and the communication channels used to spread information about the innovation. The diffusion of innovation framework is useful for understanding how and why certain innovations are adopted and diffused more quickly than others, but not useful for this study since the Valley of Death in industrial biotechnology already occurs before a product reaches the market. Therefore, the focus of this study is on the phase before adaptation making the diffusion of innovation framework not useful for this study on scale-up support of industrial biotechnology.

Sectoral innovation system framework

The Sectoral Innovation System (SIS) framework focuses on specific industries or sectors, examining the interactions between different actors and institutions within that sector. It includes suppliers, customers, competitors, and other stakeholders that contribute to innovation in the sector, as well as the policies and regulations that shape their interactions (Malerba, 2002). The sectoral focus allows for the assessment of industrial biotechnology as a sector. However, a technology perspective was considered more useful when investigating technical scale-up, the barriers and where scale-up support ecosystems can alleviate these barriers. For this approach the SIS framework was considered too general and not focused enough on the specific technology traits and its influencing conditions (Malerba, 2002).

Regional and national innovation system framework

The Regional Innovation System (RIS) framework focuses on a specific geographic region and examines the interactions between different actors and institutions within that region that contribute to innovation (Cooke, Uranga, & Etxebarria, 1998). It includes firms, universities, research organizations, government agencies, and other stakeholders within the region, as well as the policies and regulations that shape their interactions (Cooke et al., 1998). The regional innovation system framework could be useful to evaluate the different scale-up support ecosystems with their geographical proximity. In addition, innovation strengths and weaknesses of the ecosystems can be identified using the RIS framework. However, the focus of the study is more at the technology development and innovation side and what should be supported and how an ecosystem is organised to obtain this. However, the RIS framework could be used to check whether there is a link between a strong RIS (or certain profiles) and successful scale-up support. The National System Innovation (NSI) framework (Chung, 2002), is essentially a sum of all RIS's in a country. The NSI framework was considered a too broad scope to be able to catch the local effects of a scale-up support ecosystem.

Technological innovation system framework

A Technological innovation system includes all actors and factors around a particular technological innovation (Carlsson and stankiewicz, 1991). TIS go through lifecycle stages (Bergek, Jacobsson, Carlsson, Lindmark, & Rickne, 2008). At the beginning, when the fate of a TIS is uncertain, it is in the formation stage. After positive feedback loops of the TIS' functions fuel its development, it is in a growth stage. Once this mutual reinforcement. stagnates or declines, a TIS is in a maturity stage. Latest when negative feedback loops occur, the TIS is in a stage of decline.

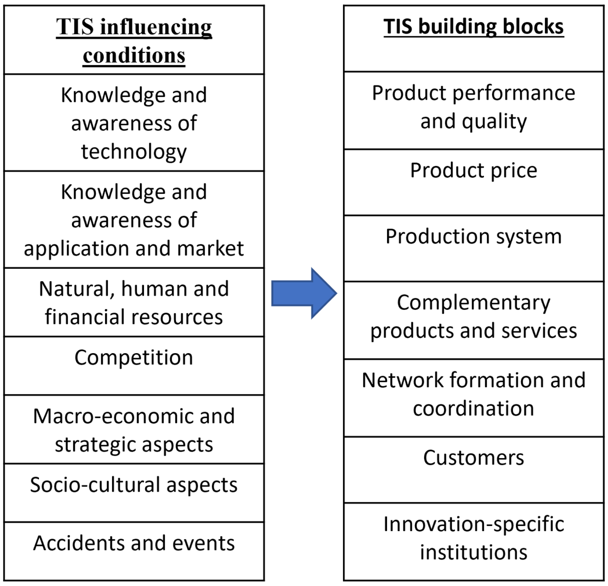

Figure 6: The Technological Innovation System (TIS) framework described by Ortt and Kamp (2022). The TIS framework has been build-up of 7 TIS building blocks and 7 TIS influencing conditions which can promote or hinder the formation of one or multiple TIS building blocks. All influencing conditions can affect several TIS building blocks which is visualised by the single arrow.

The Technological Innovation System (TIS) framework (Ortt & Kamp, 2022) identified essential actors and factors in socio-technical systems required for large-scale diffusion and is building upon the TIS functions of Bergek et al. (2008). Bergek et al. (2008) described three structural components (actors, networks and institutions) and seven functions of a technological innovation system (knowledge development, resource mobilisation, market formation, influence on the direction of search, legitimation, entrepreneurial experimentation and development of external economies). The adaptation of the TIS framework by Ortt and Kamp (2022) is focused on the innovation phase after invention but before successful market introduction. This is exactly the phase a process/ technology of industrial biotechnology is in when scaling up. Moreover, Ortt and Kamp (2022) aim to provide recommendations for policymakers on how to facilitate large-scale diffusion of radically new sustainable innovations, which is also consistent with industrial biotechnology.

The TIS framework (Ortt & Kamp, 2022) gives 7 very concrete TIS building blocks and 7 TIS influencing conditions which can help or hinder TIS building block formation. The TIS framework has been developed to assess the completeness of a TIS and evaluate the status of TIS influencing conditions to propose possible niche market introduction strategies for a technology Figure 6.

Why the Technological Innovation System framework?
The TIS framework (Ortt & Kamp, 2022) is an agnostic tool when looking at the researcher and research topic. The TIS can be adapted to different settings and uses, while still delivering insightful findings. The tool is simple and can be used across several research disciplines. Also, the framework can be used to both test theory and build theory. The TIS framework characteristics and the focus of this study are aligned on the following points:

- A scale-up support ecosystems can be seen as a type of Technological Innovation System
- TIS framework focuses on the phase after invention but before successful market introduction and (technical) scale-up of industrial biotechnology is before successful market introduction
- Can be adapted to different settings - scale-up support specific
- Can be applied in combination with a multiple case study

However, the TIS framework is limited for understanding the mechanism of evolution and change in TIS due to its static, one point in time, set-up. This was not considered to be a problem for this study, since comparison of different scale-up support ecosystems was to be done at one point in time on the status of the TIS building blocks and influencing conditions and not necessarily on the development of these ecosystems. The use of the TIS framework for the assessment and comparison of the scale-up support ecosystems and their industry allows for the translation of very context-dependent, specific and subjective case study information to a more systematic general assessment and comparison of the scale-up support ecosystems already grouping the specific aspects of the industry/ technology into specific building blocks and the scale-up support ecosystem effects into TIS influencing conditions. Therefore, the TIS framework (Ortt & Kamp, 2022) was used during this multiple case study to assess the status of the scale-up support ecosystems and their industry, as well as enable systematic comparison of the qualitative information on the scale-up support ecosystems.

3 Research Approach

The research approach depends on the nature of the research questions to be answered (see section 2.2). The answers to the research questions are context dependent and requires qualitative research that takes into account the context-dependent factors. The research questions were approached with a multiple embedded case study investigating different scale-up support ecosystems both in industrial biotechnology and in other industries which also have the four characteristics defined for industrial biotechnology (see section 1.1.2). This multiple embedded case study has been performed to determine the status and scale-up requirements of industrial biotechnology and similar industries, gain insight into the elements of scale-up support ecosystems, the best practices for successful scale-up support and look at the context dependent factors and its influences. This is needed to have the ability to determine the strategy that would be most beneficial for the development of the Planet B.io - Biotech Campus Delft scale-up support ecosystem. A case study protocol has been used for the set-up of the multiple case study.

During this study, a combination of ecosystem mapping and an extended TIS framework has been used to describe and evaluate the scale-up support ecosystems. Which is a new approach to ecosystems and its suitability to answer the research questions should be evaluated. For the research approach, first the ecosystem selection is described (see sections 3.1 & 3.2) and then an overview of the case study is presented and the six research phases with its outputs and corresponding research questions elaborated (see section 3.3).

3.1 Ecosystem Selection criteria

The industry or market focus of the scale-up support ecosystem has to adhere to the four characteristics of industrial biotechnology (see section 1.1.2) to be relevant for translation to industrial biotechnology.

Based on these characteristics other (more mature) industries could be comparable with industrial biotechnology (e.g., solar cell market (Hughes & Meckling, 2018), electric vehicle market (Hughes & Meckling, 2018), semiconductors (Ducrée, 2018), Robotics (**?**), Nuclear energy (Dixon, Todosow, Matthern, & Wigeland, 2018) and Chemical industry), but only the chemical industry was used for comparison, since that industry was the only one found that had a mature scale-up support ecosystem with a good reputation. This was required to study success stories from other (more mature) industries with characteristics similar to industrial biotechnology.

When scoping this toward the topic of interest "technical scale-up support", a requirement for selection of an scale-up support ecosystem (definition: section 2.2) is that besides business support and facilities should also contain technical scale-up support facilities, such as a piloting facility. Otherwise the ecosystem was not deemed relevant for this study. The other scale-up support ecosystem selection criteria were:

- Physical proximity within the ecosystem
  - This is the case for the Planet B.io - Biotech Campus Delft ecosystem and this provides (at least) two scale-up success factors (see Table 3:
    1. Pilot where you operate (Sanford et al., 2016)
    2. Shared piloting facilities (Biggs et al., 2021; Davison & Lievense, 2016)
- Ecosystem should be within the European Union
  - To prevent differences in terms of government, regulation and general macroeconomic conditions of the ecosystems, since this was considered a scale-up influencing factor (see Table 3) which would make ecosystem comparison more complex

- Ecosystem should be more mature than Planet B.io - Biotech Campus Delft and have a good reputation

3.2 Selection of the (technical) scale-up support ecosystems for the multiple case study

This resulted in three ecosystems studied besides Planet B.io - Biotech Campus Delft (see Table 4). The correspondence with the selection criteria has also been listed. In terms of industries, the Brightlands Chemelot scale-up support ecosystem focuses on sustainable chemistry, whereas Copenhagen and Toulouse White Biotechnology both focus on industrial biotechnology. The other ecosystems and facilities considered but not included in the case study are listed in Appendix B.7.

Table 4: Selection Criteria and Selected Scale-up Support Ecosystems for the Multiple Case Study.

Ecosystem *(founding year)*	***Industry***	***Location***	***Meet 4 industry characteristics*** (see section 1.1.2)	***Business support***	***Technical scale-up support***	***Physical proximity***
Planet B.io – Biotech Campus Delft (2020)	Industrial biotechnology	Delft, Zuid-Holland, NL	Yes	Yes	No, Bioprocess Pilot Facility (up to 4000 L) used to operate on campus until November 2022 when it went bankrupt	Proposition: all on Biotech Campus Delft
Brightlands Chemelot (2012)	Chemical conversion and process technology. Renewable/ biobased materials and sustainable chemistry	Geleen, Limburg, NL	Yes	Yes	Yes, multipurpose pilot plant up to 300 L batch, and other shared polymerisation plant	Yes
Toulouse White Biotechnology (2010)	Industrial biotechnology	Toulouse, FR	Yes	Yes	Yes, fermentation scale-up to 300 L. Also access to specialised equipment through partnerships (NMR, Mass spec.)	Yes
Copenhagen Industrial Biotechnology (no central organisation)	Industrial biotechnology	Copenhagen, DK	Yes	Yes	Yes, pre-pilot plant up to TRL 5 (about 300 L)	Yes

3.3 Overview of the multiple case study

These four ecosystems were studied during the embedded multiple case study in six distinguished research phases (see Figure 7).

3.3.1 Phase 1: Data collection through desk research and semi-structured interviews

The data collection methods used during this study are **desk research** and **semi-structured interviews** (see Figure 7). The first phase of the case study started off with desk research on the ecosystems, arranging and conducting interviews. The desk research resulted in initial ecosystem mapping (see phase 2: Ecosystem mapping), which was corrected and completed during the interviews.

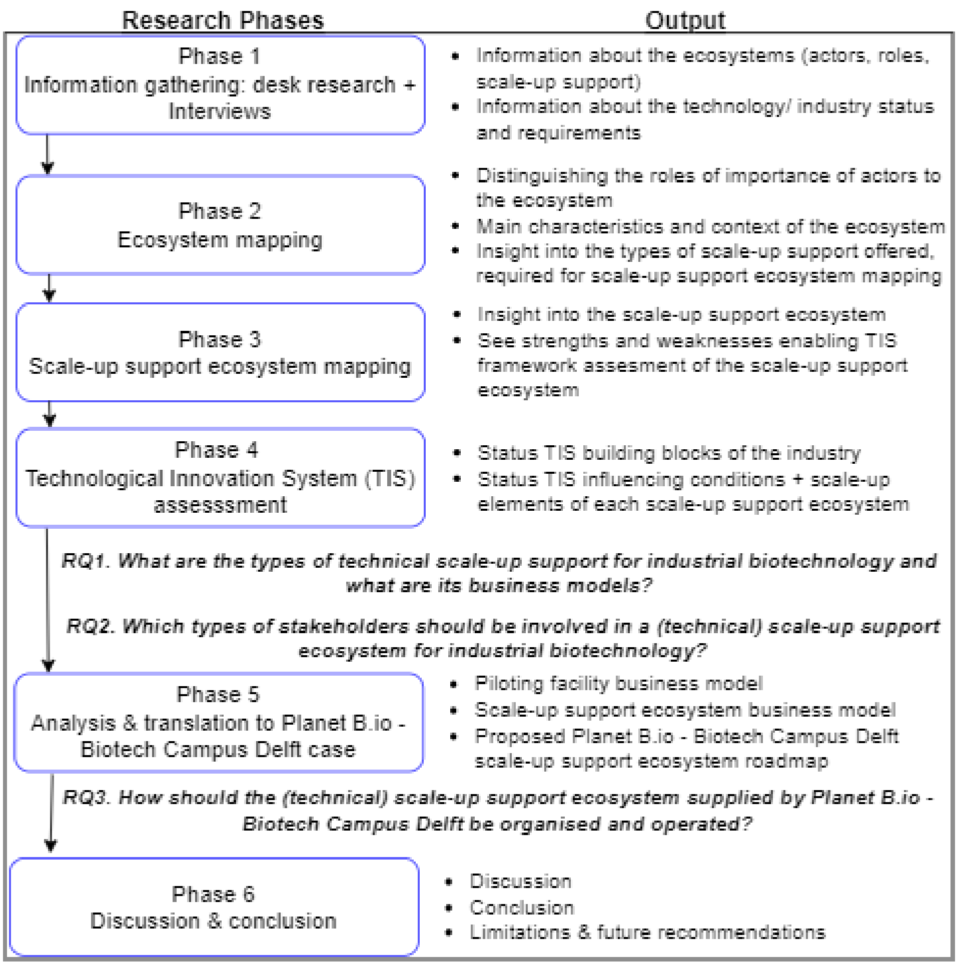

Figure 7: Overview of the study separated into six research phases. Per research phase, the research conducted, the research question it aims to answer, and the expected output are given.

For the interviews a snowballing approach and judgement sampling was used in combination with availability selection through contacts of Planet B.io to select one ecosystem expert, one technical scale-up expert and one start-up representative (e.g., CEO) per scale-up support ecosystem studied. These three types of actors were investigated to get a picture of the scale-up support ecosystem from different perspectives. The interviews were conducted in-person or via video call, since this offers advantages to clarify doubts and obtain non-verbal clues. However, downsides are that they are time-consuming, offer geographical limits, generate response bias and make confidentiality difficult. However, this was not considered to be hindering the interviews and answering the research questions. The semi-structured interviews were prepared with some structure and pre-defined questions and possible business models to evaluate (see Appendix B.2 & B.5), tailorable to new discoveries and the specific interviewee's expertise. Beforehand, the interviewee was always informed and asked to sign an informed consent form (see Appendix B.3, Figure 29). Afterwards, interviewees were asked for feedback and agreement with the interview transcript. The detailed case study data collection and interview process has been modelled as a swim lane diagram (see Appendix B.1, Figure 28).

Phase 1 was completed for the Planet B.io - Biotech Campus Delft, Brightlands Chemelot and Copenhagen industrial biotechnology ecosystem resulting in 8 interviews with 9 interviewees of which their respective scale-up support ecosystem and expertise are listed (see Appendix B.8, Table 17. However, for the Toulouse White Biotechnology (TWB) ecosystem, there was only one expert interview conducted with an expert who used to be involved on the board of advisors of TWB. This interview suggested that there is not really scale-up support present within this ecosystem. However, this should be investigated further, since the data on TWB was not sufficient to get to any real insights. Therefore, the TWB scale-up support ecosystem has not been included in the results, but the initial findings on the ecosystem have been included in Appendix D.

3.3.2 Phase 2 & 3: Data analysis. Ecosystem mapping and scale-up support ecosystem mapping, respectively

After the interview transcripts were corrected and feedback was provided by the interviewees' familiarization with the findings was performed, after which the findings were grouped into to form broader themes (e.g., scale-up requirements or ecosystem actors). For example, codes such as "founder", "partnership" and "key stakeholder" could be grouped together under the theme of "actors". These themes were analyzed by looking for patterns, connections, and relationships between them. This was done to identify key findings and draw conclusions about the case study.

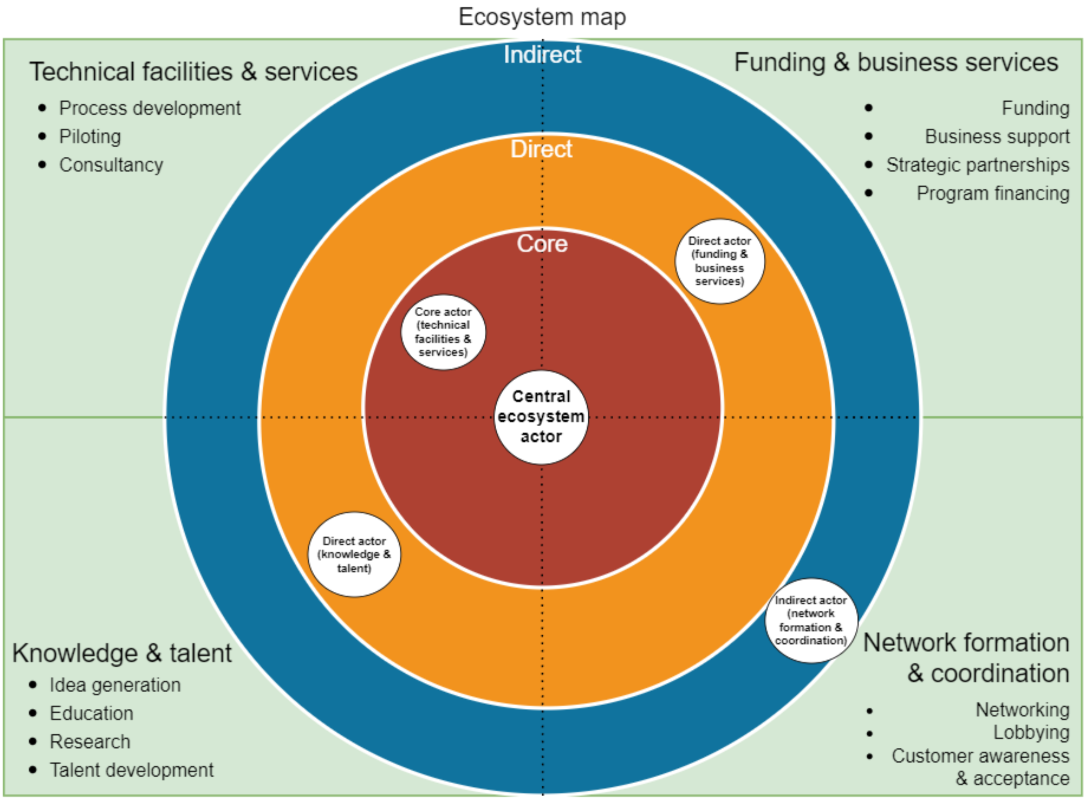

Figure 8: Example general ecosystem map used to map the different scale-up support ecosystems studied. The importance of the actors relative to the central ecosystem organisation are displayed as core, direct or indirect actors. Whereas, the type of role the actor plays has been distinguished into four quadrants: technical facilities & services, funding & business services, network formation & coordination, and knowledge & talent.

Firstly, the data analysis was summarised into general ecosystem maps (see Figure 7, phase 2) to create an overview and general characteristics of the ecosystems studied. The ecosystem maps were used to visualise the level of importance and roles of the ecosystem actors. For each ecosystem of the multiple case study (Biotech Campus Delft - Planet B.io Ecosystem, Brightlands Chemelot Ecosystem, Copenhagen Industrial Biotechnology Ecosystem), multiple ecosystem maps are made to represent the ecosystem from a different point-of-view and see the differences of the players, their importance, and their roles when looking at them from a general ecosystem perspective (see Figure 8) or a (technical) scale-up support perspective (see Figure 9). The ecosystem maps are visualised as an onion-layer figure. The ecosystem is divided into three layers, representing core, direct, and indirect contributors. These layers are further categorized into four quadrants, each representing a specific contribution type (see Figure 9) and based on the four types of scale-up success factors found (see section 2.2.2) and provide a listing of example services within each quadrant (see Figure 8 & Figure 9). If an ecosystem organisation is contributing across multiple quadrants, that organisation is being placed on the verge of both quadrants. The scale-up support ecosystem mapping was used to generate insight into the specific technical scale-up support offered and the importance of the different ecosystem actors for this, as well as identify scale-up support gaps. The ecosystem mapping helped to answer research question 1 and 2 (see Figure 7, phase 2 & 3).

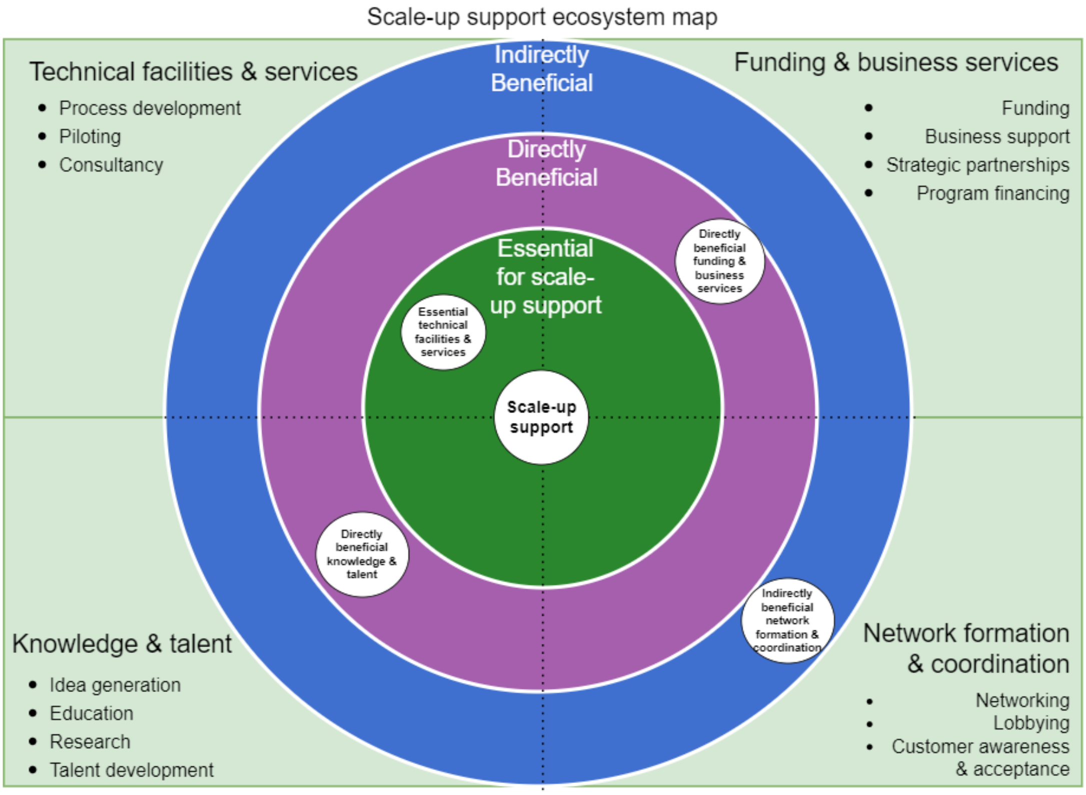

Figure 9: Example scale-up support ecosystem map used to map the different scale-up support ecosystems studied. The importance of the actors for the scale-up support ecosystem offered for the start-up are displayed as essential, directly beneficial or indirectly beneficial. Whereas, the type of role the actor plays has been distinguished into four quadrants: technical facilities & services, funding & business services, network formation & coordination, and knowledge & talent.

3.3.3 Phase 4. Technological Innovation System assessment of ecosystems to compare scale-up support ecosystems

During phase 4 of the case study, the data collected, and ecosystem maps are used to assess the status of the TIS of industrial biotechnology and sustainable chemistry as well as determine the status of the TIS influencing conditions per scale-up support ecosystem (see Figure 7, phase 4). The use of the TIS framework enables the translation of complex and context-dependent ecosystems to generally influencing conditions (see section 2.3). However, to be able to directly compare the scale-up support ecosystems, the four scale-up support elements used for the scale-up support ecosystem maps (see Figure 9) were added to the TIS framework as elements directly affecting the TIS influencing conditions (see Figure 10). These scale-up support elements have some overlap with the TIS influencing conditions, for example, technical facilities & services business support in the form of a shared piloting facility with equipment and operators can improve the TIS influencing conditions of knowledge and awareness of application and market, natural, human and financial resources, and (macroeconomic and) strategic aspects. However, to study the scale-up support ecosystem completeness and its effect on the TIS influencing conditions, the addition of the scale-up support elements to the TIS framework was considered most insightful. This enabled the assessment of the status and effect of the scale-up support ecosystems specifically and compare these. Moreover, the extended TIS framework helped identify the key elements required for a successful (technical) scale-up support ecosystem (in industrial biotechnology) and answer research question 3 (see Figure 7).

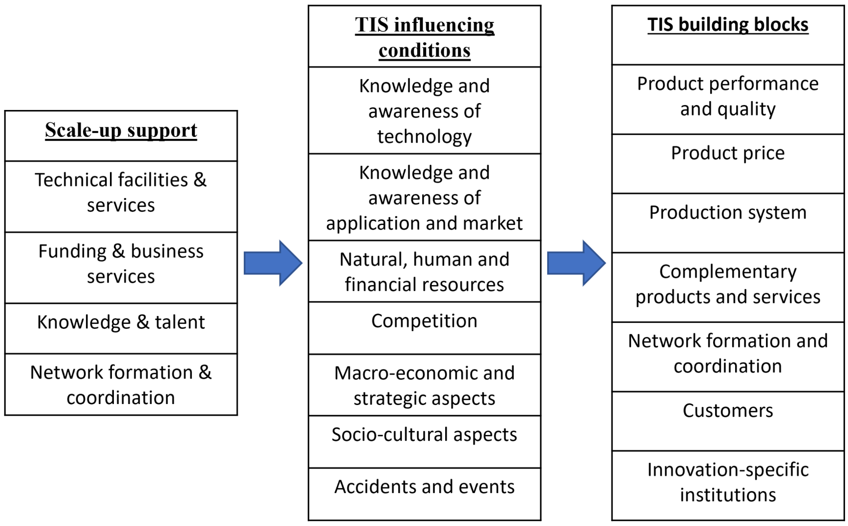

Figure 10: Extended Technological Innovation System (TIS) framework, based on the TIS framework described by Ortt and Kamp (2022). The TIS framework has been build-up of 7 TIS building blocks and 7 TIS influencing conditions which can promote or hinder the formation of one or multiple TIS building blocks. All influencing conditions can affect several TIS building blocks, which is visualised by the single arrow. The TIS framework has been extended with the hypothesised four scale-up support elements, which in turn positively or negatively influence the TIS influencing conditions.

3.3.4 Phase 5. Analysis & translation to Planet B.io - Biotech Campus Delft scale-up support ecosystem

All results of the ecosystem maps and TIS assessments, as well as the general scale-up requirements and business models, are translated to the Planet B.io - Biotech Campus Delft scale-up support ecosystem (see Figure 7, phase 5). This resulted in identified scale-up support gaps, a proposed scale-up support roadmap, and proposed business models through filling in the business model canvas, which was used to answer research question 3 (see Figure 7, phase 5).

3.3.5 Phase 6. Discussion & conclusions

During the final phase of the study (see Figure 7, phase 6), the results were discussed, conclusions were made, the limitations and recommendations for future research were presented.

4 Case Study Results

During this study the main objective was to find out how a (technical) scale-up support ecosystem for industrial biotechnology can best be organised and operated. Therefore, a multiple case study was conducted, through desk research and interviews, on the scale-up support ecosystems of Planet B.io - Biotech Campus Delft, Copenhagen and Brightlands Chemelot. These ecosystems were described using ecosystem mapping, general and from a scale-up support perspective specifically in combination with the Technological Innovation System (TIS) framework (Ortt & Kamp, 2022).

Based on the desk research and eight conducted interviews with nine interviewees (see Appendix B.8) the scale-up requirements of industrial biotechnology (see section 4.1.1 and sustainable chemistry (see section 4.1.2) were assessed and compared, resulting in general scale-up requirements grouped into four types of scale-up support (see section 4.1.4) which were used to assess the TIS scale-up support elements of each ecosystem. The TIS building blocks of industrial biotechnology and sustainable chemistry were assessed (see section 4.2 & 4.3, respectively). The ecosystems of Planet B.io - Biotech Campus Delft, Copenhagen and Brightlands Chemelot were mapped to get insight into the general characteristics of each ecosystem (see section 4.5, 4.6 & 4.7, respectively). Then, the ecosystems were mapped from a scale-up perspective and used to assess, per scale-up support ecosystem, the completeness and compatibility of the TIS scale-up support elements. In addition, the TIS influencing conditions created by each ecosystem were evaluated and linked to the TIS scale-up support status. Ending with a result synthesis comparing the scale-up support ecosystems (see section 4.8) and translating the findings to the Planet B.io - Biotech Campus Delft scale-up support ecosystem, proposing a business model (see section 4.10) and roadmap for ecosystem development (see section 4.9).

4.1 Scale-up requirements

4.1.1 Scale-up requirements of industrial biotechnology

The scale-up requirements of industrial biotechnology have been identified from a triangulation of the desk research and the interviews conducted on the Planet B.io - Biotech Campus Delft ecosystem and the Copenhagen industrial biotechnology ecosystem. The found scale-up requirements have been grouped into the four elements of scale-up found.

1. Technical services & facilities
    - Shared piloting facility
        - Up to TRL 5-6, 2000 L bioreactor scale. Beyond that scale-ups can get funding to build their own facility.
        - Fully serviced (i.e., generic equipment in place, operators, permits and utilities)
        - Should be a food grade and Genetically Modified Organism (GMO) piloting facility, to be able to test and validate the product and work with genetically modified organisms, respectively. Good Manufacturing Practices (GMP) is not required for a piloting facility, since selling is not required at pilot-scale.
        - Flexibility process set-up, able to use own equipment or change the set-up.
        - Equipment requirements:
            - Upstream processing: vessels and pre-culture equipment to get to the 2000L bioreactors.
            - Stirred bioreactors (steps of 10x until ≈2000 L, e.g., 50 L - 300 L - 2000 L)
            - Downstream processing:
                - Essential: centrifuges, microfiltration, ultrafiltration, dryer

        · Nice to have: chromatography (not always, more expensive products with higher purity), precipitation for proteins, distillation for small molecules.
    * Analysis: during the piloting but also analysis of product required at the facility or through partners. This enables process control and process improvement while piloting.
    * Generic: holding vessels, cooling, freezer, storage
- Lab to pilot- and industrial-scale technical support. Already thinking scale-up from the beginning (Davison & Lievense, 2016; Efara et al., 2019). This requires scale-up expertise to cost-effectively scale-up.
- Possibility to pilot (and produce) where the start-up operates (Sanford et al., 2016)
- Access to a flexible pool of experts (e.g., operators)

2. Funding & business services
    - Investment planning
    - Applying for grants, subsidies or funding
    - IP strategy, since this is important to raise funds for development and scale-up before having a product on the market

3. Network formation & coordination
    - Network of other industrial biotechnology start-ups and companies (e.g., substrate suppliers, equipment suppliers, VCs) to share knowledge and help each other
    - Large coordinated network (Henz et al., 2022; Vankan et al., 2020)

4. Knowledge & talent
    - Access to talent (Henz et al., 2022; Vankan et al., 2020) with the right expertise. The right talent should be developed through education, translational and scale-up activity.

These requirements have been compared to the scale-up requirements of sustainable chemistry found (see section 4.1.2

4.1.2 Scale-up requirements of sustainable chemistry

During the interviews the requirements of scaling up in sustainable chemistry were investigated. This provided the following insights.

Know your market
This has been discussed before and is also a specific example of already think scale-up from the beginning (Efara et al., 2019). If you know the market and the needs, you know what the minimum selling price should be and at what scale you need to produce to meet market demands. This also highlights the need for Lab to pilot- and industrial-scale technical support (see technical facilities & services, section 4.1.1)

Access to flexible piloting facilities including infrastructure, equipment, utilities and permits
Access to flexible piloting facilities is also crucial for scaling up processes in sustainable chemistry. Brightlands Chemelot offers a multipurpose pilot plant that fulfills this need by providing the necessary infrastructure, utilities, equipment, and permits. Start-ups benefit significantly from having these resources readily available, saving both time and money. A flexible facility

that accommodates various processes is essential to support the scaling needs of different start-ups.

Shared piloting facilities should at least be available until TRL 6
When a company reaches TRL 5 to 6, access to a shared facility for piloting becomes necessary. Beyond this stage (TRL 7 to 8), companies may consider and get the funding for building their own facility. Therefore, shared facilities play a vital role in supporting early-stage companies with their piloting requirements. This is exactly what was found for industrial biotechnology (see technical facilities & services, section 4.1.1), only the scale of the facility differs about a tenfold. Brightlands Chemelot Campus, for example, offers a 300 L multi-purpose pilot plant that serves as a shared facility for start-ups.

Fully serviced model of piloting facility including a flexible pool of operators
A fully serviced piloting facility requires knowledgeable operators to ensure smooth operations. Start-ups often lack the necessary operating knowledge and may face challenges in hiring and training operators, which can be time-consuming and expensive. To address this, it is essential to have a flexible pool of operators available for hire. This approach allows start-ups to keep fixed costs low, as they only pay for operator services when needed. Additionally, as start-ups progress and build their own plants, there is a growing need for scale-up expertise within their teams. This was also found for industrial biotechnology (see technical facilities & services and knowledge & talent, section 4.1.1).

Keeping the fixed costs for start-ups as low as possible
Minimizing fixed costs is a critical factor for start-ups. Hiring and maintaining a large workforce can strain finances and lead to delays. By tapping into a flexible pool of operators, start-ups can reduce fixed costs. Operators are only paid when there is a paying customer and plant operations are active. Utilizing existing facilities, operator pools, and partnering for research can also significantly improve the investment case for start-ups. This approach allows them to allocate resources efficiently and avoid the risk of hiring too many employees prematurely. This is seen as a general requirement for all start-ups, but a scale-up support need due to the amount of (temporary) human capital and equipment required for piloting (see technical facilities & services, section 4.1.1).

4.1.3 Comparison of industry characteristics of industrial biotechnology and sustainable chemistry and its effect on the scale-up requirements

When comparing industrial biotechnology and sustainable chemistry as well as the effects of the differences on the scale-up requirements comes forward that both industries, as expected, share the pre-defined characteristics (see Table 5). The shared characteristics and the commonalities in terms of scale-up requirements suggests that the scale-up requirements of these industries are, as hypothesised, to some extent, defined by these factors.

The comparison between industrial biotechnology and sustainable chemistry reveals differences in scale-up requirements. Notably, due to the usually more concentrated processes in sustainable chemistry the scale itself differs, with sustainable chemistry processes requiring about ten times smaller reactors compared to industrial biotechnology. The higher concentration of chemicals in sustainable chemistry processes allows for the production of equivalent amounts of product in a smaller volume, thus requiring a smaller reactor. For example, TRL 5-6 piloting in sustainable chemistry can be accomplished in a 300 L reactor, while industrial biotechnology typically necessitates a larger reactor of around 2000 L at the same stage of development. Furthermore, the chemical industry tends to exhibit slightly lower complexity, leading to lower capital expenses and fewer piloting steps for scaling up to industrial production. As a result, the technology development timeline for sustainable chemistry is generally shorter compared to industrial biotechnology.

Table 5: Comparison of the characteristics of Industrial Biotechnology and Sustainable Chemistry as well as its effect on the scale-up requirements.

Characteristics of **Industrial Biotechnology**	Findings for **Sustainable Chemistry** and its effect on the scale-up requirements
Long technology development time	Shorter technology development time: 1. Less complex processes, enabling larger scale-up steps
High capital expenses	Lower capital expenses: 1. Less piloting steps required 2. About 10x smaller volumes at industrial-scale production 3. Less complex processes, requiring less/cheaper equipment
Economies of scale	Similar economies of scale
Large scale production required due to bulk product with low profit margin	About 10x more concentrated processes, so 10x smaller process required to produce industrial-scale outputs

In summary, industrial biotechnology and sustainable chemistry share commonalities in terms of technology development time, capital investments, and economies of scale for scale-up. However, slight distinctions exist regarding reactor size, process complexity, and technology development duration. Understanding these differences is crucial for effectively scaling up processes and facilitating the transfer of insights between sustainable chemistry and industrial biotechnology.

4.1.4 Scale-up requirements as criteria for TIS assessment of completeness and compatibility of the scale-up (support) elements

Based on the scale-up requirements found for industrial biotechnology and sustainable chemistry (see section 4.1.1 & 4.1.2, respectively) and taking into account the slight differences in terms of characteristics and the effect of this on the scale-up requirements (see section 4.1.3) the scale-up requirements that should be offered through scale-up support were determined. These are used to assess the completeness and compatibility of the scale-up support ecosystem elements of each ecosystem studied.

1. Technical facilities & services
    (a) Piloting facility, modular and room for growth
    (b) Technical support lab- to pilot-scale and planning towards industrial-scale
    (c) Flexible pool of experts (e.g., operators)
2. Funding & business services
    (a) Availability of funding
    (b) IP strategy support

(c) Investment planning support

(d) Grants, subsidies and investment application support

3. Network formation & coordination

   (a) Network organisations present

   (b) Ecosystem completeness in terms of all roles present

4. Knowledge & talent

   (a) All education levels present within the ecosystem

   (b) Active translational activity

   (c) Knowledge & talent is aligned with scale-up requirements

Besides the scale-up requirements, the status of the industries could also be assessed with the findings of the desk research and interviews. This assessment was performed using the TIS framework building blocks (see section 4.2 & 4.3).

4.2 Industrial Biotechnology Technological Innovation System Building Blocks

When considering cultivated meat as an example, low TRL, radical innovation within the industrial biotechnology sector, we can refer to the evaluation of the cultured meat Technological Innovation System (TIS) in Europe conducted by Rabl (2020). This study, which involved desk research and 21 interviews, provides insights into the status of the seven factors within the TIS framework proposed by Bergek et al. (2008). The TIS assessment of Rabl (2020) combined with the conducted interviews during this study have lead to a TIS assessment of the cultivated meat TIS within the EU (Figure 11), which has been used for the industrial biotechnology TIS during this study. Cultivated meat is representative for industrial biotechnology due to the large-scale requirements, the technical difficulties in terms of development and scale-up, as well as the societal and regulation challenges which is representative for all GMO food products. However, when using industrial biotechnology to produce bulk chemicals the regulation and societal challenges are a lot less hindering. Also, the ethical concerns and customer acceptance is a more difficult issue for cultivated meat than for non-food or non-GMO products (e.g., bulk chemicals or biofuels but also insulin). It should be kept in mind that cultivated meat scale-up is at the difficult side of the industrial biotechnology spectrum in terms of regulation and customer acceptance.

4.2.1 Partially Complete and/or Compatible Product Performance and Quality

According to Rabl (2020), the challenge of creating structured 3D meat remains a long-term objective, particularly concerning product formulation. This indicates the need for further development of the product performance and quality. Attaining the long-term objective of formulating structured 3D meat will contribute to enhancing the completeness and compatibility of this TIS building block. Furthermore, the COO of Meatable mentioned that Meatable is currently in the process of conducting initial tastings in Singapore. This indicates that the product performance and quality have reached a stage where they can be showcased and tested with customers. However, there is still room for improvement in terms of the product's quality and performance. As a result, the TIS building block of product performance and quality is considered partially compatible (Figure 11).

4.2.2 Partially Complete Production System and Incompatible Product Price

Cultivated meat start-ups are currently in the advanced research and development (R&D) phase, with the pilot plant representing the next step (Rabl, 2020). This is also the current status for Meatable. The primary goal of scaling up production is cost reduction and benefiting from the economies-of-scale (Rabl, 2020). The focus of the industry is on developing an efficient production system (Rabl, 2020). This need for development of the production system in terms of efficiency was also stated by interviewee 8, COO of Meatable. The progress made in scaling up production, reducing costs (of for example cell culture media), and increasing efficiency suggests advancements in the production system. However, further improvements are required to optimize the production system for cultivated meat and achieve the desired cost-efficiency goals. Therefore, the production system building block is considered partially complete (Figure 11).

The production system and the product price are interconnected for industrial biotechnology. This connection arises from the need to compete with the efficient and cheap petrochemical or agricultural alternatives already present in the market. The product price TIS building block of industrial biotechnology is currently evaluated as incompatible to get to market (Figure 11). The cost reductions achieved in the production system will contribute to addressing the incompatible nature of the product price TIS building block (Figure 11) by bringing the production costs closer to the market price (Rabl, 2020).

4.2.3 Incomplete Complementary Products and Services

Development of the supply chain is described by Rabl (2020) as a main focus point for the cultivated meat industry. Moreover, Rabl (2020) concluded that cultivated meat will likely be produced locally, close to the inputs and relatively close to the consumer. This might be different from bulk chemicals production from industrial biotechnology, since businesses will be the main consumers of such bulk chemicals. There is a need for several complementary products and services, e.g., regulatory support, framework (especially for food) of product knowledge and product conversion support. Additionally, having partners who can provide valuable insights and expertise and offer this as a service. In addition, because one of the main costs is the media, you need to have players in the ecosystem which are focusing on actually delivering more cost effective solutions when it comes to ingredients which go into the media. These (cheaper) media components can be considered as complementary products in terms of the TIS, to help decrease the media costs for cultivated meat, but also for other processes in industrial biotechnology. There is a lack of services as well as (cost-effective) suppliers for industrial biotechnology. Therefore, the complementary products and services in the TIS of industrial biotechnology are considered incomplete (Figure 11).

4.2.4 Partially Complete Network Formation and Coordination

Another part of development of the supply chain is connected to network formation and coordination (Rabl, 2020). Cultivated meat start-ups have limited work division among them, but there are initial signs of work division are starting to emerge (Rabl, 2020). Also, the COO of Meatable, as previously described for the complementary products and services (see section 4.2.3), stated the need for an ecosystem with partners that provide complementary products and services, such as cheap media components. The emergence of initial signs of work division indicates some progress in this building block. However, further development is needed to establish more robust and effective network formations and coordination within the cultivated meat industry, and industrial biotechnology in general. Therefore, the TIS building block of network formation and coordination is considered partially complete (Figure 11).

4.2.5 Incomplete or Incompatible Customers

The need for customers in a technological innovation system has, among others, been described by (Ortt & Kamp, 2022). Additionally, during the interviews came forward that there needs to be market where you pilot otherwise there is no use for the product. This is important and links the availability of customers, for cultivated meat at least, to the innovation-specific institutions. Since Europe does not even allow for tastings of cultivated meat. On top of that, consumption of GMO food is even more strictly prohibited in the EU at the moment. Therefore, companies like Meatable move to Singapore and the US to do their piloting and tastings (i.e., product testing and development), since there the regulations allow for tasting of the product and are also moving towards possible consumption of cultivated meat, as an GMO product. In terms of customers, Europe is expected to be the slowest. Therefore, when evaluating the TIS for industrial biotechnology within the EU, there are no customers possible (yet). Whereas for other, not for human consumption, products of industrial biotechnology (e.g., biofuels, bioplastics) the market is already there or partially there. Based on this, the customers TIS building block is considered incomplete for industrial biotechnology products like cultivated meat and partially complete for non-food products (Figure 11).

4.2.6 Incomplete and Incompatible Innovation-Specific Institutions

Cultivated meat companies, like Meatable are moving towards Singapore and the US due to the lack of legislation or prohibited testing or consumption of GMO (or GMO derived) products within the EU. Therefore, as already described in section 4.2.5, at the moment there is no market for these products in the EU due to the legislation and regulatory constraints. Interviewee 8, COO of Meatable also described the bureaucracy in Europe as a major limiting factor. In addition, Mampuys and Brom (2018) already described the EU legislation for biotechnology as lagging behind with an absence of regulatory decision making. Which has led to the current regulatory limbo and innovation standstill in the EU. For other industrial biotechnology processes these EU innovation-specific institutions might be less restrictive. However, in general these are not guiding and enabling biotechnology. Therefore, the innovation-specific institutions for industrial biotechnology in the EU is considered incomplete and incompatible (Figure 11).

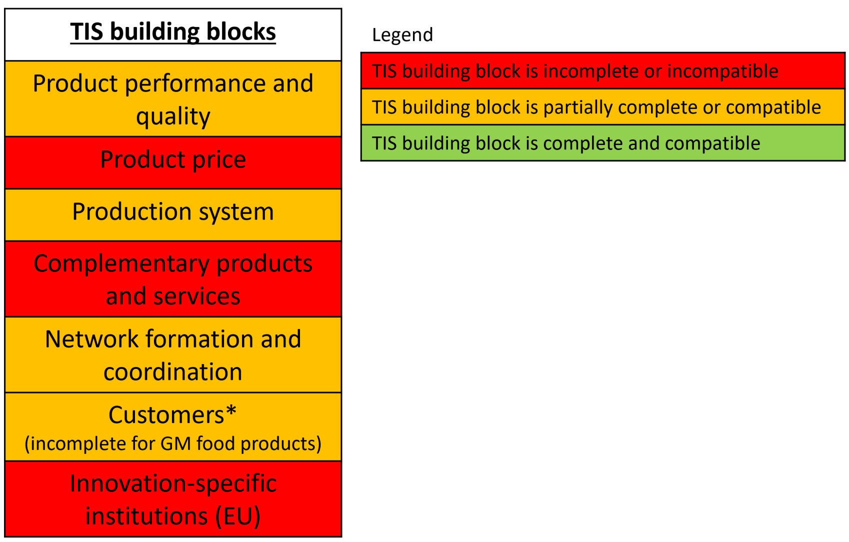

Figure 11: Technological Innovation System (TIS) framework (Ortt & Kamp, 2022) building blocks assessment for industrial biotechnology, using cultivated meat as an example, low TRL, radical innovation. Showing the immaturaty of industrial biotechnology through the lack of complete and compatible TIS building blocks.

4.2.7 Characteristics Technological Innovation System of Industrial Biotechnology within the European Union

Thus, when evaluating cultivated meat as a disruptive, low TRL, technology of industrial biotechnology, the TIS of industrial biotechnology does not have any complete building blocks (Figure 11). The partially complete or partially compatible building blocks are the product performance and quality, the production system, network formation and coordination, and the customers (for non-food GMO, or non-GMO products). The incomplete or incompatible building blocks are the product price, complementary products and services, customers (for food GMO products), and the innovation-specific institutions. It is interesting that the product price is directly reliant on the completeness and efficiency of the production system, on the availability of complementary products and services, as well as the network formation and coordination. Whereas, the customers as a building block is directly affected by the innovation-specific institutions when these institutions hinder market formation, like with cultivated meat. During this study, this TIS of industrial biotechnology demonstrates the immaturity of the TIS of industrial biotechnology and the need for the different scale-up requirements found (see section 4.1). The TIS building blocks of industrial biotechnology has been used to evaluate and see the value of scale-up support ecosystems to aid the development of the TIS building blocks (and thus the successful scale-up and commercialisation) of industrial biotechnology. First, the TIS building blocks of industrial biotechnology were compared with the TIS building blocks of sustainable chemistry (see section 4.3) to determine the differences in context between scale-up support ecosystems in industrial biotechnology (Planet B.io - Biotech Campus Delft and Copenhagen) and sustainable chemistry (Brightlands Chemelot).

4.3 Technology Innovation System Building Blocks of Sustainable Chemistry & Materials

To specify the context of the Brightlands Chemelot scale-up support ecosystem, the TIS building blocks of sustainable chemistry were also assessed (Figure 12). This shows a relatively complete TIS looking at the TIS building blocks, this indicates that sustainable chemistry is indeed emerging from an already developed industry, traditional (petro)chemical chemistry. For sustainable chemistry, the complementary products and services, network formation and coordination, customers and innovation-specific institutions are already all complete and compatible with sustainable chemistry (Figure 12). The disparities between traditional (petro)chemical chemistry and sustainable chemistry, including differences in substrates, products, and production systems, necessitate the customization and piloting of the production system for sustainable chemistry processes. Additionally, similar to industrial biotechnology, the performance, and quality of sustainable chemistry products require testing. Therefore, both the product performance and quality and the production system TIS building blocks of sustainable chemistry are considered partially complete or compatible. Moreover, given the competition between sustainable chemistry products and conventional, optimized (petro)chemical production methods, it is essential for the price of sustainable chemistry products to be competitive. Achieving this requires process optimization and additional advantages over traditional products to ensure compatibility with market prices. Therefore, the product price building block is also considered partially compatible with the current market prices.

4.4 Comparison Technological Innovation System Building Blocks of Industrial Biotechnology and Sustainable Chemistry

When comparing the TIS building blocks of industrial biotechnology (see Figure 11) with sustainable chemistry (see Figure 12) comes forward that the TIS of sustainable chemistry is more

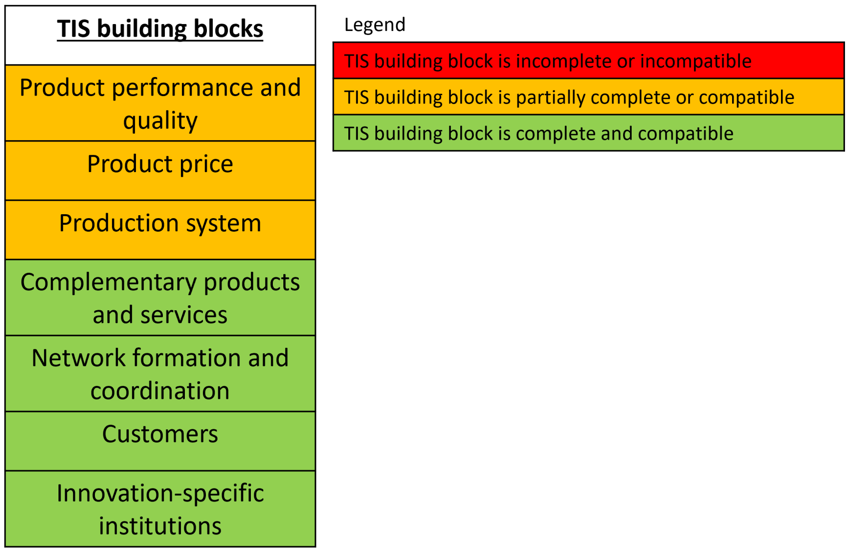

Figure 12: Technological Innovation System (TIS) Building Blocks of Sustainable Chemistry. Showing relative maturity of the industry, with four of the seven buildings blocks considered as complete and compatible.

mature than industrial biotechnology. However, both are similar in terms of status and requirements of the TIS building blocks:

- production system needs to be tailored and piloted
- Product performance and quality requires testing
- Product price competition with the traditional and optimized (petro)chemical way of producing

Thus, sustainable chemistry and industrial biotechnology share similar characteristics, only these are slightly less extreme for sustainable chemistry. In addition, the TIS building blocks of sustainable chemistry are more complete and compatible, demonstrating seniority over industrial biotechnology. However, still the status of the TIS building blocks indicating the need for piloting and scale-up support (product performance and quality, product price and production system) are similar. Thus, indicating the similarities in terms of scale-up and scale-up support requirements. Now, the findings on the scale-up support ecosystems of Planet B.io - Biotech Campus Delft ecosystem (see section 4.5), Copenhagen industrial biotechnology ecosystem (see section 4.6), and the Brightlands Chemelot ecosystem (see section 4.7) are presented also identifying the TIS influencing conditions created per specific ecosystem.

4.5 Case 1 - Planet B.io at the Biotech Campus Delft - Industrial Biotechnology

4.5.1 Introduction

Planet B.io and the Biotech Campus Delft have already been introduced as a scale-up support ecosystem focusing on industrial biotechnology (see section 1.6). The desk research and the perspectives of interviewee 1, 2 & 8 (see Appendix B.8) have provided insights into the Planet B.io - Biotech Campus Delft ecosystem. Planet B.io is a landlord and network organization coordinating the scale-up support ecosystem based at the Biotech Campus Delft. It has been founded as a triple-helix organisation by DSM as corporation, TU Delft as university, and the municipality of Delft, InnovationQuarter and province of South-Holland as governmental organisations, whereas the Biotech Campus Delft is founded by DSM and is the owner of the campus (i.e., ground, facilities and permits) where DSM, Planet B.io and its start-ups are based, and which is close to the TU Delft, thus there is physical proximity between the ecosystem actors. The ecosystem is build by and around the central ecosystem organisation Planet B.io. The ecosystem of Planet B.io - Biotech Campus Delft was investigated and the general ecosystem and its actors have been mapped (see section 4.5.2).

4.5.2 Planet B.io - Biotech Campus Delft Ecosystem

An overview of the planet B.io – Biotech Campus Delft ecosystem was created through ecosystem mapping (see Figure 13). This showed the actors, the aspect of the ecosystem they contribute to in terms of scale-up element and their relative importance to the ecosystem (core, direct or indirect). The ecosystem map shows a relatively small network for an ecosystem (see Figure 13). Still, all four scale-up elements seem to be, to some extent, present within the ecosystem.

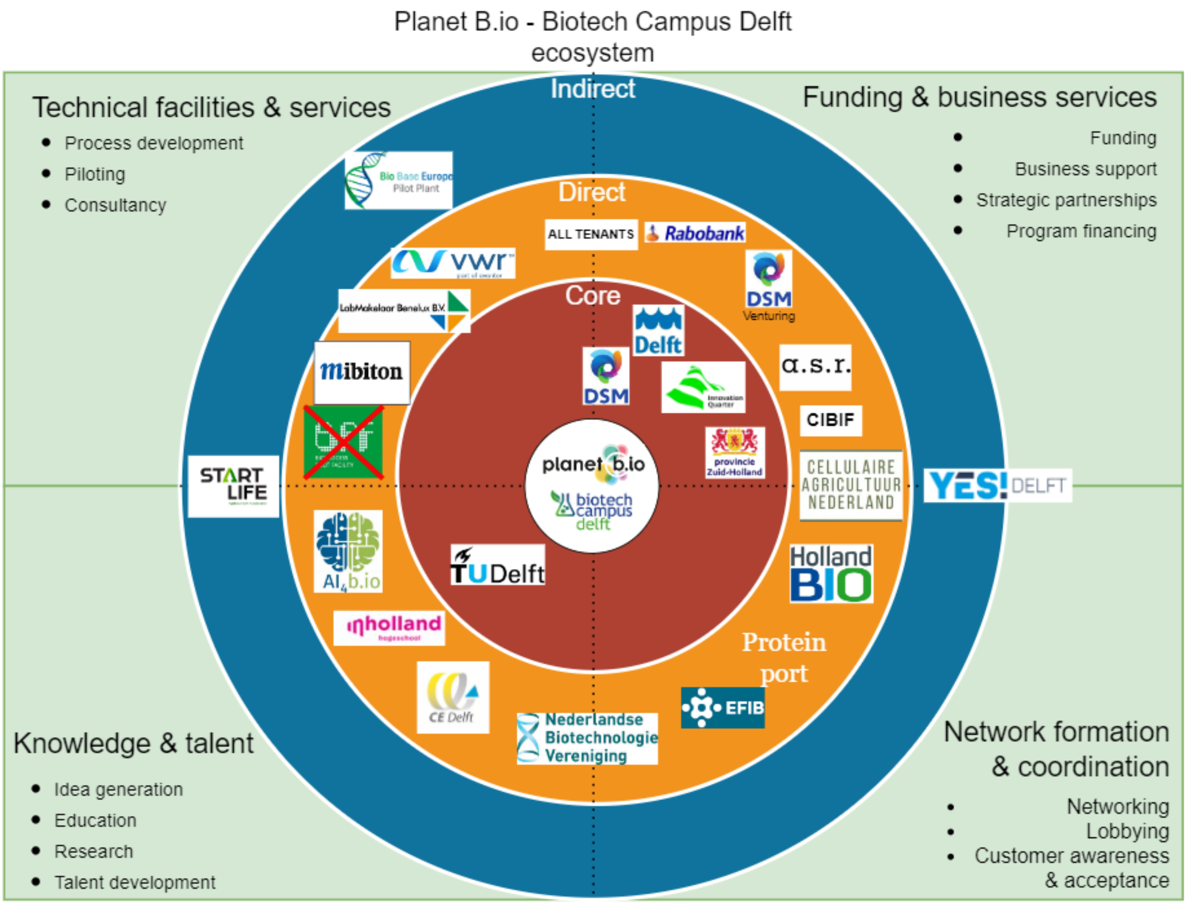

Figure 13: A visual representation of the Planet B.io - Biotech Campus Delft ecosystem, depicted as an onion layer figure. The ecosystem is divided into three layers, representing core, direct, and indirect contributors. These layers are further categorized into four quadrants, each representing a specific contribution type. The quadrants encompass technical facilities & services, funding & business services, network formation & coordination, and knowledge & talent. The figure provides a listing of the services within each quadrant.

Ecosystem core

All founders of Planet B.io are considered core actors of its ecosystem. Planet B.io and the Biotech Campus Delft are really reliant on DSM and its funding as the only core corporation of the ecosystem, whereas government organisations supply the other core part of the funding. There are no core technical facilities & services when looking at the general ecosystem. This also seems to be the case for the network formation & coordination, however Planet B.io is itself a network organisation, so there is a core network organisation present within the ecosystem. Moreover, TU Delft provides knowledge & talent to the ecosystem through education and research activities. They also have the Engineering Doctorates program, which can supply talent as interns to the start-ups.

Technical facilities & services
Planet B.io offers offices and labs for a rental fee and connect start-ups to the network as its start/scale-up supporting activities. An important part of the value proposition from Planet B.io - Biotech Campus Delft ecosystem was the Bioprocess Pilot Facility (BPF), but that went bankrupt in November 2022. This offered piloting within 100 m from the labs and offices where the start-ups operate, which was described as a scale-up success factor (see Table 3).

Funding & business services
DSM (and ASR) are the investors on the campus, so there is not a lot of funding within the direct network, no VCs for example. ASR is a new actor within the ecosystem and brings in a lot of funding, 500 million in the next 30 years, for the Biotech Campus Delft. ASR is an insurance fund, so interested in real estate and not necessarily funding start- and scale-ups themselves. The co-founder of Planet B.io and regional development fund InnovationQuarter does invest in start-ups and funds facilities if they contribute to the development of the region. Thus, will also fund scale-up support facilities like a pilot plant. Within the region, there is also the Capricorn Industrial BIotech Fund (CIBIF). CIBIF has DSM and InnovationQuarter as core investors and is a fund investing in early-stage industrial biotechnology start-ups, like DSM venturing. This can provide (part of the) money for R&D and scale-up activities of the start-ups.

Network formation & coordination
Compared to other ecosystems studied there are relatively much network organisations within/ connected to the Planet B.io - Biotech Campus Delft ecosystem, so this is the quadrant that appears to be most "complete" for the ecosystem standards.

Knowledge & talent
Besides, TU Delft, CE Delft is a direct partner of Planet B.io. CE Delft is a research organization which can be used by start-ups to perform research for them, the same holds for the Engineering Doctorates from the TU Delft, these could be used by start-ups and other companies to work on a project. AI_4BIO is a research consortium across the TU Delft and connected to Planet B.io and the Biotech Campus Delft, this helps for talent and knowledge development, but also somewhat for the networking of Planet B.io across different TU Delft faculties. Planet B.io has also started a collaboration with InHolland to offer on-campus education, which would contribute to the knowledge & talent of the ecosystem.

4.5.3 Planet B.io - Biotech Campus Delft scale-up support ecosystem and TIS assessment

To distinguish the disparities between the overall ecosystem and the scale-up support ecosystem, it is crucial to examine the roles and significance of different actors in providing scale-up support and relating this to the scale-up support requirements. Therefore, the Planet B.io - Biotech Campus Delft ecosystem was also mapped specifically from a scale-up support perspective (see Figure 14).

There is a scale-up support gap in terms of technical facilities & services
When looking at scale-up support there appears to be a gap in terms of technical facilities

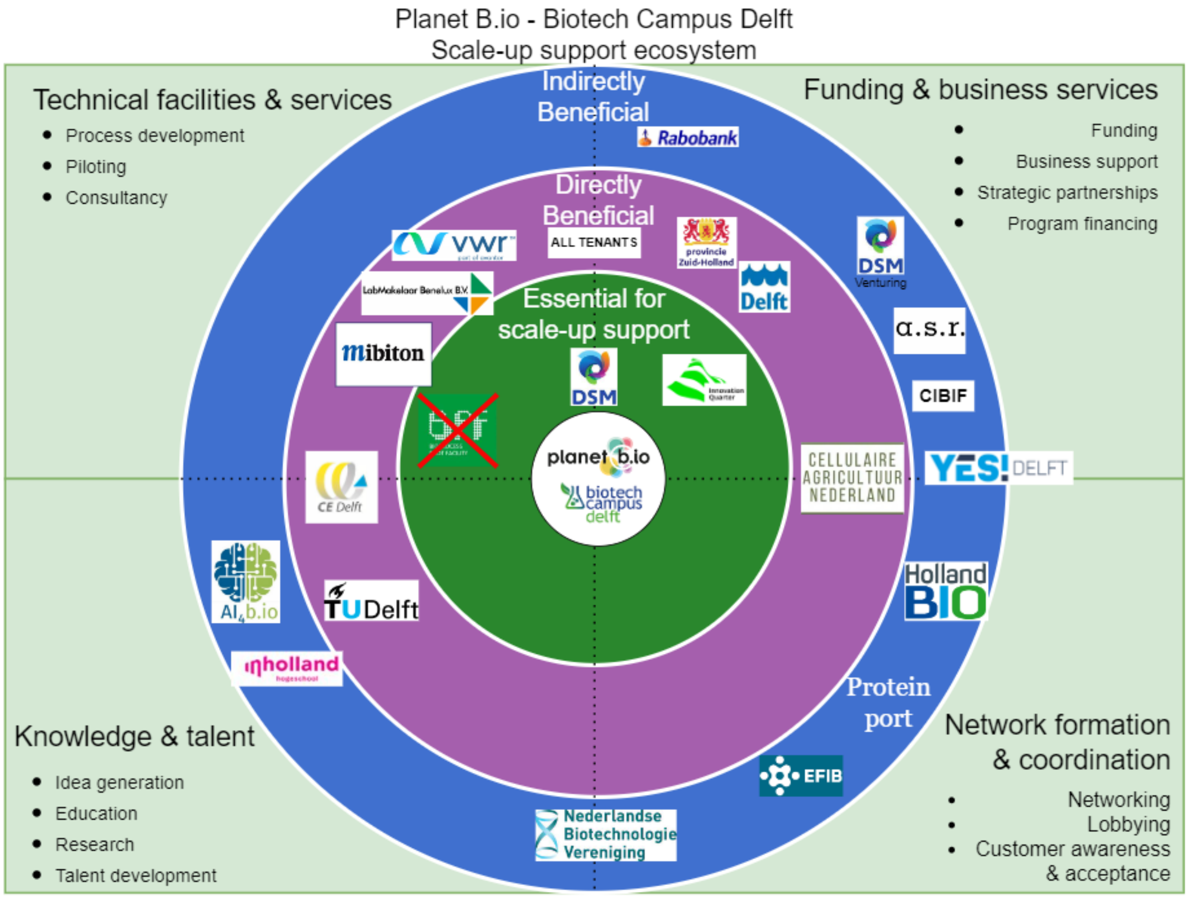

Figure 14: A visual representation of the Planet B.io - Biotech Campus Delft ecosystem from a scale-up support perspective, depicted as an onion layer figure. The ecosystem is divided into three layers, representing core, direct, and indirect contributors. These layers are further categorized into four quadrants, each representing a specific contribution type. The quadrants encompass technical facilities & services, funding & business services, network formation & coordination, and knowledge & talent. The figure provides a listing of the services within each quadrant.

& services offered since the bankruptcy of the BPF, which is considered an essential part of scale-up support (see Figure 14, 2a). The BPF was a fully-serviced scale-up facility offering piloting up to 4000 L (bioreactor), TRL 6, which is a scale-up support requirement (see section 4.1.4, 2a), but was not that flexible in terms of unit operations and configuring a tailored pilot process (see section 4.1.4, 2a). Also, for the facility itself there was not a flexible operator pool (see section 4.1.4, 2c), causing high recurring salary costs for the facility. However, in terms of technical facilities & services there is a supply of rental or refurbished lab equipment, but no lab to scale-up service or flexible human capital pool present, besides contract R&D. These were defined as scale-up support requirements (see section 4.1.4, 1b & c). Therefore, there seems to be a gap of scale-up support technical facilities & services, in terms of shared equipment, a piloting facility to scale-up beyond TRL5-6 ($\approx$ 3000 L bioreactor), and access to a pool of flexible operators/ technical workforce. Therefore, the TIS scale-up support element of technical facilities & services was considered incomplete, since the bankruptcy of the BPF (see Figure 15). Before that, it was considered partially complete.

Funding & business services for scale-up support are incomplete

Funding and business is characterized by government institutions and DSM, besides that there are no other sources of funding within the ecosystem that are applicable to scale-up support specifically (see section 4.1.4, 2a). Moreover, in terms of business services there are no parties within the scale-up support ecosystem that support with investment planning, IP strategy or applying for grants, subsidies and investments, however Planet B.io does apply for grants themselves which are also beneficial for the start-ups (see section 4.1.4, 2b, c & d). Therefore, the funding & business services scale-up support element was considered incomplete (see Figure 15).

Network formation & coordination scale-up support element is partially complete
The network formation & coordination is having a lot of indirect actors when it comes to (technical) scale-up support (see section 4.1.4, 3a), having more scale-up support specific network formation & coordination could help the ecosystem by positively influencing the development of the other quadrants of the ecosystem (see section 4.1.4, 3b). This could for example increase the availability of funding for scale-up support itself. Therefore, based on the scale-up support requirements (see section 4.1.4), the network formation & coordination element was considered partially complete (see Figure 15).

Knowledge & talent scale-up support element lacks scale-up specific knowledge and talent
Besides the knowledge & talent discussed in section 4.5.2, there is not a lot of education and research that is relevant for technical scale-up and supporting technical scale-up. Additional education (of all levels) and research into this specific part as well as aligning education with the scale-up knowledge and talent requirements would provide access to additional talent with the right expertise to aid the development of the industrial biotechnology TIS (see section 4.1.4, 4a & c). Also, the translational activity of the TU Delft could be increased to help bridge the gap between academia and industry (see section 4.1.4, 4b). Therefore, considering the scale-up requirements (see section 4.1.4) the knowledge & talent scale-up support element was considered incomplete (see Figure 15).

4.5.4 Planet B.io - Biotech Campus Delft scale-up support ecosystem appears to be immature

The TIS scale-up support elements assessment (see Figure 15) demonstrates that, based on the identified scale-up requirements (see section 4.1.4), the scale-up support ecosystem of Planet B.io - Biotech Campus Delft is immature and could especially be improved in terms of technical facilities & services, funding & business services, and knowledge & talent. Whereas, the network formation & coordination is the most developed element of this scale-up support ecosystem. The immaturity of the Planet B.io - Biotech Campus Delft scale-up support ecosystem is not surprising, since Planet B.io has only been founded in 2020, which is also when the Biotech Campus Delft started operating as an open innovation ecosystem for industrial biotechnology.

The influencing factors of the industrial biotechnology TIS were assessed based on the status of the scale-up support ecosystem of the Planet B.io – Biotech Campus Delft ecosystem (see section 4.5.5). These TIS assessments were used to compare the scale-up support ecosystems studied.

4.5.5 Scale-up support ecosystem specific Technological Innovation System influencing conditions

The scale-up support elements of the Planet B.io influence the local scale-up conditions of the start-ups within that ecosystem. The status of the industrial biotechnology TIS influencing conditions at the Planet B.io - Biotech Campus Delft ecosystem also showed no fully complete and compatible influencing conditions (see Figure 16).

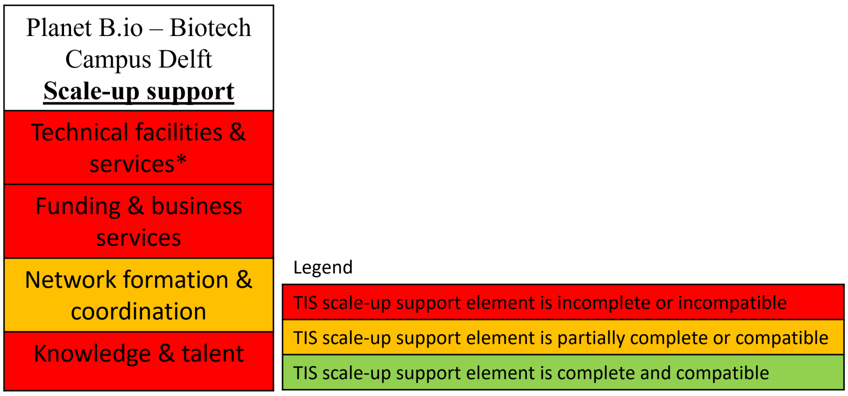

Figure 15: The assessed status of the Technological Innovation System (TIS) scale-up support elements of the Planet B.io - Biotech Campus Delft ecosystem.

Knowledge and awareness of technology is partially complete and partially compatible

Within the ecosystem there are some knowledge institutions, and one large corporation, which supply some knowledge and awareness of technology to the ecosystem. However, this is not considered complete, since there is still room for growth in terms of actors with specified knowledge and services related to supplying this knowledge. Also, the knowledge institutions their research and education are not well aligned with the requirements of industrial biotechnology in terms of technical scale-up and technical scale-up support (and necessary skills, such as operators). Therefore, knowledge and awareness of technology is considered partially complete and partially compatible (see Figure 16).

Knowledge and awareness of application and market is incomplete

Knowledge and awareness of application and market, requires practical experience with scaling up, having the end in mind, and successfully bringing a product to market. Most start-ups in industrial biotechnology are struggling with the market-fit and defining the required process and product performance and application. Scale-up support is required, that tests the underlying assumptions made, the market analysis performed and guides them in this process of defining the process and product requirements for successful market entry. Currently, this is not formalized as support within the ecosystem, while there are actors, like DSM, that have the expertise for this. Therefore, the knowledge and awareness of application and market is considered incomplete as an TIS influencing condition (see Figure 16).

Natural, human and financial resources are lacking, thus incomplete

Natural, human and financial resources are also considered incomplete TIS influencing conditions (see Figure 16), since there are some suppliers of, for example substrates or equipment, but there are currently no shared piloting facilities or equipment at the Biotech Campus Delft. Additionally, there is relevant talent educated at the TU Delft and InHolland, but there is a lack of scale-up expertise and relevant talent for this phase of the technology development, besides the availability of this expertise and talent within the ecosystem is limited. Also, there is some funding available but funding of scale-up and its support specifically is not abundant with almost only government derived funding, while scale-up in industrial biotechnology is very capital intensive and government funding requires corporate matching. Within this ecosystem, this matching is then totally dependent on DSM and its preparedness to invest in scale-up support, which does not have an attractive business model and likely requires recurring investments to cover the running costs. Therefore, additional parties with funds are required to make the available funding at least partially complete.

Competition is currently too strong, thus incompatible
As discussed before (see section 4.2), the competition of industrial biotechnology is very efficient and optimized, producing bulk products with small profit margins. This is far from the status of industrial biotechnology, thus incompatible for direct competition (see Figure 16). Its compatibility depends partly on policy and regulations regarding sustainability, since industrial biotechnology offers promising sustainable alternatives to the traditional (petro)chemical or agricultural products.

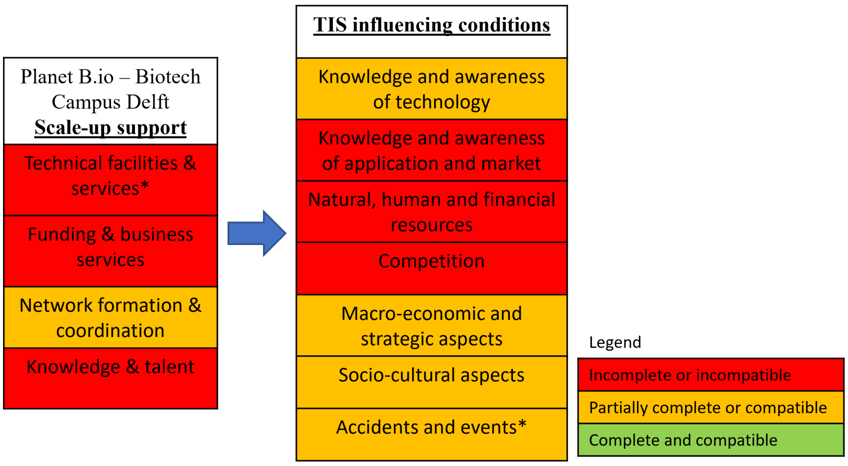

Figure 16: The scale-up support elements of the Planet B.io - Biotech Campus Delft ecosystem and its resulting ecosystem-specific Technological Innovation System (TIS) influencing conditions.

Macroeconomic and strategic aspects are partially compatible
This also links to the macroeconomic and strategic aspects. Currently, traditional agriculture and the fossil fuel industry are heavily subsidised, which hinders the development of industrial biotechnology, giving the unsustainable competition an even bigger competitive edge. However, rising concerns about the subsidies for traditional agriculture and the fossil fuel industry could shift this advantage, if this steers policy towards promoting and subsidising sustainable alternatives, like the cellular agriculture fund (see Figure 14). Furthermore, the recent macroeconomic conditions with low interest rates and high inflation were favourable in terms of investing climate. However, high energy and resource prices hinder the development of industrial biotechnology, which is relatively energy and resource intensive, since it is still in the development phase. In the long term, industrial biotechnology could benefit from these conditions, especially if the process valorises waste streams. In addition, high fuel prices increase the need for alternatives such as biofuels. Therefore, the macroeconomic and strategic aspects were considered partially compatible (see Figure 16).

Socio-cultural aspects are partially compatible
The socio-cultural aspects have two sides, like a coin, when it comes to industrial biotechnology. On the one hand, there is a cultural drive towards sustainability, which benefits industrial biotechnology as a sector. On the other hand, the norms on sustainability and the sympathy towards traditional (agricultural) industry also hinder industrial biotechnology as a sector due to the public opinion on genetic modification and its possible risks, which fuel restrictive regulations and legislation on GMO's and its use. Therefore, when it comes to genetic modification and products for human consumption, there is an adversity against industrial biotechnology and its application. Therefore, the socio-cultural aspects of the industrial biotechnology TIS are considered partially compatible (see Figure 16).

Accidents and events are generally compatible, but the BPF bankruptcy makes the ecosystem-specific accidents and events partially compatible
Part of the socio-cultural aspects overlaps with the accidents and events TIS influencing condition. Which is considered compatible, due to the international focus on sustainability, which is considered favourable towards industrial biotechnology and its development. Moreover, the current environmental change and global warming provide a good "climate" for industrial biotechnology TIS development and application on a larger scale. For example, initiatives such as the Paris Agreement to get to Net Zero greenhouse gas emission (GHG) emissions by 2050 (Horowitz, 2016). It might be that the war between Russia and Ukraine has some negative effects on the development of the TIS due to lower availability of substrates which are partly originating from Ukraine or Russia, but also the increased energy prices could have negatively affected the development of industrial biotechnology. However, the increased fuel and energy prices make alternative fuels, produced with biotechnology, relatively more attractive. Therefore, the accidents and events appear to be compatible to promote the TIS formation for industrial biotechnology. However, locally the bankruptcy of the BPF has greatly hindered the TIS development within the scale-up support ecosystem, therefore the general conditions are considered compatible, but the local ecosystem conditions are considered partially compatible (see Figure 16).

This TIS assessment of the Planet B.io - Biotech Campus Delft scale-up support ecosystem was used as a base case scenario for comparison with the "successful" Copenhagen and Brightlands Chemelot scale-up support ecosystems. Therefore, Copenhagen industrial biotechnology scale-up support ecosystem was mapped and assessed (see section 4.6).

4.6 Case 2 - Copenhagen Industrial Biotechnology Ecosystem

4.6.1 Introduction

The desk research and perspectives of Interviewees 5, 6, and 9 (see Appendix B.8) provided insights into the Copenhagen industrial biotechnology scale-up support ecosystem. The Copenhagen region of Denmark is extremely full of innovation and business activity, with a scarcity of space as a result. The Copenhagen region has a focus on both industrial biotechnology and pharmaceutical biotechnology, with large, successful biotechnology companies like Novo Nordisk and Novozymes and universities like the Denmark Technical University (DTU) and the University of Copenhagen, there is both a business and an innovation culture within this region.

Differences Industrial Biotechnology and Pharmaceutical Biotechnology
During this case study there is specifically focused on the industrial biotechnology side of the Copenhagen ecosystem, however it should be noted that these are, of course, somewhat interconnected in terms of ecosystem players, activities and support. Pharmaceutical biotechnology does not meet the set industry characteristics (see section 1.1.2), what was already discussed when comparing pharmaceutical biotechnology and industrial biotechnology (see section 1.1.1). This was also confirmed by interviewee 9, associate business development BII, when discussing differences between pharmaceutical and industrial biotechnology:

> "I've definitely encountered the difficulty of scaling, which is a much more evident feature of the whole process for companies working in that industry [Industrial Biotechnology] compared to companies working in therapeutics." - Interviewee 9, Associate Business Development, BioInnovation Institute

Decentralised network with a lot of funds and knowledge
There is not a central network and support organisation within the ecosystem, but there is more of a decentralised ecosystem with multiple parties involved but running in an uncoordinated

manner. Within the Copenhagen ecosystem there is a lot of funding available, but this is almost all originating from the Novo Nordisk Foundation investing this through Novo Holdings, Novo Seeds, and the BioInnovation Institute. The Novo Nordisk Foundation does investments that Venture Capital would not do, due to the tax system in Denmark, where a foundation pays less tax if they reinvest their profits into the Danish community. Besides, some funding is supplied by the Danish government through Innovation Fund Denmark. So, both funds and knowledge appear to be in excess within the Copenhagen region. The actors of the Copenhagen industrial biotechnology ecosystem and their roles have been mapped (see section 4.6.2).

4.6.2 Copenhagen Industrial Biotechnology Ecosystem

Ecosystem core

The general ecosystem map of industrial biotechnology in Copenhagen shows the decentralised nature of the ecosystem with no organisation in the center that connects the actors of the ecosystem (see Figure 17). In the core, there is an ecosystem actor present in each quadrant, but mostly at the technical facilities & services. The BioInnovation institute, is an accelerator type of organisation (BII, n.d.), and helps with the translation of research to businesses. BII not only funds pre-seed and seed start-ups but also provides facilities, business support, and a network. Start-ups can receive substantial support from BII, although it requires a proportionate equity stake in return for its support. Niras, a consultancy firm, offers process development services, and through their Green Tech Hub, they provide start-ups with office space, storage, and production facilities. They also facilitate connections between start-ups and corporations via their Green Tech Co-Pilot Program (*NIRAS Green Tech Hub*, n.d.). Ferm Hub Zealand is located about 1.5 hour drive from Copenhagen, but kept reoccurring when talking about scale-up facilities. Ferm Hub offers space and facilities to do some piloting and process development on a larger scale, this is EU-funded, which is visualised by the arrow in Figure 17.

Technical facilities & services

Within the Copenhagen ecosystem there are several hubs with labs and offices (Symbion, CPH labs, Niras Green Tech Hub), there is one accelerator organisation (e.g., BioInnovation Institute) and there are piloting facilities (Ferm Hub, Alfa Laval, and in the future probably 21st Bio) (Figure 17). However, only Ferm Hub and 21st Bio seem to actually provide support with scaling up besides offering their facilities for rent. Another key characteristic is that the DTU is very active in translating research into business with also supplying fully-serviced (equipment, analytics and operators) piloting facilities up to TRL5 (300 L, Biosustain (n.d.)) and an active technology transfer department with DTU Skylab, which is an incubator, also offering both services & facilities as well as talent development (Figure 17).

Funding & Business services

In terms of business services and funding the majority of the funding and the actors that fund activities within the Copenhagen industrial biotechnology ecosystem are in the end a part of the Novo Nordisk Foundation (e.g., Novo Holdings, Novo Seeds, BII) (see Figure 17). Moreover, the foundation's investments extend to initiatives such as 21st Bio to deliver services and facilities to start-ups to scale up their processes. Thus, the Copenhagen ecosystem is extremely reliant on the funding activities of the Novo Nordisk Foundation. The other important part of the funding is from the Danish government (Innovation Fund Denmark). The Danish government also offers some business support services and events for start-ups and entrepreneurs (Copenhagen Business Hub, thus also network formation & coordination, see Figure 17). Besides, in terms of business services the Copenhagen ecosystem appears quite empty, with only Nordic BioVentures offering programs for entrepreneurs. There are also some indirect parties that provide funding (Industriens Fund, European fund for regional development). The European fund for regional development has provided funding to Ferm Hub Zealand (FermHub, n.d.).

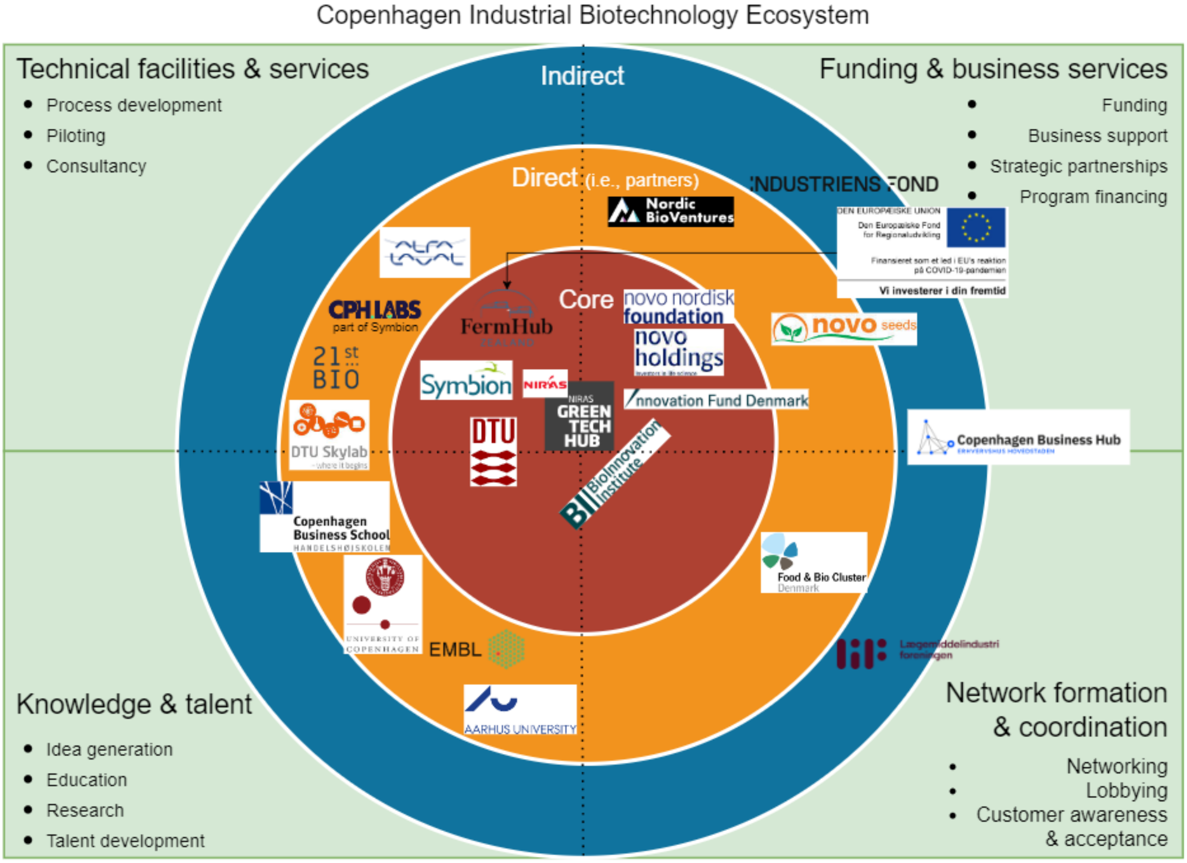

Figure 17: A visual representation of the Copenhagen Industrial Biotechnology Ecosystem, depicted as an onion layer figure. The ecosystem is divided into three layers, representing core, direct, and indirect contributors. These layers are further categorized into four quadrants, each representing a specific contribution type. The quadrants encompass technical facilities & services, funding & business services, network formation & coordination, and knowledge & talent. The figure provides a listing of the services within each quadrant.

Network formation & coordination

In terms of network formation & coordination, there is only one pure networking organisation focused on industrial biotechnology, among others. This is the Food & Bio Cluster (Figure 17), so there is little network formation & coordination present within the ecosystem. Since, Copenhagen Business Hub focuses on entrepreneurs and start-ups in general and Lägemiddelindustriforeningen (LIF) is the Danish association of the pharmaceutical industry, which at best have some indirect contributions to the industrial biotechnology ecosystem of Copenhagen (Figure 17).

Knowledge & talent

In terms of knowledge & talent there appears to be quite a lot in the Copenhagen ecosystem with universities as the DTU, University of Copenhagen, Copenhagen Business School, Aarhus University and EMBL (see Figure 17). Also, the DTU has active translational activity (see technical facilities & services) ensuring more knowledge and talent in the direction of scale-up of biotechnology.

4.6.3 Copenhagen industrial biotechnology scale-up support ecosystem and TIS assessment

To distinguish the disparities between the overall ecosystem and the scale-up support ecosystem, it is crucial to examine the roles and significance of different actors in providing scale-up support and relating this to the scale-up support requirements. This causes a shift in the roles and importance of various players within the ecosystem. Therefore, the Copenhagen industrial biotechnology ecosystem was also mapped specifically from a scale-up support perspective (see Figure 18) and the scale-up support elements assessed using the previously defined scale-up requirements (see section 4.1.4).

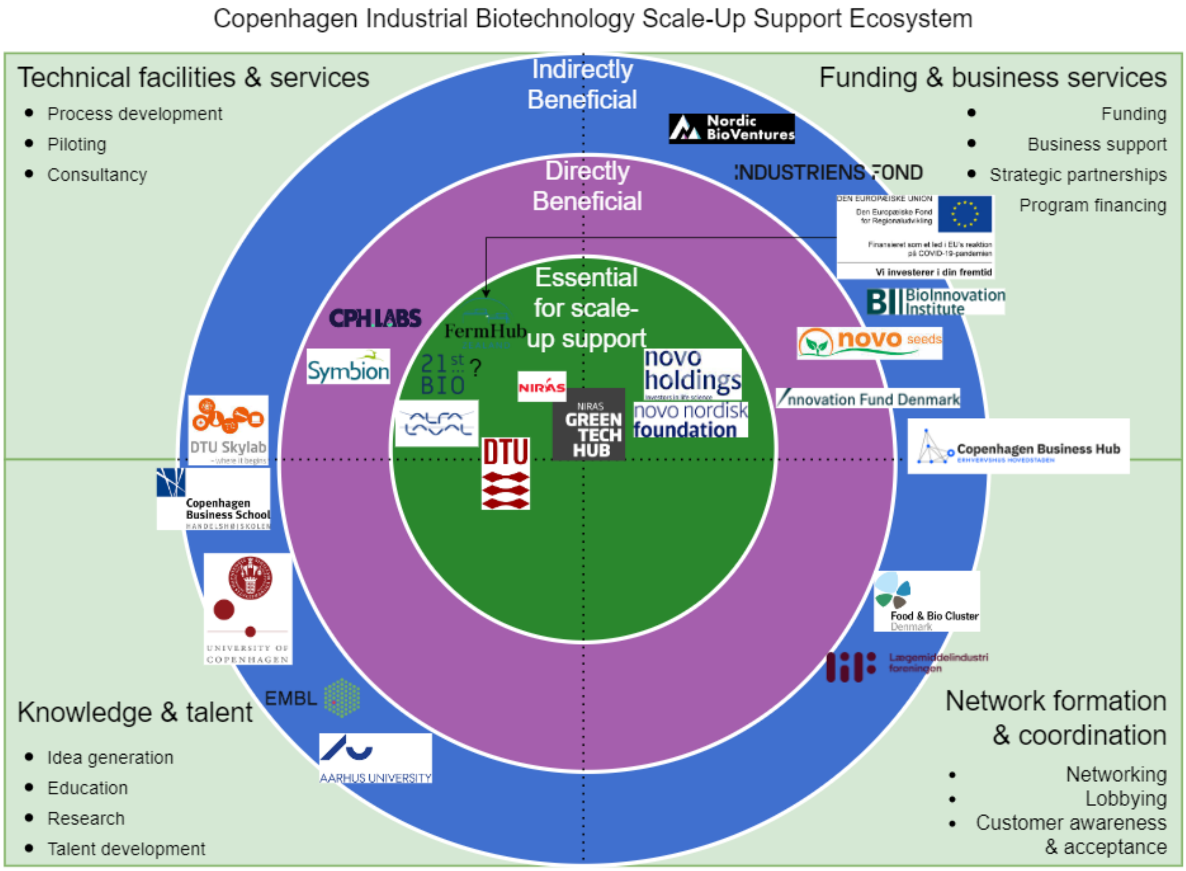

Figure 18: A visual representation of the Copenhagen Industrial Biotechnology Ecosystem from a scale-up support perspective, depicted as an onion layer figure. The ecosystem is divided into three layers, representing core, direct, and indirect contributors. These layers are further categorized into four quadrants, each representing a specific contribution type. The quadrants encompass technical facilities & services, funding & business services, network formation & coordination, and knowledge & talent. The figure provides a listing of the services within each quadrant.

Technical facilities & services scale-up support element is partially complete

In terms of technical facilities and services for scale-up support in industrial biotechnology, several organizations play significant roles (see Figure 18). Alfa Laval operates the "Innovation House", offering office space, storage, and a network of partners and suppliers to accelerate process development (Alfa Laval, n.d.). Niras Green Tech Hub provides storage and production facilities for scale-up ventures and is at the core of the support ecosystem due to its 5000 m^2 of dedicated space for green tech start-ups (*NIRAS Green Tech Hub*, n.d.). Ferm Hub Zealand is responsible for the real technical scale-up and piloting facilities, offering a comprehensive range of equipment and services for industrial biotechnology processes on a larger scale. Besides, 21st Bio, although planning to build a pilot plant, does not currently provide scale-up support facilities. On the other hand, DTU Skylab and Symbion play a minor role in scaling as they primarily provide labs and require partners for scaling up. Whereas, Nordic Bioventures is completely unrelated to scale-up support.

Thus, there are several scale-up facilities offered, some are under development. There is a pre-piloting facility at the DTU until TRL5 (300 L). No local fully serviced piloting facility present (yet), (Ferm Hub Zealand and 21st Bio working on this) and there is not a lot of room to grow and build own facilities (see section 4.1.4, 1a). The DTU does offer some translational support from research to their pre-piloting facility, but the ecosystem lacks sufficient industrial biotechnology scale-up services and expertise to effectively translate processes from the laboratory to pilot-scale and plan for further growth (see section 4.1.4, 1b). Experts interviewed in the Copenhagen ecosystem highlighted challenges in accessing shared facilities, equipment, and analytical methods for measuring product quality. While 21st Bio and Ferm Hub Zealand may partially address these challenges, Niras and Alfa Laval do not seem to provide adequate expertise and support for scale-up and piloting. There is some flexible expert pools that can be used by start-ups (see section 4.1.4, 1c), for example at the piloting facilities of the DTU an Ferm Hub Zealand. Therefore, the scale-up support ecosystem of Copenhagen was considered partially complete in terms of technical facilities & services (see Figure 19). Ferm Hub Zealand and 21st Bio should be tracked, since these might complete the scale-up support ecosystem in terms of technical facilities & services.

Funding & business services scale-up support element is partially complete
In terms of technical scale-up support for industrial biotechnology, the Copenhagen industrial biotechnology ecosystem appears to be well-funded, relying on corporate funding from the Novo Nordisk Foundation, besides there is some funding from the Danish government via the Innovation Fund Denmark (see section 4.1.4, 2a). Whereas **BII**, **Nordic BioVentures** are considered indirectly beneficial, since they will only be able to connect to scale-up supporting organisations, but do not help with scaling the technology themselves (see Figure 18). Besides funding, the business services required: IP strategy support, investment planning support and grants, subsidies and investment application support (see section 4.1.4, 2b, c & d, respectively) appear to be lacking within the Copenhagen scale-up support ecosystem. However, some services might be offered by investors and the huge funds availability might render some of these requirements obsolete. Still, based on the defined scale-up requirements (see section 4.1.4) the Copenhagen scale-up support ecosystem was considered partially complete in terms of funding & business services (see Figure 19).

Network formation & coordination scale-up support element is incomplete
The network formation & coordination within the Copenhagen ecosystem is very minimal and indirect (see Figure 18), with only the Food & Bio cluster as a network organisation for industrial biotechnology, but not solely for industrial biotechnology and also not focused on scale-up support (see section 4.1.4, 3a). Moreover, the ecosystem is uncoordinated with a lack of alignment between the scale-up support ecosystem actors (see section 4.1.4, 3b). Therefore, the Copenhagen industrial biotechnology scale-up support ecosystem appears to be lacking in terms of network formation & coordination (see Figure 19).

Knowledge & talent scale-up support element is partially complete
Furthermore, in terms of knowledge & talent for scale-up support, all universities and research organisations not directly involved in scale-up/ piloting activities are moved to indirectly beneficial, keeping only the DTU in the core due to its piloting facilities and technology transfer activities (Figure 18). Thus, the DTU is crucial for the scale-up support ecosystem in terms of

knowledge & talent and technology transfer. Besides, the Copenhagen ecosystem exhibits significant research and translational activity, along with the presence of two universities (DTU and Copenhagen university) several early-stage start-up support organizations such as DTU Skylab, BII and Symbion, and a business school (see Figure 18). The supply of scale-up knowledge & talent is limited, with only some knowledge derived from the piloting activities of the DTU (see section 4.1.4, 4b, c). However, this knowledge is not applicable on a large-scale beyond a few hundred liters. Consequently, when scaling beyond this capacity, the expertise from DTU is insufficient (see section 4.1.1, 4c). In terms of scale-up requirements for industrial biotechnology in terms of knowledge & talent (see section 4.1.4) the Copenhagen industrial biotechnology scale-up support ecosystem appears almost complete, only the alignments of all education levels with the industry requirements in terms of knowledge and education (see section 4.1.4, 4a) is lacking due to the uncoordinated nature of the ecosystem. Therefore, the Copenhagen industrial biotechnology scale-up support ecosystem is considered partially complete in terms of knowledge & talent (see Figure 19).

4.6.4 Copenhagen industrial biotechnology scale-up support ecosystem appears to be mature but is lacking in terms of network formation & coordination

The TIS scale-up support elements assessment (see Figure 19) demonstrates that, based on the identified scale-up requirements (see section 4.1.4), the scale-up support ecosystem of Copenhagen appears to be mature but is lacking in terms of network formation & coordination and is missing at least one scale-up support requirement identified for the other scale-up support elements. However, some limitations might be overcome by the strengths of the Copenhagen ecosystem in terms of funding, technical facilities and technology transfer.

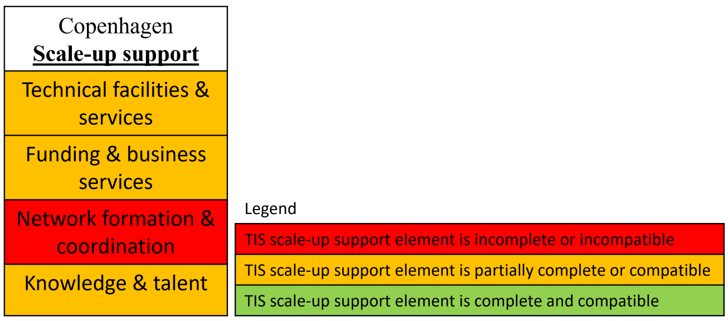

Figure 19: The assessed status of the Technological Innovation System (TIS) scale-up support elements of the Copenhagen industrial biotechnology ecosystem.

4.6.5 Requirements for an Ideal Copenhagen Scale-up Support Ecosystem

Based on the Copenhagen industrial biotechnology scale-up support assessment (see Figure 19) and the identified industrial biotechnology scale-up requirements (see section 4.1.4) the required development for an ideal Copenhagen industrial biotechnology scale-up support ecosystem have been identified as:

- Improving ecosystem and shared resources coordination
- Scale-up support TRL focus until TRL 7 and about 2000 L scale
- Dedicated pilot plant for flexibility and a pool of expert operators
- Service to translate from lab to pilot scale
- Fully serviced facility for proof-of-principle and guidance

The specific influencing conditions for the industrial biotechnology TIS were assessed based on the status of the Copenhagen industrial biotechnology scale-up support ecosystem (see section 4.6.6). These TIS assessments were used to compare the scale-up support ecosystems studied.

4.6.6 Copenhagen scale-up support ecosystem specific Technological Innovation System influencing conditions

The TIS of industrial biotechnology within the EU showed no complete building blocks (Figure 11). Besides the building blocks, there are also the influencing conditions that affect the formation of one or more TIS building blocks. These influencing conditions are evaluated per scale-up support ecosystem studied due to the effect of scale-up support on these influencing conditions. Based on the status of the Copenhagen scale-up support ecosystem (see Figure 19) the TIS influencing conditions within the Copenhagen ecosystem were defined (see Figure 20).

Knowledge and awareness of technology is partially complete
Based on the conducted interviews within the Copenhagen industrial biotechnology ecosystem comes forward that there is some knowledge and awareness of industrial biotechnology, but that most start-ups struggle with scaling up due to a lack of scale-up expertise and knowledge, which is also lacking as hire-in expertise. Therefore, scaling up in industrial biotechnology remains very experimental, time consuming and expensive. The performance of the process and product on a larger scale is insecure and requires several intermediate scale-up steps to pilot the process and technology. Therefore, the knowledge and awareness of technology within the Copenhagen scale-up support ecosystem was considered partially complete (Figure 20).

Knowledge and awareness of application and market is partially complete
When evaluating the knowledge and awareness of application and market of industrial biotechnology (start-ups) within the Copenhagen ecosystem comes forward that the technical know-how of the application, more specifically scaling up expertise is usually lacking. In addition, among start-ups there is both a lack of awareness of application and a lack of awareness of the market. The application and market are connected through the concept of having the end-in-mind, which already has been described as crucial to overcome the Valley of Death of industrial biotechnology (Table 3). If the technology targets defined by the end market cannot be achieved in the lab, scaling up does not even make sense to begin with. Thus, having a support system in place that assists in aligning scientific ideas with scaleability is of utmost importance, but not present within the Copenhagen scale-up support ecosystem (see section 4.6.4). Therefore, the knowledge and awareness of application and market TIS influencing condition is considered partially complete for the Copenhagen scale-up support ecosystem (Figure 20.

Natural, human and financial resources are partially complete and partially compatible
Looking into the TIS influencing condition of natural, human and financial resources in Copenhagen there appears to be sufficient financial resources within the Copenhagen ecosystem (see section 4.6.4). However, for the start-ups there is a lack of shared equipment and facilities to cut costs and time. In addition, there is a need for human resources with the right background. Even though there is an abundance of education within the Copenhagen region to develop talent (Figure 17), the education is not well aligned with the scale-up requirements in terms of talent (see section 4.6.4). Thus, the need for cost reducing solutions for scale-up together with the lack of sufficient human capital with the right background demonstrates that the natural, human and financial resources influencing conditions are partially complete and partially compatible (Figure 20).

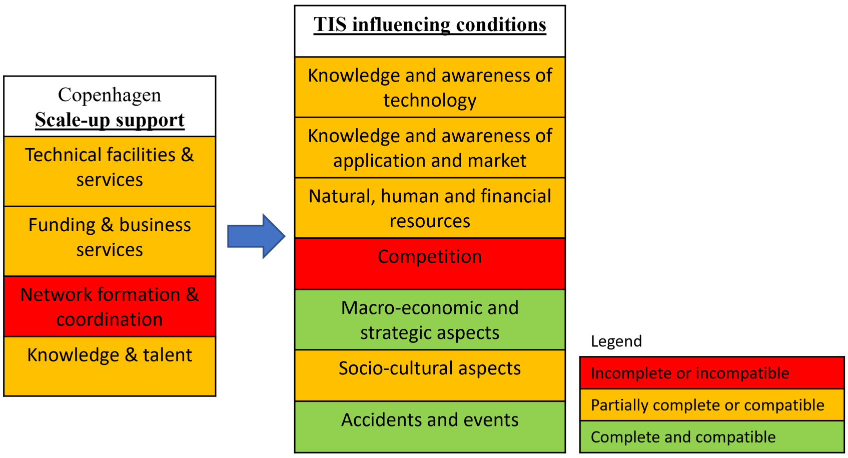

Figure 20: The scale-up support elements of the Copenhagen industrial biotechnology ecosystem and its resulting ecosystem- specific Technological Innovation System (TIS) influencing conditions. The influencing conditions considered are: knowledge and awareness of technology; knowledge and awareness of application and market; natural, human & financial resources; competition; macro-economic and strategic aspects; socio-cultural aspects; accidents and events as defined by Ortt and Kamp (2022). The figure offers insights into the current state of knowledge, resources, competition, economic factors, societal aspects, and potential risks or events that can impact the advancement of industrial biotechnology in the region.

Competition is too strong, thus incompatible

The competition, as described in section 4.5.5, is strong. The lack of success for the industrial biotechnology industry came also forward during the interviews about the Copenhagen industrial biotechnology ecosystem. Therefore, the TIS influencing condition of competition, as for the Planet B.io - Biotech Campus Delft ecosystem (see section 4.5.5), is considered incompatible, since industrial biotechnology is currently unable to compete on performance, efficiency and costs (Figure 20). As interviewee 5, DTU Professor Biochemical Engineering (see Appendix B.8), stated:

> ”To me it [success] would be to get much more biotech actually implemented at a big scale because I think that we [Industrial Biotechnology] have not actually done very well. I fully admit that biotechnology is complicated. Also that it has changed a lot along the road as we became better and better at molecular biology. But I think we could have gone much, much further if you look at what happened to the chemical industry 100 years ago, that was truly impressive what they put in place. Perhaps they were a bit a bit too successful if we look at global warming today. But they've really made a huge impact on the world. We have not yet managed that with biotechnology. Everybody says we will. They talk about it endlessly, but we are not quite there yet.”

Macro-economic and strategic aspects are compatible

In terms of macro-economic and strategic aspects, the Copenhagen ecosystem is well-suited for the development of the TIS of industrial biotechnology. There is overall economic growth. Also, strategic aspects are present with successful biotechnology companies such as Novo Nordisk and Novozymes, knowledge institutions with applied knowledge (e.g., biochemical engineering, DTU) knowledge, as well as fundamental knowledge (e.g., biochemistry, University of Copenhagen). In addition, the Danish model of these big corporations, like Novo Nordisk, being owned by a foundation ensures these companies and its knowledge, innovation and talent stay in Denmark. Moreover, the revenues are reinvested back into the community and invested into more risky, but beneficial initiatives as well. On top of that, the Danish governmental institutions such as Innovation Fund Denmark invest into the ecosystem. All together, this creates favourable strategic aspects for the development of the industrial biotechnology TIS, thus the macro-economic and strategic aspects of the Copenhagen industrial biotechnology TIS were considered compatible (see Figure 20).

Socio-cultural aspects are partially compatible
The socio-cultural aspects between Planet B.io - Biotech Campus Delft ecosystem in the Netherlands and the Copenhagen ecosystem in Denmark is considered similar. Therefore, the influencing condition of socio-cultural aspects is considered partially compatible for the development of the Copenhagen industrial biotechnology TIS (see Figure 20), as was determined for Planet B.io - Biotech Campus Delft (see section 4.5.5).

Accidents and Events are compatible
The accidents and events are generally considered similar for the Copenhagen ecosystem as for the Planet B.io - Biotech Campus Delft ecosystem (see section 4.5.5). Therefore, the accidents and events appear to be compatible to promote the TIS formation for industrial biotechnology (see Figure 20).

Beneficial and hindering effects of the Copenhagen scale-up support ecosystem on the TIS influencing conditions
To summarise, the Copenhagen scale-up support ecosystem elements positively influence:

- Knowledge and awareness of application and market: both technical facilities & services and knowledge & talent being partially complete or compatible
- Natural, human and financial resources: especially funding (funding & business services) is in excess, but also knowledge & talent with mostly compatible background is available
- Macro-economic and strategic aspects: economic growth, knowledge institutions, successful biotech companies with ample funds, and talent retention
- Accidents and events: compatible, not necessarily due to scale-up support, but here is investment in and development of piloting facilities, whereas at the Biotech Campus Delft the bankruptcy of the BPF hinders TIS development

However, the lack of network formation & coordination hinders the other scale-up support factors, which, among others, resulted in a partially complete natural, human and financial resources due to a lack of alignment of education with scale-up requirements.

To compare the Planet B.io - Biotech Campus Delft and Copenhagen industrial biotechnology scale-up support ecosystems with the "successful" scale-up support ecosystem focused on sustainable chemistry, the Brightlands Chemelot ecosystem was mapped and assessed (see section 4.7).

4.7 Case 3 - Brightlands Chemelot Ecosystem - Sustainable Chemistry & Materials

4.7.1 Introduction

The industry focus of the Brightlands Chemelot ecosystem is the Chemical industry, biobased materials, sustainable/ renewable materials, recycling of materials, sustainable chemistry (Brightlands, n.d.; Vankan et al., 2020). Sustainable chemistry will serve as the overarching term referring to these industries.

Sustainable chemistry is similar to industrial biotechnology
The industries of sustainable chemistry and industrial biotechnology were found to be similar (see section 4.1.3) in terms of the pre-defined four characteristics of industrial biotechnology (see section 1.1.2). From now on, the industry focus of Brightlands Chemelot will be referred to as

sustainable chemistry. The characteristics are somewhat less strict and complex for sustainable chemistry, due to slightly less complex and more concentrated processes (see Table 5).

Brightlands Chemelot build-up

At the Brightlands Chemelot site in Geleen (Limburg, The Netherlands) there is the Brightlands Chemelot Campus with start-ups, universities, service providers. Moreover, Brightlands Chemelot offers offices, labs and a multipurpose pilot plant with up to 300 L batch reactors (up to TRL5-6). Thus, Brightlands Chemelot provides technical facilities & services. There are already 3000 people working and 1000 students only at the Brightlands Chemelot Campus. Whereas there is also the Brightlands Chemelot production site, which is one of the largest in Europe. Here is also room for the building of pilot plants and actual production facilities. Thus, this is a centralised ecosystem around Brightlands Chemelot and there is also physical proximity of R&D, piloting and even production (see Table 3). Besides, Brightlands Chemelot also offers a network of partners (e.g., corporations, universities, service providers, suppliers). So, Brightlands Chemelot takes care of the network formation & coordination within the ecosystem. Brightlands Chemelot was, like Planet B.io, founded as a triple-helix organisation in 2012 as a cooperation of DSM, University of Maastricht and the province of Limburg. At the Brightlands Chemelot Campus they are also looking into the business model of scale-up support, more specifically piloting facilities, which demonstrates the relevance of this research even for more mature ecosystems like Brightlands Chemelot. The Brightlands Chemelot ecosystem is a large ecosystem and network that has been mapped to gain insight into its actors and roles (see section 4.7.2).

4.7.2 Brightlands Chemelot Ecosystem

The players in the Brightlands Chemelot ecosystem can be categorized into core, direct, and indirect players. These players have distinct roles within the ecosystem, and they can be grouped based on their functions into the four scale-up categories (see section subsubsection 2.2.2) and resulted in the ecosystem map (see Figure 21).

Ecosystem core

Brightlands Chemelot is heavily funded by the province of Limburg and its regional development fund called LIOF ("LImburg Ontwikkelings Fonds"), which makes it a key stakeholder (see Figure 21). Another founder, DSM has sold most of its activities at Brightlands Chemelot in 2022 (DSM, 2022), thus it appears that this core stakeholder is fading from the ecosystem (see Figure 21). This could mean that the triple-helix organisation DSM - University of Maastricht - Province of Limburg has turned into a double-helix organisation of only University of Maastricht and the Province of Limburg (and LIOF), which could have some interesting implications for the ecosystem in the long-term (see Figure 21).

Technical facilities & services

The Brightlands Chemelot Campus itself offers laboratories, offices, cleanrooms, and a multi-purpose pilot plant capable of batch piloting up to 300 L (TRL5-6). This multi-purpose pilot plant was originally destined for Chemelot InSciTe to pilot spin-out projects. Chemelot InSciTe was founded by Brightlands Chemelot, the University of Maastricht, DSM, and the province of Limburg (see Figure 21). Besides, at the Brightlands Chemelot Campus there is a comprehensive range of technical facilities and services due to the presence of industry suppliers, education providers, and service providers (see Figure 21). Notably, there is a concentration of specialized service providers, including a flexible operator pool (e.g., Innosyn). While suppliers of raw materials play a crucial role in supplying necessary resources to the laboratories and pilot plants, they are not considered direct contributors to the ecosystem's technical facilities and services (see Figure 21). However, their presence and network connections benefit the labs and pilot facilities at Chemelot.

The CHemelot Innovation and Learning Labs (CHILL) serves as a significant facility directly contributing to the ecosystem (see Figure 21). CHILL offers shared laboratory facilities for contract research projects and collaborates with vocational education institutes such as VISTA College, Zuyd Applied Sciences University, and Maastricht University. This collaboration involves student and coworker teams working on outsourced research programs, making CHILL's services affordable and attractive to start-ups.

All tenants of the Brightlands Chemelot Campus, including over 110 companies ranging from corporations to start-ups, contribute significantly to the ecosystem (see Figure 21). Corporations avail and pay for services, invest in shared facilities, and enhance the real estate aspect of the campus. Start-ups bring in innovative ideas and solutions, fostering a culture of continuous growth. Institutions contribute valuable talent to the ecosystem. Each new tenant further enhances the overall value proposition of the campus and can directly contribute to different quadrants, including technical facilities & services, funding & business services, and knowledge & talent (see Figure 21).

Funding & business services

The province of Limburg and LIOF (Regional Development Company Limburg) play significant roles in providing financial support to start-ups within the ecosystem (see Figure 21). LIOF offers vouchers that can be utilized at the CHemelot Innovation and Learning Labs (CHILL) for contract research projects, which include students via internships. As a co-founder of the Brightlands Chemelot Campus, the Province of Limburg holds a central position within the ecosystem, especially with DSM gone (see Figure 21). Besides the funding in the campus itself, there is also funding for the start-ups via, for example, Brightlands Venture Partners, a venture capital firm located on the Brightlands Chemelot Campus (see Figure 21). In additions, Brightlands Chemelot has established partnerships with various investing entities, including venture capitalists, corporate venturing, and business angels, indicating the presence of diverse investment sources (see Figure 21).

Besides funding, there are also business services offered within the Brightlands Chemelot ecosystem. The Brightlands Chemelot Campus offers business services such as assistance in writing investment plans. Additionally, tenants such as PNO Consultants, Innovencio, and EP&C / IPecunia Patents directly contribute to the Brightlands Chemelot ecosystem by offering innovation management advice, assistance in securing subsidies, and support in IP strategy, respectively (see Figure 21).

Network formation & coordination

The Brightlands Chemelot Campus provides the network within the ecosystem to support the successful commercialization of start-ups in sustainable chemistry. Brightlands Chemelot is a part of the broader Brightlands network, which encompasses four high-tech campuses in Limburg, they have a larger influence in terms of lobbying, customer awareness, acceptance, and coordination across the campuses (Figure 21). Besides, no additional organizations dedicated to network formation & coordination were identified within the Brightlands Chemelot ecosystem.

Knowledge & talent

Within the Brightlands Chemelot ecosystem, the University of Maastricht plays a crucial role as a teaching institution and tenant at the Brightlands Chemelot Campus. They are a co-founder and facilitate internships for students in companies located on the campus. The presence of teaching labs and collaborations with educational institutions like ZUYD Hogeschool and VISTA College provides direct access to talent for start-ups (Figure 21).

CHILL, Eindhoven Technical University (TU), and the Aachen-Maastricht Institute for Biobased Materials (AMIBM) are partners in research and projects within the Brightlands

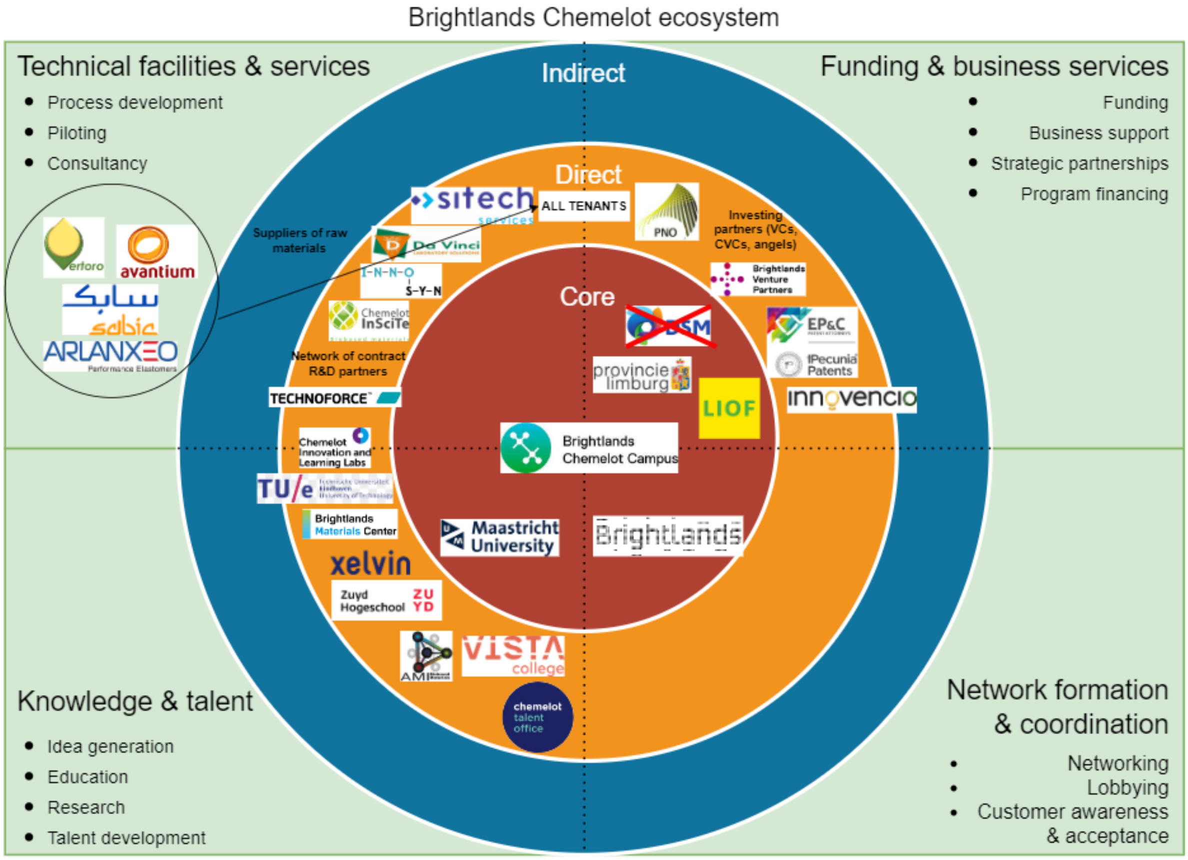

Figure 21: A visual representation of the Brightlands Chemelot ecosystem, depicted as an onion layer figure. The ecosystem is divided into three layers, representing core, direct, and indirect contributors. These layers are further categorized into four quadrants, each representing a specific contribution type. The quadrants encompass technical facilities & services, funding & business services, network formation & coordination, and knowledge & talent. The figure provides a listing of the services within each quadrant.

Chemelot ecosystem (see Figure 21). TU Eindhoven and Brightlands Chemelot have a technology transfer cooperation, as exemplified by the scaling start-up Vertoro, currently building a demo-plant in Rotterdam. AMIBM acts as a bridge between basic and applied research and the market, focusing on producing advanced bio-based materials sustainably and economically (Brightlands, n.d.). Xelvin provides technical recruitment services as a tenant within the ecosystem. The University of Applied Sciences Zuyd and VISTA College also contribute to the talent pool, with Zuyd facilitating connections between students and companies through on-campus education, internships, and collaboration with CHILL. VISTA College offers vocational education, providing a different form of talent (see Figure 21). Besides, the Chemelot Talent Office plays an influential role by offering management traineeships and actively recruiting talent from various schools and universities. This strategic effort ensures a continuous influx of skilled workforce, benefiting the companies within the ecosystem (see Figure 21).

4.7.3 Brightlands Chemelot scale-up support ecosystem and TIS assessment

To distinguish the disparities between the overall ecosystem and the scale-up support ecosystem, it is crucial to examine the roles and significance of different actors in providing scale-up support and relating this to the scale-up support requirements. This causes a shift in the roles and importance of various players within the ecosystem. Therefore, the Brightland Chemelot ecosystem was also mapped specifically from a scale-up support perspective (see Figure 22) and the scale-up support elements assessed using the previously defined scale-up requirements (see section 4.1.4).

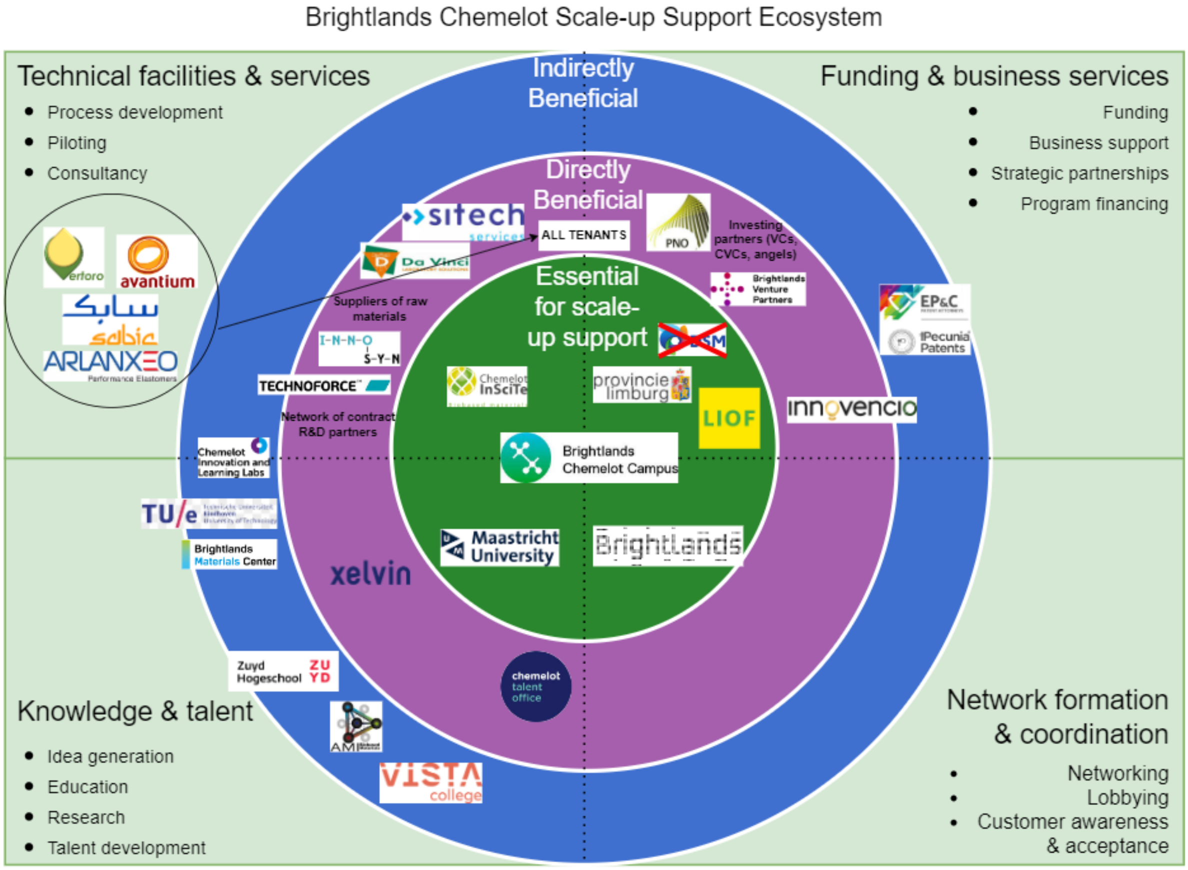

Figure 22: A visual representation of the Brightlands Chemelot ecosystem from a scale-up support perspective, depicted as an onion layer figure. The ecosystem is divided into three layers, representing core, direct, and indirect contributors. These layers are further categorized into four quadrants, each representing a specific contribution type. The quadrants encompass technical facilities & services, funding & business services, network formation & coordination, and knowledge & talent. The figure provides a listing of the services within each quadrant.

Technical facilities & services scale-up support element is partially complete
The Brightlands Chemelot ecosystem relies on technical facilities and services to support scale-up processes. The multipurpose pilot plant, established by Chemelot InSciTe, offers batch piloting up to 300 L (TRL5-6) and is crucial scale-up support in terms of technical facilities & services (see section 4.1.4, 1a). Besides, there is a lot of room to grow and build an own pilot plant or industrial-scale plant. However, there is no technical scale-up support to help translation from lab- to pilot-scale and beyond (see section 4.1.4, 1b). However, there is safety analysis conducted on the lab processes before using the multipurpose pilot plant. Additionally, the network of service providers, including the pool of flexible operators or contract R&D, like InnoSyn, which contributes significantly to the ecosystem's technical scale-up support (see section 4.1.4, 1c). Therefore, the Brightlands Chemelot scale-up support ecosystem was considered partially complete in terms of technical facilities & services (see Figure 23).

Funding & business services scale-up support element is partially complete
Funding and business services are essential components of the Brightlands Chemelot ecosystem.

The Province of Limburg and LIOF, a regional development company, play key roles in providing financial support to start-ups as well as investing in equipment and facilities if that contributes to the development of the region. Especially now that the main corporate stakeholder (DSM) has left the ecosystem. Therefore, the availability of funding within the ecosystem seems limited (see section 4.1.4, 2a). Start-ups receive funding from LIOF, which can be utilized at the CHILL for contract research projects. The Brightlands Chemelot Campus offers business services, such as investment planning support which is only billed for when a start-up leaves the campus, network access, and facilities, to make investment cases more appealing (see section 4.1.4, 2c). The presence of Brightlands Venture Partners, a venture capital firm, further enhances the funding opportunities for companies within the ecosystem. Besides, looking at business services present within the Brightlands Chemelot ecosystem, EP&C / IPecunia Patents are focused on IP consultancy and application, which does not directly contribute to scale-up support, since this is more focused on early-stage start-up support but essential to obtain funds for scale-up (see section 4.1.4, 2b). However, a good IP strategy is essential to raise funding for scale-up. Especially, because these start-ups don't have a product on the market, IP is the thing of value within a start-up to raise funding. Also, PNO and Innovencio and other investing partners can help provide funds (grants, subsidies or investments) for the piloting or even for the facilities and equipment (see section 4.1.4, 2d). Therefore, the Brightlands Chemelot scale-up support ecosystem funding & business services were considered partially complete, due to the limited direct corporate funding present within the ecosystem (see Figure 23).

Network formation & coordination scale-up support element is complete and compatible

Brightlands Chemelot Campus acts as the core organization for network formation & coordination within the ecosystem. It builds and supplies the necessary network to support the successful commercialization of start-ups' processes (see section 4.1.4, 3a). As part of the larger network of Brightlands campuses in Limburg, the campus has a significant influence in terms of lobbying, customer awareness, acceptance, and coordination. Moreover, the extensive network of the Brightlands Chemelot ecosystem seems to hold all necessary actors (see Figure 22 & see section 4.1.4, 3b), thus the network formation & coordination scale-up support element is considered complete and compatible (see Figure 23).

Knowledge & talent scale-up support element is complete and compatible

In terms of knowledge and talent, many organizations lose significance when considering scale-up support. However, the University of Maastricht remains at the core as it is the founder of both Brightlands Chemelot Campus and Chemelot InSciTe, which serve as the foundation for the entire scale-up support ecosystem (see section 4.1.4, 4b). Recruitment organizations such as Xelvin and the Chemelot Talent Office also provide direct benefits by supplying flexible talent to assist with piloting or scaling processes, but also other flexible experts are supplied via service providers like InnoSyn (see section 4.1.4, 4c). While all educational institutions (e.g., TU Eindhoven, University of Applied Sciences Zuyd, VISTA College) indirectly contribute to scale-up support, their primary focus lies elsewhere. However, all eduction levels are present within the ecosystem (see section 4.1.4, 4a). Additionally, the Brightlands Materials Center and AMIBM conduct research that can only indirectly contribute to the offered scale-up support (Figure 22). All together, the knowledge and talent scale-up support element is considered complete and compatible (see Figure 23).

4.7.4 Brightlands Chemelot Scale-up support ecosystem appears to be mature but its technical facilities & services and funding & business services are still only partially complete

The TIS scale-up support elements assessment (see Figure 23) demonstrates that, based on the identified scale-up requirements (see section 4.1.4), the scale-up support ecosystem of Brightlands Chemelot appears to be mature but is missing at least one scale-up support requirement identified for the technical facilities & services and the funding & business services. However, some limitations might be overcome by the strengths of the Copenhagen ecosystem in terms of network, knowledge and talent as well as by the maturity of the sustainable chemistry industry itself (see Figure 12).

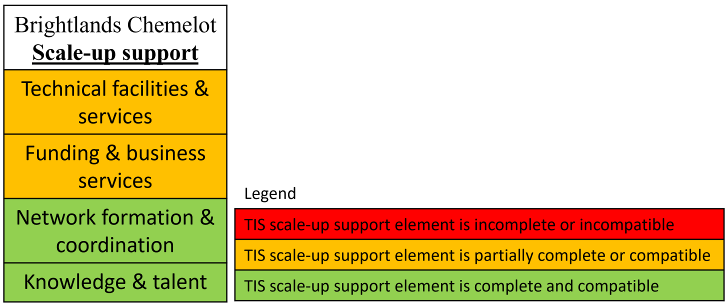

Figure 23: The assessed status of the Technological Innovation System (TIS) scale-up support elements of the Brightlands Chemelot ecosystem.

4.7.5 Requirements for an Ideal Brightlands Chemelot scale-up support ecosystem

The main strengths of the Brightlands Chemelot scale-up support ecosystem are ample technical facilities & services, the large network and the availability of compatible knowledge & talent. Besides, the scale-up requirements described earlier (section 4.1.2) show some particular requirements that could still be adressed by the Brightlands Chemelot ecosystem to become the ideal scale-up support ecosystem:

- Offering in-depth chemical know-how to translate from lab- to pilot-scale process and plan beyond
- Binding a large corporation with a lot of funds as a core stakeholder within the Brightlands Chemelot scale-up support ecosystem

The specific influencing conditions for the sustainable chemistry TIS were assessed based on the status of the Brightlands Chemelot scale-up support ecosystem (see section 4.7.6). These TIS assessments were used to compare the scale-up support ecosystems studied.

4.7.6 Brightlands Chemelot scale-up support specific Technological Innovation System influencing conditions

The sustainable chemistry industry was assessed as relatively mature (see Figure 12). Still, the product performance and quality, production system, product price and competition were partially complete TIS building blocks which could use beneficial TIS influencing conditions through a scale-up support ecosystem. Therefore, the scale-up support resulting TIS influencing conditions were determined (see Figure 24). This shows no incomplete or incompatible influencing conditions (or scale-up support factors).

The technical facilities & services scale-up support element only seems to be missing a service to help start-ups translate their lab process to pilot-scale and help to plan towards industrial scale (see section 4.7.3). This would contribute to, knowledge and awareness and the natural, human and financial resources which are now considered partially complete (see Figure 24).

The Funding & business services only miss direct corporate funding for scale-up support (see section 4.7.3), which would contribute to the natural, human and financial resources and help develop further to become competitive with the traditional (petro)chemical industry (competition, see Figure 24). Sustainable chemistry provides partially compatible competition to traditional chemical processes and products, due to the potentially higher costs of the emerging and less optimised sustainable chemistry processes (see Figure 24).

Other scale-up support factors seem to be complete and compatible (see Figure 23), this contributed to the TIS influencing factors at the Chemelot ecosystem to be (partially) complete and compatible (see Figure 24). Overall, the macroeconomic and strategic aspects, socio-cultural aspects and accidents and events are favourable because of the sustainability reasons supplied for industrial biotechnology (see section 4.5.5), but without the worries about GMO or it being a new industry. Sustainable chemistry is emerging from the traditional (petro)chemical industry which allows for an easier development in terms of policy, regulation, customer acceptance and market development.

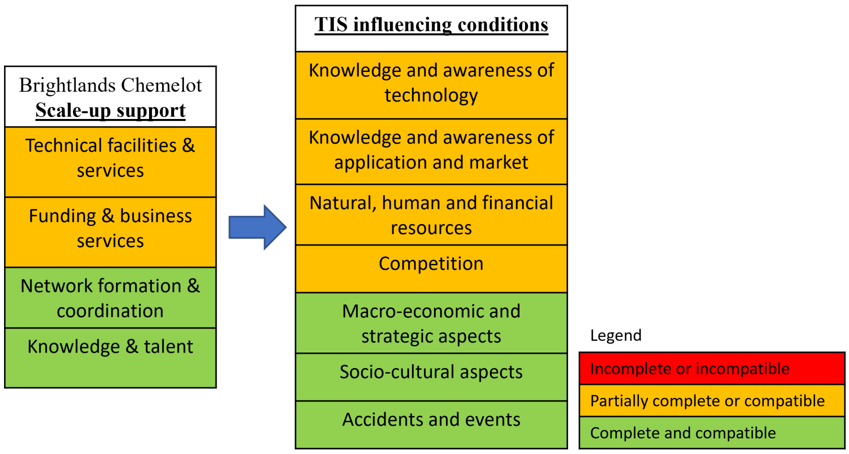

Figure 24: The scale-up support elements of the Brightlands Chemelot ecosystem and its resulting ecosystem-specific Technological Innovation System (TIS) influencing conditions.

This concludes the comprehensive evaluations of the scale-up support ecosystems, providing valuable insights into their respective characteristics and functionalities. The next step involved a comparative analysis of these case study results. This comparative examination aims to identify commonalities, differences, and key factors that contribute to the effectiveness and success of these scale-up support ecosystems (see section 4.8).

4.8 Scale-up support ecosystem comparison

The general characteristics of the scale-up support ecosystems studies were compared (see Table 6).

When linking the general ecosystem characteristics (see Table 6) with their respective scale-up support ecosystem completeness (see Figure 25) comes forward that a centrally organised scale-up support ecosystem and a large network is preferred for a scale-up support ecosystem. Whereas, a more mature industry, i.e., sustainable chemistry, enables easier scale-up support due to a higher availability of complementary services, the right knowledge and talent, the presence of consumer acceptance and at least not hindering policy and regulation. Another possible insight is that a high availability of corporate funding is highly beneficial for a scale-up support ecosystem and its development, as was seen for the Copenhagen scale-up support ecosystem. None of the scale-up support ecosystems investigated appears to be complete according to

Table 6: Comparison of Industrial Biotechnology and Sustainable Chemistry Ecosystems

General Characteristics	Planet B.io – Biotech Campus Delft	Copenhagen Ecosystem	Brightlands Chemelot Ecosystem
Industry:	Industrial Biotechnology	Industrial Biotechnology	Sustainable Chemistry
Industry maturity, TIS building blocks:	No complete TIS building blocks	No complete TIS building blocks	More mature industry than industrial biotechnology, building on traditional chemistry
Type of organization and coordination:	Centralised ecosystem around triple-helix organisation (Planet B.io)	Decentralised and uncoordinated ecosystem with multiple important organisations	Centralised ecosystem around triple-helix organization that is now a double-helix (government-university) organisation
Ecosystem density:	Small network	A lot of relevant ecosystem actors with different specialties/ foci, Novo Nordisk, DTU and the government are the most important actors	Large, interconnected ecosystem with a lot of local activity

the identified scale-up requirements (see section 4.1.4), but the Brightlands Chemelot scale-up support ecosystem is considered the most complete, then the Copenhagen scale-up support ecosystem and the Planet B.io - Biotech Campus Delft ecosystem appears to be the least mature scale-up support ecosystem (see Figure 25). Looking at the differences between the industrial biotechnology scale-up support ecosystems and the sustainable chemistry scale-up support ecosystem, the most intriguing differences are observed in terms of the size and number of companies in the sector. There are more and larger companies within the chemical industry which offers more complementary service providers and more industrial experts for chemical scaling up. The full ecosystem comparison overview has been listed in Appendix E, Table 18.

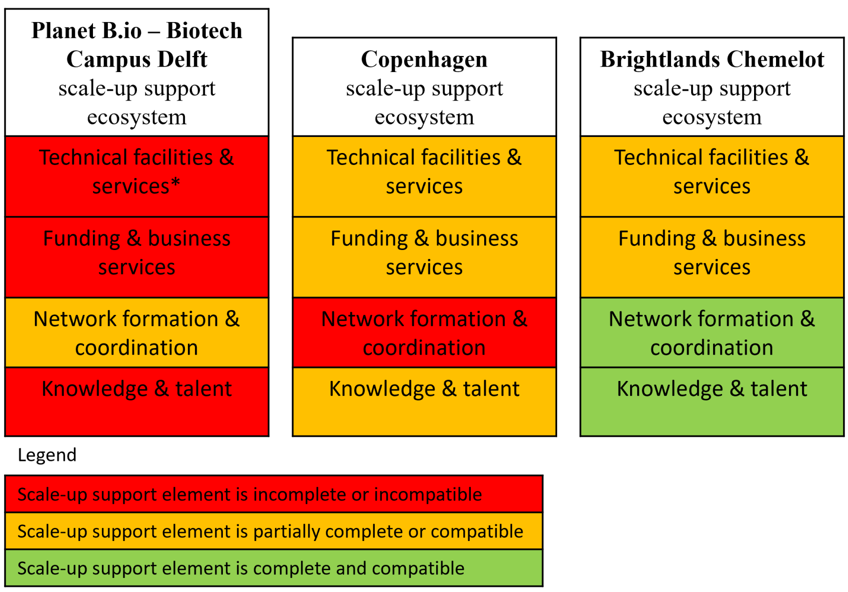

Figure 25: Comparison of the completeness and compatibility of the scale-up support elements of the scale-up support ecosystems studied.

The scale-up support elements can positively or negatively affect the local TIS influencing conditions. Even the "successful" scale-up support ecosystems are not complete in terms of scale-up support (see Figure 25), however if a scale-up support ecosystem is partially complete it can still have a very beneficial effect on the TIS influencing conditions. However, this study focuses specifically on the (technical) scale-up support, whereas an ecosystem is more than just scale-up supporting. Based on the case study results and the status of the Planet B.io - Biotech Campus Delft scale-up support ecosystem, a roadmap for the development towards a complete and "successful" scale-up support ecosystem has been proposed (see section 4.9). Additionally, a business model to operate a piloting facility and a scale-up support ecosystem have been proposed (see section 4.10).

4.9 Planet B.io - Biotech Campus Delft: Proposed Scale-up Support Development Roadmap

The current, incomplete status of the Planet B.io - Biotech Campus Delft scale-up support ecosystem (see Figure 15) is logical due to the organisation only existing since 2020 and the unfortunate event of the BPF bankruptcy. Based on the scale-up requirements identified (see section 4.1.4) and the current status of the Planet B.io - Biotech Campus Delft scale-up support ecosystem (see Figure 15) a roadmap of scale-up support ecosystem development has been proposed (see Figure 26). This roadmap is the answer obtained to research question 3 (see section 2.2.6): How should the (technical) scale-up support ecosystem supplied by Planet B.io and the Biotech Campus Delft be organised and operated?

4.9.1 Stage 1: strengthen the network, knowledge, talent, and funding of the ecosystem before improving the technical facilities & services by offering a piloting facility

The proposed roadmap has been staged in two phases (see Figure 26), but the order of the development is not necessarily set in stone. Nonetheless, the proposed roadmap appeared to be the most logical order of events, especially the extension of the network, attracting funds and expanding the knowledge & talent pool of the ecosystem should be done before setting up a fully-serviced shared piloting facility. This could all contribute to (setting up) the piloting facility.

First set up the lab- to pilot- and industrial-scale support service before offering a piloting facility and pay for the service using government vouchers
Help and expertise to translate a start-up's lab-scale process to pilot-scale and help them plan towards industrial-scale was found as crucial scale-up support. This should be linked and aligned with the shared piloting facility. Moreover, it is strongly recommended for the scale-up support ecosystem development to first set up this service before offering a piloting facility. Also, the lab- to pilot-scale translational service could be paid for with a government voucher system (see Figure 26). Whereas using a voucher to pay for piloting itself was not considered useful, piloting is simply too expensive. Thus, requires private funding. This government voucher system was actually used for piloting at the BPF, but did not work as intended. Because, to get the voucher approved, the personnel costs per hour were restricted to an unrealistically low maximum price, thus the piloting wages could not be covered with the voucher. Additionally, it added a lot of paperwork to the work of the BPF, while the voucher could only cover about 10% or less of the piloting expenses. The technical scale-up support requirements of a shared piloting facility and lab- to pilot-scale translational support are interconnected. Setting up this translational service will ensure a pipeline of start-ups (becoming) ready to pilot, with a clear plan for the piloting and having their needs identified. This service would also provide additional insights into the specific requirements of the emerging technologies and start-ups scaling up, to which the shared fully services piloting facility could be tailored. The fully serviced, shared piloting facility should offer the requirements as identified in section 4.1.1 and enable piloting until at least TRL5-6.

Attracting funds through an additional large corporation invested into the scale-up support ecosystem
The Planet B.io - Biotech Campus Delft ecosystem is heavily dependent on DSM and its corporate funding (see Figure 14), besides there is no large corporation that is based on the campus and heavily invested into making the Planet B.io - Biotech Campus Delft into a successful ecosystem. An additional large corporation invested in the scale-up support ecosystem is something that would be very beneficial and might even be essential for setting up scale-up support facilities, e.g., piloting facility, which adds a lot of value to the scale-up support ecosystem and is essential technical scale-up support. However, by itself a piloting facility is not an investment that would yield direct returns, since piloting is costly and difficult, likely requiring periodic investments to sustain. This was seen for the BPF, where DSM was the only stakeholder with funds. At the moment that for DSM the added value did not outweigh the costs, the facility went bankrupt, even though it was fully booked. Therefore, it is important to have multiple sources of funding within the ecosystem that are invested in making the scale-up support ecosystem successful and that reap the indirect benefits of successful scale-up and ecosystem development, which is way easier when the costs are shared. On top of that, the scale-up support ecosystem would become less fragile, since strategy change of one corporation would have less impact when there are multiple corporations invested that the ecosystem can lean on. Therefore, **attract funds** through at least one additional large corporation with available funds is included at stage 1 (see Figure 26).

Crucial to expand the knowledge & talent pool of the ecosystem and ensuring a pipeline of talent of all levels required for the start-ups
The current status of the Planet B.io - Biotech Campus Delft ecosystem shows the lack of aligned education and research and its resulting talent (see Figure 15). First, the knowledge & talent scale-up support element should become complete and compatible, since it is the slowest element to develop and would ensure that there is a pool of knowledge & talent to enable scale-up and growth of these companies (see Figure 26). The knowledge & talent present at the Brightlands Chemelot ecosystem was seen to contribute highly to its success (see section 4.8). Whereas, a lack of the right talent was identified as a major limitation of scale-up within industrial biotechnology. This was also seen when comparing the TIS building blocks of industrial biotechnology and sustainable chemistry in terms of complementary products and services, and network formation and coordination (Figure 11 & Figure 12, respectively. This shows the completeness of these building blocks for sustainable chemistry, whereas for industrial biotechnology these are, respectively, incomplete and partially complete.

Expand network
The small network of the planet B.io - Biotech Campus Delft ecosystem compared to the other "successful" ecosystems highlights the need for increasing the ecosystem network (Figure 25). This network should be increased by attracting additional start-ups as well as complementary service and product providers (e.g., media, substrate, equipment and services providers). This network expansion was proposed for stage 1 of the ecosystem development, but is not limited to phase 1 and will remain an ongoing process (see Figure 26). It should start during phase 1, since the right complementary products and service providers are required to offer the fully serviced shared piloting facility, where a lot of ecosystem actors should actually offer a part of it. For example, equipment suppliers should help to set up the piloting facility by sponsoring a part of the equipment and maintenance, whereas in return they get insights into the needs of the emerging technologies, thus can provide a good market fit and successful scale-up would result in additional customers who piloted their processes using their equipment. Similar holds for industrial-grade substrate and media suppliers, which should be partners of the piloting facility.

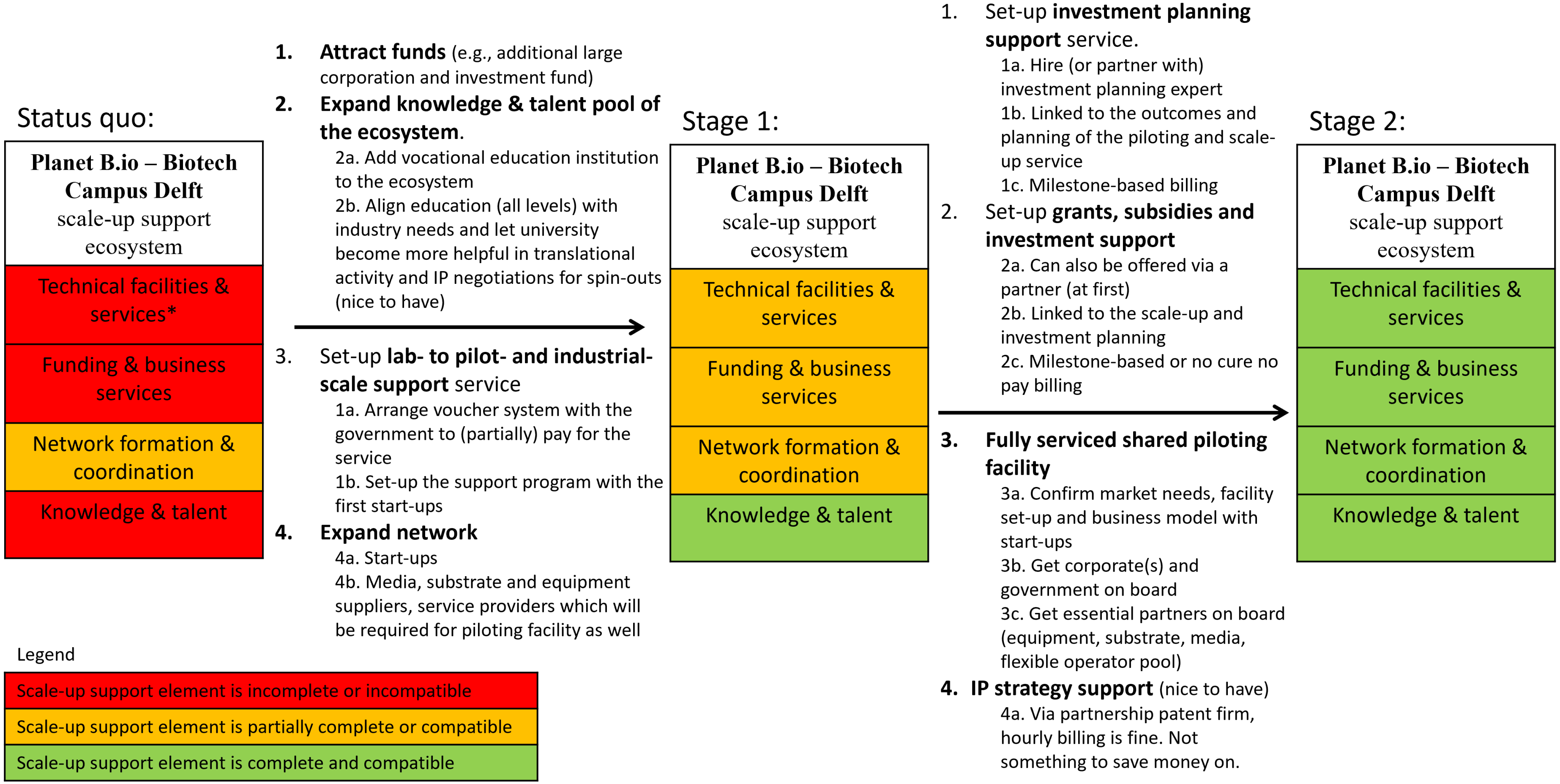

Figure 26: Proposed roadmap for the development of the ideal scale-up support ecosystem from the current status of the Planet B.io - Biotech Campus Delft scale-up support ecosystem.

4.9.2 Stage 2: Set up the funding & business services and the fully serviced shared piloting facility

After attracting both the important ecosystem actors and increasing and aligning the knowledge & talent supply with the industry scale-up requirements, the funding & business services should be set up (see Figure 26). Of which, **investment planning has to be aligned to the lab- to pilot-scale service as well as the piloting facility**, and help them plan the R&D, piloting, and scale-up steps together with a strategy to raise the required funds. The funding & business services would best be paid for through **milestone-based billing, or no cure no pay billing instead of hourly based billing**. This type of revenue model would ensure the alignment of all parties to help the start-up successfully scale up. With this type of revenue model, the start-ups would share in their successes, which creates the environment and cooperation beneficial for a scale-up support ecosystem. In addition, milestone-based billing or no cure no pay billing would increase the willingness of start-ups to pay more for a service if it is linked to success.

Grants, subsidies, and investment support should be aligned to the piloting, scale-up process and investment planning
In addition, grants, subsidies, and investment support should be offered (see Figure 26). This could be offered by Planet B.io, but also via a partner. Linking this to the investment plan would be really beneficial. Helping with the application for grants, subsidies or other funding as well as guiding start-ups to the types of funding to apply for can ease the process of raising funds. A lot of resources go into fundraising, but could be better spent on actual process development, which proper business scale-up support could ensure.

A fully serviced shared piloting facility with flexible operator pool is essential to a successful scale-up support ecosystem, but also the hardest to realise and maintain viable
A fully serviced shared piloting facility is essential to a successful scale-up support ecosystem. However, it requires a fundamentally strong and well-organised scale-up support ecosystem to ensure viability. This is also highlighted by the struggles of operating a shared piloting facility for an extensive scale-up support ecosystem like Brightlands Chemelot, which is lacking a core funding corporation (see Figure 22). It requires multiple corporations with funds to invest and ensure viability, it requires government funding to set up the facility, and requires a lot of relevant partners to supply the complementary products and services needed to run the piloting plant, and keep the operating expenses bearable. Moreover, a flexible pool of operators is highly beneficial to keep the operating expenses low, especially when the facility is not running at full capacity or requires different expertise. The piloting could be paid for, as for most piloting, through rental fees. Instead, it would be beneficial to have milestone-based billing which aligns the piloting facility's goals with the start-up's goals towards success. Whereas, the pipeline of start-ups should be well aligned with the piloting facility ensured through the lab- to pilot service offered. This has been elaborated further when discussing the proposed business models for the piloting facility and scale-up support ecosystem organisation like Planet B.io, respectively (see section 4.10).

Offering IP strategy support would be beneficial, since IP is the only value of a biotechnology start-up before validating its technology
A start-up in industrial biotechnology has to raise a lot of funds before reaching validation, and even more before reaching the market. Therefore, the IP strategy is really important and should be strong enough to be able to raise sufficient funds. Thus, IP strategy is considered beneficial to be offered within a scale-up support ecosystem even though it is not directly related to scaling up.

If all these steps are taken for the Planet B.io - Biotech Campus Delft, it could be a "complete" scale-up support ecosystem for industrial biotechnology. However, the scale-up support ecosystem development roadmap cannot be considered separately from the business model which should be used to ensure viability of a scale-up supporting ecosystem organisation like Planet B.io. Therefore, a proposed business model for the shared piloting facility as well as for a scale-up support ecosystem organisation has been provided (see section 4.10).

4.10 Business models for scale-up support

The types of funding and revenue model for a shared piloting facility and other scale-up support services has been investigated. This resulted in an evaluation of possible funding types (see Table 7) and possible revenue models (see Table 8).

4.10.1 Types of funding for a shared piloting facility: multiple corporations and government should fund this

The types of funding (see Appendix B.5) were evaluated to investigate how a shared piloting facility should be funded (see Table 7).

Table 7: Types of funding for a scale-up supporting shared piloting facility

Funding Type	Importance and Possibility
Possible funding options	
Corporate funding from large companies within industrial biotechnology	**Essential**, best with multiple corporations co-funding. These companies should have alignment in equipment needs
Corporate donations	Could work for funding
Corporate social responsibility funds	Possible option for funding
Governmental funding (region)	**Important** part of funding
Governmental funding (EU)	Possible grants, also funding FermHub Zealand in Denmark
Governmental funding (municipality)	Possible, but not an important source of funding due to lack of sufficient funds
Investment from educational/research institutes	Possible option, but will not be much (e.g., university, TNO)
Upfront contracts	Good option for investment in the facility
Unlikely funding options	
Crowdfunding, Crowd investing	Highly unlikely as funding sources
Equity funding	Not realistic due to lack of profitability
Governmental funding (national)	Unlikely, more something for regional funding, but could be through grants
Pension funds, Insurance companies	Highly unlikely as funding sources
VC funding	Unlikely to invest in piloting facilities

From this followed that corporate funding from multiple large corporations within industrial biotechnology is essential for a shared piloting facility. However, these companies should be aligned or complementary in terms of industry focus and piloting equipment requirements, otherwise it is hard to create a piloting facility with a good industry fit that meets the requirements of its investors if they would need to pilot. Besides, regional government funding and possibly some EU funding are likely to help set up a shared piloting facility, where regional government is considered important as a co-founder. Moreover, having upfront contracts for use of the piloting facility could help raise funding and get upfront investment from the companies that want to use the piloting facility. Besides, it could be beneficial to have an educational or research institution as a co-founder, but these organisations will not provide a lot of funding. Similar holds for funding by the municipality. Other funding options were considered unlikely for a shared piloting facility (see Table 7). For example, the shared piloting facility requiring large capital investment which is unlikely to be raised through crowdfunding, crowd investing and national government funding. Whereas the business case of a shared piloting facility is not profitable enough to attract venture capital funds or other equity funding and not secure enough for pension funds or insurance companies to invest. The types of funding that should be used and combined are used for the proposed shared piloting facility business model (see 4.10.3).

4.10.2 Types of revenue models for a shared piloting facility and other scale-up support services

The types of possible revenue models were investigated (see Appendix 4.10) to identify its possibility for a shared piloting facility and evaluate whether is could be a good fit for the other scale-up support services (see Table 8). This showed that the shared piloting facility should probably use a revenue model with either milestone-based billing or rental fees that vary according to the piloting needs and use. Besides that, a part of the income could be raised through corporate sponsoring, and possibly a salary could be paid for through a grant. Resulting in lower operating costs and increased viability of the business model. Moreover, some additional revenues can be raised through teaching, events and workshops, although at best would only cover a small part of the operating costs. Other revenue options investigated were found to be unattractive for a shared piloting facility (see Table 8).

The revenue model for scale-up support services were also investigated (see Table 8). From this followed that no cure no pay or milestone-based billing is a good option to pay for funding & business services type of scale-up support (e.g., grants & subsidies application support) (see Table 8). Moreover, milestone-based billing was found as a good model for all scale-up support (see Table 8). However, milestones need to be determined per service. Besides, corporate sponsoring could be used to pay for all types of services. Also, government vouchers, subsidies, or grants would be a good option to pay for technical scale-up support services, like the translating lab- to pilot-scale and beyond support (see Table 8). Whereas for the BPF, **vouchers** were used for start-ups to cover a part of the **piloting** costs, but this is **not worthwhile** to run a viable business model as a **shared piloting facility**. Since the amount of money is too little, and it creates a lot of work and restrictions for the piloting facility. Therefore, vouchers should not be used for piloting. These options were used to get to a proposed business model for a shared piloting facility (see section 4.10.3).

Licensing or selling intellectual property of the shared piloting facility to the companies that have piloted turned out to be too expensive for the scale-ups, which usually are already licensing IP from the university or lost equity to the university. For similar reasons, equity was not considered useful as a way of generating income. Though start-ups could be interested in piloting in exchange for equity, this only generates income far in the future and only for the successful companies. Therefore, this would cause even bigger problems of running out of funds for a shared piloting facility and would require a buffer of about 10 years of operating expenses.

For the scale-up support ecosystem organisation itself and the network of partners, facilities and services, a membership model is considered the way to monetize the value of the ecosystem created. Larger companies and companies that earn money from the start-ups should pay more for their membership and there should be a commission model in place where, for example, a percentage of the order value per referral should be paid to the ecosystem organisation. This way, the important organisation that creates value for the different ecosystem actors also gets paid proportional to the value it delivers to an ecosystem actor. This finding has been used to set up the business model for a scale-up support ecosystem organisation (see section 4.10.4).

Table 8: Types of revenue models for a shared piloting facility and other scale-up support services

Type	**Importance or Possibility for Shared Piloting Facility**	**Good Income Model for**
No cure no pay	Unattractive option	Good option for business services (e.g., grants & subsidies application support)
Milestone-based billing/ payment	Good option for piloting facility	Piloting facility and scale-up support services
Equity payment	Difficult and requires long-term commitment	None
Similar billing for all customers	Good option	Piloting facility
Membership model	-	Good option for scale-up support ecosystem
Rental model with varying fees	Essential option based on servicing needs	Facilities and equipment
Corporate sponsoring	Good option, with or without equity play	All services
Government vouchers/subsidies	Not enough to pay for piloting	start-ups to pay for scale-up support services
Grants	Good option, for a salary	Also a good option for scale-up support but also for services with hourly billing, e.g., consultancy
Additional revenue from teaching	Possible additional revenue source	Piloting facility through e.g., lifelong learning courses
Additional revenue from events/workshops	Possible additional revenue source	Piloting facility
Licensing or selling intellectual property	Unattractive option	None

4.10.3 Proposed business model for a fully-serviced shared piloting facility

These findings in terms of funding and revenue models (see section 4.10), together with scale-up requirements (see section 4.1.1) and the ecosystem findings (see section 4.8) has led to the proposed business model for a fully-serviced shared piloting facility (see Figure 27).

Key partners: multiple large corporations, government, university, and suppliers
Thus, for setting up a fully-serviced shared piloting facility, multiple large corporations with available funds, and government institutions are required as founding partners for the piloting facility. In addition, it would be beneficial for the business model to have a university as a founding partner to involve the development of knowledge & talent with the scale-up support ecosystem. Besides, a flexible operator pool provider, equipment supplier, industrial media

components supplier and an industrial substrate supplier (e.g., Alfa Laval, GEA, Tetra Pak, Kerry) would all be very beneficial as (founding) partners, since all these partners deliver a part of the piloting process and can make sure that the shared piloting facility has access to all required resources and equipment for a friendly price and keep the operating expenses bearable. These partnerships could be leveraged by mentioning the scaling start-ups that will make use of their products or equipment to scale up their processes, which will provide a pipeline of scaling processes that will make use of their products. That is why they should partner with the shared piloting facility and the scale-up support ecosystem. The partnerships with suppliers and the availability of industrial (cheap) substrates was lacking for the BPF. For example, if industrial-grade, cheap, substrates are not available for the piloting facility it has much higher operating costs using lab-grade substrates. Because these founders and partners are required for the piloting facility, this was included into the first stage of the Planet B.io - Biotech Campus Delft scale-up support ecosystem development roadmap (see Figure 26).

Key activities: lab- to pilot-scale technical support and a flexible fully-serviced food grade piloting facility

The technical facilities & services required as scale-up support for industrial biotechnology (see section 4.1.1) should be supplied with the piloting facility. This also resulted in the key resources (see Figure 27). Not everything needs to be offered by the facility, but the general equipment that is required for almost all industrial biotechnology processes should be offered and be flexible enough to adapt the set-up or add a specific piece of equipment that is process-specific. The product produced during piloting should be food grade, since it also needs to be validated and tested if it is a food product.

Revenue streams: hardware funding through grants and corporate funding and operating costs through partnerships and milestone-based billing

As was described in section 4.10, it was likely best to have corporate funding and grants to cover the hardware costs of setting up a piloting facility, whereas partnerships, corporate funding and milestone-based billing should cover the operating expenses. Milestone-based billing could be linked to the investment planning provided as a service within the scale-up support ecosystem (See Figure 26). Otherwise, simple rental fees could also work and are less risk for a piloting facility. However, a higher price could be asked for shared success and aligned interests of the piloting facility and start-up (see Figure 27). Milestone-based billing is in-line with what a scale-up support organisation stands for, first helping the start-up, then asking for something in return. This has not been seen for other scale-up support or piloting facilities, but the need for aligned interests did reoccur frequently during interviews. An example of aligned interests due to the business model can be seen for C(D)MO's which get equity or a part of a revenue for their production services. Then it is also in the interest of the C(D)MO to produce the best quality product most effectively, since this would result in increased revenues and profits, thus generate more income for the C(D)MO.

The other business model canvas elements for the piloting facility are linked to the described elements and are self-explanatory (see Figure 27). In short, the shared piloting facility is essential for the scale-up support ecosystem creating overall value for the ecosystem and the industry as a whole, but this should be acknowledged and supported by the ecosystem actors since it does not have a self-sustaining business model. The fully serviced shared piloting facility does not necessarily need to be run by Planet B.io itself, but it needs to be well aligned with the other scale-up support services. Therefore, the proposed business model of a scale-up support ecosystem organisation like Planet B.io has been set up separately from the shared piloting facility (see section 4.10.4).

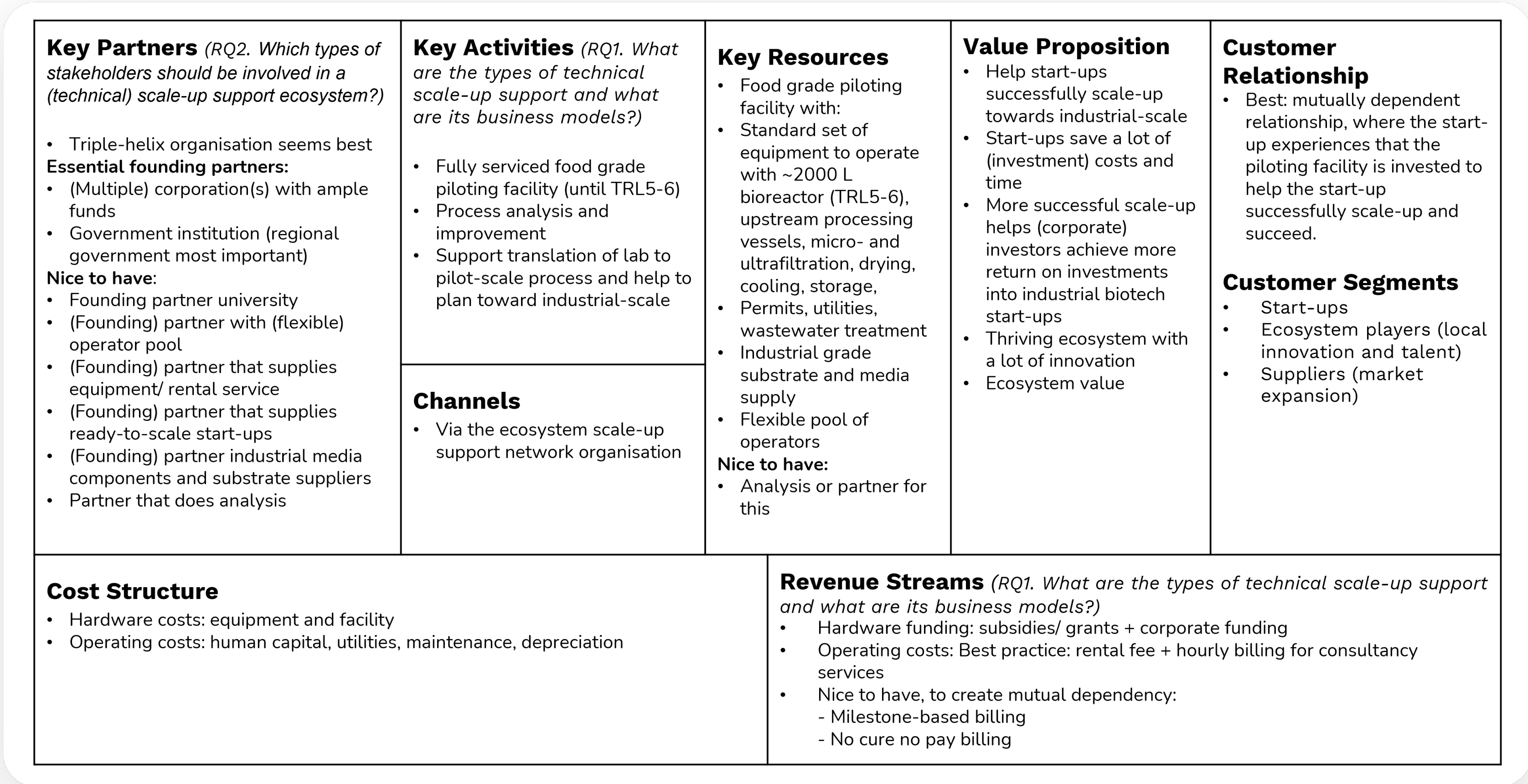

Figure 27: Business model canvas filled in for a fully-serviced shared piloting facility required as scale-up support in terms of technical services & facilities.

4.10.4 Proposed business model for a scale-up support ecosystem organisation like Planet B.io

The proposed business model for a scale-up support ecosystem organisation like Planet B.io has also been listed according to the corresponding business model canvas elements (see Table 9). The proposed business models (see Figure 27 & Table 9) present an answer to research question 1 and 2 (see section 2.2.6) giving the types of scale-up support, its actors and their roles as well as the business model that should be used. The proposed business model was a product of the identified revenue models (see section 4.10) linked to the identified key activities from the scale-up support requirements (see section 4.1.1), and its key partners required (see section 4.8).

Table 9: Proposed Business Model for a Scale-up Support Ecosystem Organization like planet B.io

Business Model Canvas Element	**Description**
Key Partners	Triple-helix (corporation - government - university)
	Multiple corporations within the industry that have ample funds and are willing to invest in the ecosystem
	University investing in translational activities from academia to industry and aligning education with industry needs
	Network of suppliers providing equipment, resources, technical services, funds, business services, knowledge, and talent
Key Activities	Operating as a network organization
	Supporting start-ups along their scale-up journey
	Providing shared facilities such as offices, labs, and connections to piloting facilities (offered at rental fees)
	Providing technical services to translate lab-to-pilot scale with “the end in mind” (ideally paid for with government vouchers)
	Providing business services including grant/subsidy application assistance, investment planning, and IP strategy (via consultancy partners)
Revenue Streams	Ecosystem membership, with corporations paying more than start-ups
	Commissions from corporations/partners for referrals that monetize
	Milestone-based billing (or no cure no pay) for services such as grant/subsidy applications, investment planning and lab-to-pilot scale support
	Government vouchers to (partially) pay for lab- to pilot-scale support

Key partners required: large corporation with ample funds, translational activity from the university and a bigger network of suppliers
Planet B.io is already a triple-helix organisation (see subsection 4.5), but only has DSM as a large corporation with funds, thus requires an additional large corporation for the scale-up support ecosystem (see Table 9). Besides, the TU Delft is a co-founder of Planet B.io but not actively investing into translational activity of industrial biotechnology from lab- to industry, which would help narrow the Valley of Death and provide additional scale-up knowledge & talent (see section 4.1.1. Besides, growing the network with suppliers would enable setting up

a shared piloting facility within the ecosystem, increase the ecosystem value and increase the membership revenues.

Key activities: increase network, set up piloting facility and scale-up support services

Currently, Planet B.io at the Biotech Campus Delft is offering labs and offices for a rental fee, and a network for a membership fee. The leveraging of the memberships could be extended with higher membership fees for larger corporations, whereas the facilities should be extended with a shared piloting facility. This piloting facility is not necessarily offered by Planet B.io itself, but should be aligned with its lab- to pilot-scale service, which would ideally be paid for with government vouchers. Therefore, the order of events was as described in the scale-up support ecosystem roadmap (see Figure 26. And the identified scale-up support business services (see Table 9) are not present within the scale-up support ecosystem and need to be set up (see Figure 26).

Revenue streams: increase revenues through memberships and commissions, as well as through milestone-based billing of the scale-up support services

The proposed roadmap (see Figure 26) should result in increased revenues from ecosystem memberships and commissions (see Table 9). This is important to leverage the value of the ecosystem created and ensure automatic increase in revenues when the value of the ecosystem to a certain actor increases. This could be done through an additional commission model. Milestone-based billing fits the model of a scale-up support ecosystem and setting up these scale-up support services supplies additional value to the ecosystem, enable successful scale-up and sharing success. Besides, a voucher system to pay for the crucial lab- to pilot-scale support should be set up to replace the voucher system that was in-place for the piloting at the BPF and prevent unnecessary costs and time losses during the piloting, due to a lack of end-in-mind.

5 Discussion

This study aimed to address the factors influencing successful scale-up in industrial biotechnology and the optimal support for these scale-ups. The following research questions were formulated:

RQ1. *What are the types of technical scale-up support for industrial biotechnology, and what are their associated business models?*

RQ2. *Which types of stakeholders should be involved in a (technical) scale-up support ecosystem for industrial biotechnology?*

RQ3. *How should the (technical) scale-up support ecosystem supplied by Planet B.io and the Biotech Campus Delft be organized and operated?*

This research focused on understanding the factors that contribute to successful scale-up and the role that scale-up supporting ecosystems should play, as well as how these ecosystems can be effectively organized. The research was limited to ecosystems within the European Union due to the influence of policy and regulation on technology development (Biggs et al., 2021; Kampers et al., 2021; Linton & Xu, 2021). Moreover, only ecosystems containing both business support and technical scale-up support were considered.

First, the insights generated by the literature review and multiple case study are discussed. These insights will guide the offering of technical scale-up support and the organization of scale-up supporting ecosystems. Additionally, the findings were applied to the context of Planet B.io at the Biotech Campus Delft, resulting in a proposed roadmap and business models. These will support strategic decision-making and the organization of its scale-up support ecosystem. Lastly, the research approach and the scientific contributions of this research were discussed.

5.1 Research findings

5.1.1 Scale-up success factors and requirements

The identified scale-up requirements (see section 4.1.1) for both industrial biotechnology and sustainable chemistry were found to be similar, only the more concentrated (about 10x more concentrated) and less complex processes of sustainable chemistry make its four characteristics less stringent. The scale-up requirements found were not entirely the same as the scale-up support requirements used for the TIS scale-up support element assessment (see 4.1.4), some criteria were already used for the ecosystem selection itself (i.e., piloting where the start-up operates, Sanford et al. (2016)), thus not included into the TIS scale-up support elements assessment. The scale-up support requirements were grouped into the four scale-up elements found (see section 2.2.2). The generated overview of scale-up success factors for (industrial) biotechnology (see Table 3) contributes to the existing knowledge through the identification of common themes among specific requirements or factors mentioned, these "scale-up success factors" have proven useful to triangulate the interviews findings, which are context dependent and subjective. Moreover, the scale-up success factors have helped to relate the found scale-up requirements to a more general, industry-wide need that has been highlighted in literature already.

5.1.2 Scale-up support elements and its requirements were obtained through triangulation

The identified scale-up support requirements that were included for the scale-up support element assessment had to be mentioned at least twice during separate interviews and should link to the scale-up success factors found in literature (see Table 3) before including it as a scale-up requirement for TIS scale-up support element assessment. This was considered important to identify the more important and general scale-up support required. If the requirement was only mentioned by one interviewee or could not be linked to a scale-up success factor, it was considered a more context specific requirement or personal opinion, thus likely not representative of industrial biotechnology as an industry. To further elaborate this, each scale-up support requirement used for the TIS assessment has been linked to their corresponding success factors found in literature.

1. Technical facilities & services
   - (a) Piloting facility, modular and room for growth is linked to the process scaling success factor (Biggs et al., 2021; Sanford et al., 2016) (see Table 3). This was identified as a key scale-up support element
   - (b) Technical support lab- to pilot-scale and planning towards industrial-scale is linked to pricing (Obloj et al., 2023) and process scaling (Davison & Lievense, 2016; Efara et al., 2019) as scale-up success factors (see Table 3)
   - (c) Flexible pool of experts (e.g., operators) also lowers the costs of piloting
2. Funding & business services
   - (a) Availability of funding is linked and evaluated based on success factors found on funding (Biggs et al., 2021; Duruflé et al., 2017; Strömsten & Waluszewski, 2012) (see Table 3)
   - (b) IP strategy support linked to raising funds (nice to have)
   - (c) Investment planning support is linked to business scaling (Coad et al., 2020), and connects the process of scaling to its funding (see Table 3)
   - (d) Grants, subsidies, and investment application support is linked and evaluated based on success factors found on funding (Bains et al., 2014) (see Table 3)
3. Network formation & coordination
   - (a) Network organisations present acts as a bridge between academia and industry (Kampers et al., 2021)
   - (b) Ecosystem completeness in terms of all roles present (Chen et al., 2022; Davison & Lievense, 2016; Obloj et al., 2023)
4. Knowledge & talent
   - (a) All education levels present within the ecosystem to supply the right knowledge & talent is linked to workforce and technical knowledge (Biggs et al., 2021; Noorman, 2011) (see Table 3)
   - (b) Active translational activity can act as a bridge between academia and industry (Kampers et al., 2021) (see Table 3)
   - (c) Knowledge & talent is aligned with scale-up requirements is also linked to workforce and technical knowledge (Biggs et al., 2021; Noorman, 2011) (see Table 3)

These scale-up support elements and its obtained requirements proved to be a step required to enable systematic assessment of the TIS scale-up support elements per ecosystem. The specific scale-up support requirements and its respective importance for a successful scale-up support ecosystem is something that could be researched further and could lead to addition or removal of scale-up support requirements, however the triangulation does make a strong case for most of the scale-up support ecosystem requirements and the technical services & facilities of a shared piloting facility and lab- to pilot-scale support service were shown as essential scale-up support. The lab- to pilot-scale service as scale-up support was not expected beforehand, but can afterwards be linked to the scale-up knowledge and expertise also helping with the end-in-mind strategy.

5.1.3 Maturity of industrial biotechnology and sustainable chemistry and its influence on scale-up support ecosystems

The Technological Innovation System framework assessment showed relative immaturity of industrial biotechnology compared to sustainable chemistry (see Figure 11 & Figure 12). This was expected based on the history of sustainable chemistry emerging from traditional (petro)chemical industry and industrial biotechnology being a new industry. This is especially seen for the TIS building blocks of complementary products and services, network formation and coordination, customers and innovation-specific institutions which are hindering the successful market introduction of industrial biotechnology, whereas this is already in-place for sustainable chemistry. The scoring of the TIS building blocks is still a matter of perspective due to the subjective assessment and could be evaluated further. Moreover, one technology, like cultivated meat, does not directly represent a whole industry. Therefore, the generalisability of these results towards industrial biotechnology as a whole should be critically assessed. However, this TIS building blocks assessment did provide systematic insight into the status of the industries and the ability to compare them. This was considered sufficient for this study to understand the industry context of the scale-up support ecosystems.

This industry maturity is important as context of the scale-up support ecosystems. The incompleteness or incompatibility of a TIS building block will directly influence the scale-up support ecosystem's completeness. For example, a lack of complementary products and services makes it much harder for a scale-up support ecosystem to build a network including complementary products and services. If there are no companies offering these services, it is impossible to partner with such a company. Therefore, it makes sense that the Planet B.io - Biotech Campus Delft and Copenhagen scale-up support ecosystem are less mature than the Brightlands Chemelot ecosystem, already based on the status of the industry itself (see section 4.8). For example, the complementary product and services are incomplete for industrial biotechnology and results in the network being incomplete for the scale-up support ecosystem. This will limit the possible completeness of a scale-up support ecosystem. Therefore, the effort of a scale-up support ecosystem should then be directed at the supply of the knowledge and talent required to develop and deliver this TIS building block, which was implemented in the proposed Planet B.io - Biotech Campus Delft scale-up support ecosystem roadmap through the knowledge & talent pipeline focus of stage 1 (see section 4.9).

5.1.4 Scale-up support ecosystem completeness and comparison

The scale-up support ecosystems and their scale-up support element completeness were assessed and showed that the Brightlands Chemelot scale-up support ecosystem was the most complete scale-up support ecosystem investigated (see Figure 25) with complete and compatible network formation & coordination and knowledge & talent. This was expected based on the sustainable chemistry industry maturity (see Figure 12). Moreover, Brightlands Chemelot has started as focused on traditional chemistry and is now transitioning into sustainable chemistry, therefore both the industry and the Brightlands Chemelot ecosystem are more complete in terms of TIS.

However, what was not expected is that even the Copenhagen scale-up support ecosystem which was considered a "successful" scale-up support ecosystem had no complete scale-up support elements (Figure 19), however this makes more sense based on the immaturity of industrial biotechnology together with the uncoordinated nature of the ecosystem (see Table 6). The Planet B.io - Biotech Campus Delft scale-up support ecosystem, since the bankruptcy of the

BPF does not even offer a shared piloting facility anymore, which is crucial for scale-up support, resulting in an incomplete scale-up support ecosystem with only a partially complete network formation & coordination. This study has demonstrated the need for a scale-up support ecosystem development strategy, which has been proposed in the form of a roadmap and business model. Also, the status of the Copenhagen scale-up support ecosystem shows the ability to be at least partially complete as a scale-up support ecosystem even at the current immature state of industrial biotechnology. Thus, this study has contributed insights into the industry status of industrial biotechnology and sustainable chemistry, assessed the completeness of the Planet B.io - Biotech Campus Delft, Copenhagen and Brightlands Chemelot scale-up support ecosystems and has identified the gaps in terms of scale-up support offered within each of these ecosystems.

5.1.5 Planet B.io - Biotech Campus Delft scale-up support ecosystem should first increase the network and align the development of knowledge & talent before offering the essential services and piloting facility

The TIS scale-up support element assessment (see Figure 15), the scale-up requirements identified (see section 4.1.4) and the ecosystem maps (see Figure 14) resulted in the proposed scale-up support ecosystem development roadmap (see Figure 26), which clearly shows the need for expansion of the network and attracting at least one other large corporation with funds besides DSM, to reduce the dependency of the ecosystem on DSM and its funds. Besides, the pipeline of knowledge & talent should be enlarged and aligned with the scale-up requirements. Knowledge & talent development increases the pool of talent with relevant expertise as well as leads to the development of the technology, new start-ups and complementary products and services. Which is all required looking at the TIS building blocks of industrial biotechnology (see Figure 11) and enable growth of the current industrial biotechnology start-ups. If this pipeline of sufficient and compatible knowledge & talent is lacking then there is limited possibility for industry development, successful scale-up and company growth. This direct need for industrial biotechnology was somewhat expected, but its importance for scale-up was not.

Besides, all activities in stage 1 of the proposed roadmap contribute to setting up a viable shared piloting facility (see Figure 26). This is the most important part of the scale-up support ecosystem and offers many benefits to scaling start-ups. A shared piloting facility increases the scale-up support ecosystem's added value and delivers direct and indirect value to its actors. Even for the companies that don't use the piloting, like equipment suppliers or other large companies, benefit from the market expansion resulting from successful scale-up and being close to the new technology. However, it is very expensive to run a piloting facility and its business model usually requires additional funding to cover the operating costs. It is hard to valorise the importance and value of a shared piloting facility, since it offers more value than simply the piloting gets paid for. Therefore, a piloting facility like BPF went bankrupt the moment that DSM stopped providing additional funds to cover the operating losses. However, the indirect added value of the shared piloting facility should be monetised and incorporated into the business model to enable running a sustainable shared piloting facility, not depending on one sponsor for survival, but being a shared good paid for by the whole ecosystem, which was incorporated into the proposed business model (see Figure 27).

The order of ecosystem development was chosen based on the maturity of the scale-up support ecosystem required before setting up a viable shared piloting facility (see Figure 27). The network should be expanded first, because a lot of different actors should be involved in setting up and funding a shared piloting facility. Besides, the supply of ready-to-scale start-ups should be there and its requirements for the piloting facility should be clear, therefore first aligning the knowledge & talent and setting up the lab- to pilot-scale service was proposed. However, the roadmap allows for limited flexibility, whereas the process of ecosystem development is more complex and messy. The roadmap (see section 4.9) only serves as a proposed order of ecosystem development, but does not mean that one part should be complete before the next part can begin.

5.1.6 Shared piloting facility requires multiple founding companies, government, and a network of partners to run a viable business model

As already discussed, a lot of actors should be involved to run a viable shared piloting facility requiring at least two large corporations and government to fund the facility, whereas these large corporations should cover a part of the operating costs (see Figure 27). These operating costs should be as low as possible, requiring several types of partners from industrial equipment and media suppliers to a flexible pool of operators (see Figure 27). This is the way to monetise the indirect value of the shared piloting facility, letting the companies sponsor the shared piloting facility since it generates new growing customers thus increasing the market for these suppliers, whereas the large corporations benefit from the insights into the emerging technologies and increasing maturity of the industry and even first pick to invest in or acquire these scale-up companies. The business model did not result directly from the framework used, but was a synthesis combining all findings. Therefore, the proposed business model is not a fully scientifically validated result of this study, but a more practical synthesis of the findings applied to the required shared piloting facility.

5.1.7 Planet B.io as an ecosystem organisation should both offer scale-up support services and monetise its network through memberships and commissions

The shared piloting facility could be set-up as a separate entity, as long as it is well aligned with the offered scale-up support services and the scale-up requirements of the start-ups. The key partners required for Planet B.io as a scale-up support ecosystem providing organisation are aligned with its current status of it being a triple-helix organisation but extended with the additional requirements for setting up a shared piloting facility (see Table 9). Thus, everything is somewhat connected for the ecosystem organisation. Therefore, its key activities of offering a network, labs, and offices should be extended with the required scale-up support services (lab- to pilot-scale service, grant/subsidy application service, investment planning service, and possibly even IP strategy service) (see Table 9). The value of Planet B.io should be monetised through ecosystem memberships where large corporations pay more than start-ups and commissions will be earned for referrals. Whereas, the services should be either paid for through milestone-based billing (or no cure no pay). Also, the current voucher system that was used for the BPF should be used to pay for the lab- to pilot-scale support (see Table 9). These proposed business models can be used to guide strategic decision-making for Planet B.io and other comparable scale-up support ecosystem organisations. However, this proposed business model is still dependent on a lot of contextual factors and provides limited practical usefulness. For example, the specific costs and prices of such services are still to be investigated and to be validated with the start-ups.

5.1.8 Alternative perspectives on roadmap and business models possible

The proposed roadmap for the development of the Planet B.io - Biotech Campus Delft scale-up support ecosystem and the proposed business models for scale-up support are opinions fuelled by the conducted research. There are alternative options and opinions possible, and these propositions are subject to change based on additional findings or contextual information. Therefore, it is important to understand the background and context of this study before using its findings to guide decision-making.

5.2 Research approach

5.2.1 Four Industrial Biotechnology Characteristics useful as Industry Selection Criteria

In order to compare the scale-up ecosystems across industries, four characteristics of industrial biotechnology were defined and used as industry selection criteria. Despite the slight variations in the characteristics of industrial biotechnology and sustainable chemistry, the assessment revealed that they shared similar scale-up requirements. It is important to note that the evaluation was limited to two ecosystems from industrial biotechnology and one ecosystem from sustainable chemistry. While this allowed for a focused analysis, further investigations involving a broader range of ecosystems would provide a more comprehensive understanding of the applicability and effectiveness of the four characteristics as scale-up requirements selection criteria. However, future research should consider expanding the scope of analysis to include a wider range of industries and ecosystems for a more robust comparative study.

5.2.2 Ecosystem selection criteria

The ecosystem selection criteria for the multiple case study were:

- Should offer a piloting facility, this was found as essential to scale-up support
- Physical proximity within the ecosystem, is relevant for the Planet B.io - Biotech Campus Delft and offered the scale-up success factors (see Table 3):

    1. Pilot where you operate (Sanford et al., 2016). However, Sanford et al. (2016) did not specify what type of operating should be conducted close to the piloting. Still, both R&D and commercial production where is piloted is considered very beneficial. R&D close to the piloting allows for frequent testing and iterations between the laboratory and the pilot plant. This is needed for an immature industry like industrial biotechnology, since a lot of iterations of process improvement are needed before reaching a commercially viable process, highlighting the benefit of R&D close to the piloting facility. Whereas production close to piloting ensures the context is similar, e.g., availability of the same substrates, which would enable smoother scale-up.
    2. Shared piloting facilities (Biggs et al., 2021; Davison & Lievense, 2016)

- Ecosystem should be within the European Union to prevent differences in terms of the TIS building blocks of innovation-specific institutions as well as the TIS influencing conditions of macroeconomic and strategic aspects and socio-cultural aspects. Therefore, it was considered a good decision for the scale-up support ecosystem comparison with the Planet B.io - Biotech Campus Delft scale-up support ecosystem to restrict the ecosystem selection to within the EU.
- Ecosystem should be more mature than Planet B.io - Biotech Campus Delft and have a good reputation. Both Copenhagen and Brightlands Chemelot proved to be more mature scale-up support ecosystems and could be used to identify best practices for scale-up support. This was very useful to determine the proposed roadmap and business models for the Planet B.io - Biotech Campus Delft scale-up support ecosystem.

Still, the scale-up support ecosystems and their status is very context dependent. Therefore, what might work for one scale-up support ecosystem does not necessarily work for another. However, these ecosystem selection criteria have helped to increase the usefulness of the findings and align some context-dependent factors. Thus, enabling easier comparison and translation to another scale-up support ecosystem.

5.2.3 Ecosystem mapping valuable to identifying scale-up support ecosystem

Ecosystem mapping allowed for a comprehensive understanding of the scale-up support ecosystems. During this study, a framework comprising the identified four types of scale-up elements: technical facilities & services, funding & business services, network formation & coordination, and knowledge & talent, was used. These categories were used to encompass all relevant actors within the ecosystem and effectively map their roles. It is important to note that all assumed roles demonstrated significance to the ecosystem's functioning. Among the identified elements, as expected, the technical services & facilities emerged as particularly vital for supporting scale-up. Network formation & coordination, while beneficial, was found to be non-essential based on insights from the Copenhagen ecosystem case study. Instead, network formation & coordination was found to primarily influence other aspects of the scale-up support ecosystem. Nevertheless, it is crucial to acknowledge that network formation & coordination was found to improve the overall scale-up support ecosystem effectiveness.

Several limitations were encountered during the ecosystem mapping process. Mapping actors with multiple roles proved challenging, especially when these roles were not situated in adjacent quadrants of the framework. Additionally, certain specific roles were not readily visible, making it difficult to assess their importance to the ecosystem. Moreover, ecosystems are extremely complex and can never be fully mapped. Therefore, the level of detail for the ecosystem mapping required to answer the research questions should be kept in mind while using the ecosystem mapping. Otherwise, it can lead to a time-consuming process and an ecosystem map where the strength of the visualisation depletes due to a clogged ecosystem map. Finally, it is important to acknowledge the inherent subjectivity involved in ecosystem mapping.

In short, ecosystem mapping served as a valuable tool for comprehensively evaluating the scale-up support ecosystems. By considering the separate scale-up elements and their associated roles, insights into the ecosystem's structure were obtained and the significance of various ecosystem actors were identified. Nonetheless, limitations related to the complexity of an ecosystem and the subjectivity of the mapping itself underscore the need for careful interpretation and consideration of the findings.

5.2.4 The Technological Innovation System building blocks are dependent on the technology (status) and (type of) product

The TIS building blocks assessment for industrial biotechnology using mostly cultivated meat as an example of disruptive low TRL technology showed the technology dependency of the TIS building blocks status. Therefore, one should be aware of the dependency of the TIS building block completeness on the representative process and product. For example, GMO food products would generate mostly incomplete TIS building blocks, whereas already mature processes, like Chymosin production, will yield mostly complete TIS building blocks. This was kept in mind during this study, using general industry-wide representative characteristics to determine the TIS building block status. The problem of defining the industry characteristics was not considered easier when using the sectoral innovation system theory (Malerba, 2002). Also, the TIS framework dividing the building blocks and influencing conditions allowed to capture the ecosystem-specific conditions and enabled ecosystem comparison.

5.2.5 Extended technological Innovation System (TIS) framework, useful to study scale-up ecosystems but could be more refined

The TIS assessment provided valuable insights into the existing scale-up support ecosystems, highlighting the areas where scale-up requirements are not adequately addressed. The TIS framework proved to be a useful tool for comparing different scale-up support ecosystems. Originally, the TIS framework was intended to determine the best suited niche market introduction strategy for a technology in the phase between invention and large-scale diffusion (Ortt

& Kamp, 2022). For this study, the TIS framework has been applied to a completely new context to study scale-up support ecosystems and enable comparison. However, it is important to note that due to its intended application, the TIS framework is static in nature and does not capture the dynamic development over time. As a result, it is not suitable for proposing a roadmap for ecosystem development. Also, the TIS assessment is not able to capture and evaluate the possible business models, therefore, the business model canvas was separately applied to propose business models. Furthermore, the evaluation of the TIS status is subjective and heavily influenced by the specific viewpoint and chosen assessment criteria. In this study, was focused on the identified requirements for scale-up support factors. While the framework provides a generic overview of the technology status and influencing conditions, it does not offer insights into the individual interactions among the scale-up support elements, TIS influencing conditions or TIS building blocks. However, this was still considered sufficient for its purpose during this study. The addition of colour coding to indicate TIS completeness resulted in predominantly orange or red influencing conditions and building blocks, which limited the visualization of subtle differences. For instance, two factors may both appear orange, but one ecosystem may be significantly more complete than the other (see Figure 25). The colour coding could be improved, including more stages of completeness to capture more subtle differences.

Besides, in evaluating and comparing the scale-up support ecosystems and their status, the TIS influencing conditions alone proved insufficient. To address this limitation, an additional column specifically dedicated to the scale-up support ecosystem elements was added, allowing for a more comprehensive assessment and to be able to focus specifically on the scale-up support ecosystem completeness and its effect on the TIS influencing conditions. With these adaptations, the extended TIS framework with ideally more stages of completeness (and colour coding) is a valuable tool to investigate scale-up support ecosystems.

In short, the TIS framework served as a valuable tool for assessing the maturity levels of the industrial biotechnology and sustainable chemistry industries. While it facilitated comparisons between scale-up support ecosystems, its static nature and subjective evaluation require careful interpretation. To provide a better understanding in terms of scale-up support ecosystem completeness and its effect on the TIS, the framework needed to be complemented with an additional column containing the scale-up support ecosystem elements and for future research would be suggested to use more than three stages of completeness to identify more subtle differences.

5.2.6 Technology Readiness Levels

To identify the more subtle differences of the TIS building blocks of product performance and quality, product price and production system, the Technology Readiness Levels were used. This scale from 1 till 9 is purely focused on the technology and its development phases towards large-scale production. Since the product performance and quality, product price and production system required more in-depth study when looking into technical scale-up of an industry like industrial biotechnology and to know more specifically what TRL level scale-up support should focus on. There was identified that the Valley of Death for industrial biotechnology is between TRL 4 and TRL 7 and that a shared piloting facility should offer piloting until TRL 6, which is at a bioreactor scale of about 2000 L for industrial biotechnology and corresponds with 200-300 L for sustainable chemistry. Still, the TRL scale did not offer complete insights into the status and requirements of the different TIS building blocks, however there are several other scales comparable to the TRLs that could offer additional insights, for example the BioManufacturing Readiness Levels (BioMRLs) could be used for future research to specifically adapt the system and scale-up requirements to the BioMRLs (Smanski et al., 2022).

5.2.7 Scientific contribution: scale-up support ecosystem framework

The TRL level of the technology and its scale-up requirements are linked to the TIS framework through the extension of the TIS framework with the four scale-up support elements. This has resulted into the scientific contribution of this study in the form of a framework to investigate scale-up support ecosystems, investigate the status of the technology (TRL) and identify the scale-up needs (four categories) and translate this to the TIS framework. Within the TIS framework, its effect on the TIS influencing conditions and building blocks was used to identify possible business models to offer the required support and that suits the context.

Based on this, the answers to the research questions could be given and recommendations for Planet B.io and future research could be done (see section 6).

6 Conclusions

This chapter concludes this thesis by answering the research questions and reflecting on the limitations and relevance of the study and presenting suggestions for Planet B.io and future research, ending with a personal reflection. This study aimed to answer **what are the factors affecting successful scale-up in industrial biotechnology, and how should scale-ups be supported?** The literature review resulted in a list of scale-up success factors (see Table 3), which all would fall into one of the four scale-up categories:

1. Technical
2. Funding & Business
3. Network
4. Knowledge & Talent

Furthermore, the knowledge gap was identified on the verge of technical scale-up, industrial biotechnology and scale-up support ecosystems (see Figure 5). This led to the three research questions posed (see section 2.2.6). A multiple case study on the scale-up support ecosystems of Planet B.io - Biotech Campus Delft, Copenhagen and Brightlands Chemelot has been conducted to answer these research questions.

6.1 RQ1. What are the types of technical scale-up support for industrial biotechnology, and what are their associated business models?

6.1.1 Required scale-up support for industrial biotechnology

The types of technical scale-up support required for industrial biotechnology were identified through the desk research and interviews. The characteristics (long technology development, high capital expenses, economies of scale, the product is a bulk product with low profit margins, see section 1.1.2) and scale-up requirements of sustainable chemistry were found to be similar to industrial biotechnology (see section 4.1.3)) resulting in the following **scale-up support requirements for industrial biotechnology**:

1. Technical Facilities & Services
   (a) Piloting facility accommodating up to TRL 5-6 (≈2000 L bioreactor scale). Beyond this scale, scale-ups can raise funding for their own facilities. Further requirements are:
      - Fully serviced facility with generic equipment, operators, permits, and utilities.
      - Food-grade and Genetically Modified Organism (GMO) piloting facility to enable product testing and validation, as well as work with genetically modified organisms. Good Manufacturing Practices (GMP) certification is not necessary at pilot-scale, since commercial sales are not involved.
      - Flexible process setup, allowing the use of either the facility's equipment or alternative setups.
      - Possibility to pilot (and produce) where the start-up operates (Sanford et al., 2016). This is useful for continuous interaction with R&D and process improvement, as well as for piloting under industrial-scale conditions if production is also going to be close to the piloting facility.

   (b) Technical support lab- to pilot-scale and planning towards industrial-scale
   (c) Flexible pool of experts (e.g., operators)
2. Funding & Business Services

(a) Availability of investment planning support for cost-effective scale-up.
(b) Assistance in applying for grants, subsidies, and funding opportunities.
(c) IP strategy guidance to secure necessary funds for development and scale-up.

3. Network Formation & Coordination
   (a) Access to a network of other industrial biotechnology start-ups, companies, and stakeholders for knowledge sharing and mutual support.
   (b) Inclusion in a large, well-coordinated network to leverage collective expertise and resources.
4. Knowledge & Talent
   (a) Access to a talent pool of all education levels with the required expertise in industrial biotechnology, supported by education and translational activities.
   (b) Alignment of knowledge and talent with the specific requirements of scale-up processes.

6.1.2 Business models for scale-up support

To get to the proposed business models, the case study findings had to be combined and the business model canvas was used. The "best" business model found for a shared piloting facility is:

- Key partners: multiple large corporations, government, university, and suppliers
- Key activities: lab- to pilot-scale technical support and a flexible fully-serviced food grade piloting facility up to TRL 6 ($\approx$ 2000 L bioreactor)
- Revenue streams: hardware funding through grants and corporate funding and operating costs through partnerships and milestone-based billing (or rental fee)

The preferred revenue model for other scale-up support services is milestone-based billing or no cure no pay, whereas for the lab- to pilot-scale and planning for industrial-scale service a government voucher system would be even more preferred. This should be set up instead of the voucher system for piloting at the BPF, a voucher (typically €10,000,-) is not enough to pay for piloting. An important learning for scale-up support that it is best to have the goals of the scale-up and the scale-up support service or facility aligned, which can be done through linking the payment to the success of the scale-up.

6.2 RQ2. Which types of stakeholders should be involved in a (technical) scale-up support ecosystem for industrial biotechnology?

The actors that should be involved within a scale-up support ecosystem and what role they should play has been answered through the proposed business model canvas given for a fully-serviced shared piloting facility (see Figure 27) and for a scale-up support ecosystem organisation, like Planet B.io or Brightlands Chemelot, also according to the corresponding business model canvas elements (see Table 9). Two types of roles were distinguished, key partners for a shared piloting facility and key partners for a scale-up support ecosystem organisation like Planet B.io. Whereas other beneficial actors and their related scale-up support element are also listed.

1. Key partners for setting up a fully-serviced shared piloting facility:
   - Multiple large corporations with available funds.

- Government institutions as founding partners for the piloting facility.
- University as a founding partner to facilitate the development of knowledge and talent within the scale-up support ecosystem.
- Flexible operator pool provider, equipment suppliers, industrial media components suppliers, and industrial substrate suppliers (e.g., Alfa Laval, GEA, Tetra Pak, Kerry) as (founding) partners to ensure access to necessary resources and equipment at reasonable prices.

2. Founding partners required for a scale-up support ecosystem organisation:
   - Multiple large corporations with ample funds.
   - University with translational activity to bridge the Valley of Death and enhance scale-up knowledge and talent.
   - Government, most likely regional government

3. Other beneficial actors for a scale-up support ecosystem:
   - Suppliers and service providers to enable the establishment of a shared piloting facility and increase ecosystem value and membership revenues.
   - All types of education (university, university of applied sciences and vocational education) to provide knowledge & talent
   - IP strategy firm, investment planning firm, venture capital firm(s) investing in all stages of industrial biotechnology from pre-seed till demo-plant scale. These actors would all help provide funding & business services.
   - Network of start-up and other companies within the industry (industrial biotechnology) to share knowledge, experiences, partner-up and help each other. Can provide multiple scale-up support elements, but would help complete the network formation & coordination of the scale-up support ecosystem.

6.2.1 RQ3. How should the (technical) scale-up support ecosystem supplied by Planet B.io and the Biotech Campus Delft be organized and operated?

Research question 3 has been answered through the proposed business models (see Figure 27 & Table 9) and roadmap for further scale-up support ecosystem development (see Figure 26). The scale-up support that should be offered by the scale-up support ecosystem has been given as an answer to research question 1 (see section 6.1) and the different actors and their required roles have been given as an answer to research question 2 (see section 6.2). This leaves the proposed roadmap for the planet B.io - Biotech Campus Delft scale-up support ecosystem (see Figure 26) to answer research question 3.

Roadmap for Planet B.io - Biotech Campus Delft scale-up support ecosystem development

The current status of the Planet B.io - Biotech Campus Delft scale-up support ecosystem was considered immature with the technical facilities & services, funding & business services, and knowledge & talent scale-up support elements incomplete or incompatible and the network formation & coordination partially complete (see Figure 15). To develop the scale-up support ecosystem towards a "complete" scale-up support ecosystem, a roadmap for scale-up support ecosystem development was proposed (see Figure 26). The development has been separated into two stages.

Stage 1: strengthen the network, knowledge, talent, and funding of the ecosystem before improving the technical facilities & services by offering a piloting facility.

First set up the lab- to pilot- and industrial-scale support service before offering a piloting facility, and pay for the service using government vouchers. Planet B.io should also attract more funds through an additional large industrial biotechnology corporation invested into the scale-up support ecosystem. Moreover, during the first stage it is crucial to expand the knowledge & talent pool of the ecosystem and ensuring a pipeline of talent and knowledge of all types (university, university of applied sciences, and vocational education) required for the start-ups. This is essential due to the immaturity of industrial biotechnology as an industry (see section 4.2). Moreover, the network should be expanded overall already adding the suppliers and service providers required as partners for the shared piloting facility (e.g., substrate, media, equipment and flexible operator pool).

Stage 2: Set up the funding & business services and the fully serviced shared piloting facility
During the second stage of the scale-up support ecosystem development, the grants, subsidies, and investment support and investment planning should be set up. These services should be aligned to the piloting and scale-up process, thus also with the lab- to pilot-scale and beyond planning. During the second stage, a fully-serviced shared piloting facility with flexible operator pool should be set-up, with the essential founders and required partners (see section 6.2). This is essential to a successful scale-up support ecosystem, but also the hardest to realise and maintain viable. Also, offering IP strategy support would be beneficial, since IP is the only value of a biotechnology start-up before validating its technology and is required for a start-up to raise funding.

Proposed business model for Planet B.io
The proposed business model for Planet B.io has also been described using business model canvas elements. This resulted in:

- Key partners and activity required for the Planet B.io - Biotech Campus Delft scale-up support ecosystem:
  - Additional large corporation with ample funds to complement the existing partnership with DSM.
  - Translational activity from the TU Delft to bridge the Valley of Death and enhance scale-up knowledge and talent.
  - Expanded network of suppliers to enable the establishment of a shared piloting facility and increase ecosystem value and membership revenues.
- Key activities: increase network, set up piloting facility and scale-up support services
- Revenue streams: increase revenues through memberships, where large corporations pay more, and commissions, as well as through milestone-based billing of the scale-up support services

6.2.2 Scientific contributions

The multiple case study has been successful to study scale-up support ecosystems and answer the research questions. This study presents a unique approach to study scale-up support ecosystems, a type of R&I ecosystems, by combining an extended TIS framework with scale-up support elements and identifying the TIS status through ecosystem mapping from a general ecosystem perspective and from a scale-up support perspective specifically. In addition, the business model canvas was used to capture the case study findings into a proposed business model. This study provides a framework to study scale-up support ecosystems through the linkage of the scale-up requirement and TRLs to the TIS framework by the four scale-up support elements. This application of the TIS framework to a completely new context to study the effect of ecosystems on the TIS influencing conditions has been proven to be insightful.

6.3 Reflection

6.3.1 Limitations

This study is not without limitations, and it is important to acknowledge and address them to provide a balanced assessment of the findings. The limitations of this research lie most heavily with the case study selection and the interviews. The quality of the cases selected, the quality of the interviewees, and the insights generated through the interviews will be limited by the willingness of the interviewees and organisations to participate in the study and share information about their organisation. Firstly, the scale-up support requirements were derived from desk research and interviews conducted with three ecosystems representing two industries, namely industrial biotechnology and Chemistry. Although efforts were made to ensure a diverse sample, the limited number of ecosystems and interviewees may restrict the generalisability of the results. Furthermore, the contextual nature of interviews and case studies introduces subjectivity and limits the ability to draw broad conclusions. so there are a lot of limitations in terms of external validity. Therefore, the selection criteria for the cases serve as a basis for external validity between industrial biotechnology and the other industries to be studied. Additionally, the depth of complexity and understanding of the studied ecosystems may be inadequate due to time and resource constraints. The inclusion of only three ecosystems through nine expert interviewees may not capture the full range of perspectives and nuances within the scale-up support ecosystem.

Various types of biases may have influenced the study. Selection bias could arise from the pre-defined characteristics used to choose the ecosystems and experts interviewed. To mitigate sampling bias, there was aimed to include a range of ecosystem actors with the interviews. Interviewer and interpretation bias were addressed through directed questions and seeking feedback from interviewees on the findings. Furthermore, confirmation bias was mitigated by employing triangulation techniques to ensure multiple perspectives were considered. However, it is important to acknowledge that biases can still persist despite these efforts, especially due to the subjective nature of the research tools used (ecosystem mapping and TIS framework). Finally, the interplay between interviewees during joint interviews may introduce additional biases. The influence of one interviewee on another can potentially impact the responses and skew the data collected. Furthermore, the study's context and timeframe introduce limitations in terms of the generalisability and applicability of the results to other ecosystems or future scenarios. Moreover, the TIS framework is static in nature and offers no insights to directly study ecosystem development, thus the used framework was not useful to propose the scale-up support ecosystem roadmap. Moreover, the TIS building blocks are technology and product dependent, and the chosen technology and its characteristics should represent well the subject of the study.

Awareness of these limitations is crucial when interpreting and applying the findings of this study. Future research should aim to address these limitations by expanding the sample size, incorporating a wider range of ecosystems, and employing more comprehensive research methodologies to enhance the depth and breadth of understanding within the field of scale-up support ecosystems.

6.3.2 Management of Technology relevance

This thesis is relevant in the context of Management of Technology (MoT), since it touches upon the development of high-tech technologies, with in this context, industrial biotechnology. This multiple embedded case study (Research Methods) will focus on identifying the actions and interactions that are relevant to the innovation process of (technical) scale-up in industrial biotechnology by identifying the actions and interactions that are relevant to the innovation process (Technology, Strategy & Entrepreneurship). Also, it applies knowledge of innovation processes at the project (TRL levels) as well as the discipline level of industrial biotechnology, also applying the concept of the Valley of Death to industrial biotechnology specifically (Emerging and Breakthrough Technologies). The technology development problems can be distinguished into four types of problems: Funding problem, problem with technology, shared vision problems, and network formation problems. Where the funding and network formation problems are investigated and has been searched for solutions to overcome these by looking at other "successful scale-up support ecosystems" across industries. The study involves and acknowledges the complexity and context dependency of research & innovation networks and involving different stakeholders. Therefore, ecosystem mapping was performed, to capture the context of each ecosystem and visualise the actor-specific roles and importance within that ecosystem. In the end, trying to translate the findings into relevant insights for the Planet B.io - Biotech Campus Delft scale-up support ecosystem. Moreover, the whole case study design and triangulation are research methods taught during the MoT program. Besides, the need for the management to be aligned with the business model, the types of business models and funding touch upon economic foundations and financial management. Moreover, the business model canvas has been used as a framework for the proposed business model of a shared piloting facility. Thus, this thesis applies several elements taught during the MoT program and adds to the technology innovation literature by presenting a scale-up support ecosystem framework, identifying the industrial biotechnology scale-up success factors, its scale-up support requirements, and proposing a possible roadmap and business models for scale-up support.

6.3.3 Practical Relevance

The results of this thesis can directly be used by Planet B.io and the Biotech Campus Delft to determine their strategy and approach in terms of scale-up support facilities and services to be offered. As well as identify the required stakeholders and business model. Besides, the presented roadmap will guide Planet B.io and the Biotech Campus Delft. Moreover, policymakers but also other support ecosystems can benefit from the insights generated by this thesis and use it to guide strategic decision-making. Also, a new approach to study ecosystems has been introduced by this study, which could prove useful for future research, when studying (scale-up support) ecosystems. The relevance of this research for other, even more mature, scale-up support ecosystems was also demonstrated during the interviews, since a "mature" scale-up support ecosystem like Brightlands Chemelot is still struggling with, or at least working to improve, their support ecosystem and their business model.

6.3.4 Societal Relevance

The successful scale-up support for industrial biotechnology can help industrial biotechnology contribute to at least 8 of the 17 United Nations Sustainable Development Goals (SDGs), including:

- SDG 2: Zero Hunger - Industrial biotechnology can contribute to food security by enabling the production of sustainable and nutritious food ingredients and additives, such as proteins and sweeteners. It can also support the development of sustainable agricultural practices, including the use of bio-based fertilizers and crop protection products, that can improve crop yields and reduce environmental impact. Additionally, industrial biotechnology can play a role in reducing food waste by enabling the development of new and more sustainable packaging materials that help to extend the shelf life of food products. Therefore, successful scale-up support for industrial biotechnology can help to address the root causes of hunger and malnutrition and contribute to the achievement of SDG 2.

- SDG 3: Good Health and Well-being - Industrial biotechnology can contribute to health and well-being by enabling the development of sustainable and healthier food ingredients and additives, such as plant-based proteins and natural sweeteners. It can also support the development of new and more effective pharmaceuticals, vaccines, and diagnostic tools. Additionally, industrial biotechnology can help to reduce environmental pollution and exposure to harmful chemicals, which can have a significant impact on human health. Therefore, successful scale-up support for industrial biotechnology can help to promote good health and well-being and contribute to the achievement of SDG 3.

- SDG 7: Affordable and Clean Energy - Industrial biotechnology can provide sustainable alternatives to fossil fuels, reducing greenhouse gas emissions and helping to achieve the goal of affordable and clean energy.

- SDG 9: Industry, Innovation and Infrastructure - Successful scale-up support can help to promote innovation and build resilient infrastructure to support sustainable industrial processes.

- SDG 12: Responsible Consumption and Production - The development of sustainable alternatives to fossil-fuel-derived chemicals and plastics can promote responsible consumption and production, helping to reduce waste and pollution.

- SDG 13: Climate Action - The use of industrial biotechnology can contribute to climate action by reducing greenhouse gas emissions and even re-use waste and convert it into valuable compounds.

- SDG 14: Life Below Water - Industrial biotechnology can contribute to the conservation and sustainable use of marine resources by enabling the development of sustainable and eco-friendly aquaculture practices, such as the use of bio-based feeds and probiotics or even cultivating fish. It can also support the development of new and more effective tools for monitoring and managing marine ecosystems, such as biosensors and microbial-based monitoring systems. Additionally, industrial biotechnology can play a role in reducing the environmental impact of activities that affect marine ecosystems, such as aquaculture and shipping, by enabling the development of more sustainable and eco-friendly technologies and practices. Therefore, successful scale-up support for industrial biotechnology can help to promote the conservation and sustainable use of life underwater and contribute to the achievement of SDG 14.

- SDG 15: Life on Land - Industrial biotechnology can enable more sustainable agriculture and help to protect and restore ecosystems, supporting biodiversity and life on land.

Overall, successful scale-up support for industrial biotechnology can help to promote sustainable development and address a range of social, economic, and environmental challenges.

6.3.5 Recommendations for Planet B.io

1. Use the proposed scale-up support ecosystem roadmap and business models as a guideline for strategic decision-making

2. To test and validate the proposed scale-up support business model(s) identified in this study. This will provide practical insights into the viability and effectiveness of different business models in supporting the (technical) scale-up process.

3. The current business model of Planet B.io can be complemented through the distinction of large corporations and start-up for its membership model and increasing the value of its membership model through network expansion and offering scale-up support services

4. Additional income can be generated through the offering of lab- to pilot-scale and planning towards industrial-scale as a support service. This service is best paid for with the government voucher system, offering investment planning and help with grant, subsidy, or funding application should all be billed for through milestone-based billing or no cure no pay billing to link the income of scale-up support with the start-up's needs

5. The proposed services and business models should be validated with the start-ups (market validation)

6. Before setting up the shared piloting facility examine the operations, funding, and revenue models of the BioBased Europe Pilot Plant (BBEPP) and FermHub Zealand. These case studies can provide valuable insights into the practical implementation of shared piloting facilities.

7. Explore partnerships with suppliers and service providers such as GEA, Kerry, Tetra Pak, Alfa Laval. Large companies like Corbion and a piloting facility with equipment and operator pool like the BBEPP in Ghent.

8. Extend and align the knowledge & talent within the ecosystem through promoting the translational activity of the TU Delft, as well as adding and aligning an university of applied sciences and vocational level education.

6.3.6 Recommendations for future research

In order to advance the understanding of scale-up support ecosystems and their dynamics, the following recommendations are proposed for future research:

1. Conduct additional interviews with a wider range of stakeholders. This should include key actors such as scale-up/piloting facilities and relevant governmental institutions to gain a comprehensive perspective on the ecosystem.

2. Explore and study the scale-up support ecosystem of Toulouse White Biotechnology. This ecosystem should be investigated in-depth, including an analysis of its operating mechanisms, funding sources, and revenue models. The initial ecosystem maps and desk research findings for this ecosystem can be found in Appendix D.

3. Refine the scale-up support ecosystem framework presented in this study using a more refined colour coding than the three colours (complete (green), partially complete (orange), incomplete (red)) currently used.

4. Evaluate the extended Technological Innovation System (TIS) framework in a new and related context. Assess its applicability and effectiveness in understanding and analysing the dynamics of another scale-up support ecosystem with similar characteristics as industrial biotechnology and sustainable chemistry.

5. Include an additional industry in the study to expand the scope and breadth of the research. By comparing scale-up support ecosystems across multiple industries, a more comprehensive understanding of the factors influencing (scale-up support) ecosystem development can be achieved.

6. Investigate the dynamics of ecosystem development, which could not be fully explored using the TIS framework alone. Analyse the factors, interactions, and mechanisms that drive the growth and evolution of scale-up support ecosystems over time.

7. Determine the contextual factors and roadmaps for ecosystem development. Explore the specific conditions and pathways that enable the successful establishment and growth of scale-up support ecosystems in different contexts.

These recommendations aim to enhance the knowledge and understanding of scale-up support ecosystems, their functioning, and their potential for facilitating technological innovation and economic growth. By addressing these research areas, future studies can contribute to the development of effective strategies and policies to support scale-up ventures and foster sustainable innovation ecosystems.

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A Literature Review Approach and Searches

A.1 Search Description

To answer the question: what are the factors affecting successful scale-up in industrial biotechnology, and how can scale-ups be supported? It was necessary to have a closer look at the issues faced by scale-up and start-up businesses. When looking into scale-up and its obstacles, initial topic searches revealed that the Valley of Death was important. Other subjects of interest included technical scale-up, piloting, Technology Readiness Levels (TRLs), and support ecosystems, as well as their business models and stakeholders. Also, when looking for relevant industries and support ecosystems, the characteristics of industrial biotechnology (long technology development, capital intensive, economies of scale, and the product is a bulk product with low profit margins) were taken into consideration.

A.2 Keywords and Related Search Queries

First, to be able to properly define a search query, the separate parts of the topic were searched for keywords using a dictionary. This provided keywords and synonyms related to the topic. This was done for start-up, scale-up, Valley of Death, growth chasm, industrial biotechnology, support, ecosystems and business model and resulted in Table 10, which was complemented with other synonyms and keywords found during the literature research.

Table 10: Keywords and related search queries used for the literature review.

Keywords	**Related search queries**
Start-up	startup, start?up
Scale-up	scale-up, scaleup, scale?up, scaling up, grow(ing) company OR enterprise, OR business OR firm, high?growth, scalability, growth OR direction phase
Technical scale-up	technical scale-up, techn* AND scal*up, pilot*
Challenges	requirements, challenges, issues, problems, causes, pitfalls, bottlenecks, needs, hurdles, limiting factors, barriers
Valley of Death	valley?of?death
Industrial Biotechnology	biotech, industrial biotech*, economies of scale, capital intensive OR high CAPEX, long technology development
Support	support, help, aid, assistance, type of support, focus
Ecosystem	ecosystem, facilit*, incubat*, hub, accelerat*
Business model	business model(s), fund*, support model(s) AND manag* OR management
Stakeholders	stakeholders OR actors

A.2.1 Information Sources and Queries

The SCOPUS database was used to find relevant literature since, together with Web-of-Science, it offers the most comprehensive literature database that exclusively includes peer-reviewed publications and patents. Searches for literature will now be more pertinent than they would be using Google Scholar. This literature was connected to (technical or business) scale-up, its requirements, and support. Mendeley was also employed as a method for gathering and arranging the literature.

When searching the Scopus database only searching on scale?up* OR "scale up*" OR scaleup* resulted in 39,527 hits. Adding "requirements" gives 1630 hits and 206 review papers. Selecting the relevant subject areas reduces this literature search to 134 articles (Table 11), which provided Allan et al. (2019); Ellwood et al. (2022); Sanford et al. (2016). Further, relevant literature searches on start-up and scale-up are listed in Table 11 resulting in Coad et al. (2020); Ducrée (2018); Duruflé et al. (2017); Noorman (2011); Strömsten and Waluszewski (2012); Takors (2012).

Table 11: Queries on start-up and scale-up and challenges/ requirements

Database used	Date of Search	Query	Articles Found
Scopus	25-5-2022	TITLE-ABS-KEY ((scale?up OR "scale up" OR scaleup) AND requirements) AND PUBYEAR >2009 AND (LIMIT-TO (DOCTYPE , "re")) AND (LIMIT-TO (SUBJAREA , "ENGI") OR LIMIT-TO (SUBJAREA , "CENG") OR LIMIT-TO (SUBJAREA , "BIOC") OR LIMIT-TO (SUBJAREA , "CHEM") OR LIMIT-TO (SUBJAREA , "ENVI") OR LIMIT-TO (SUBJAREA , "AGRI") OR LIMIT-TO (SUBJAREA , "BUSI") OR LIMIT-TO (SUBJAREA , "MULT"))	134
Scopus	25-5-2022	TITLE-ABS-KEY ((scaleup OR "scale up" OR scale-up OR "scaling up") AND (start-up OR startup OR "start up") AND (challenges OR bottlenecks OR hurdles OR cause AND failure)) AND PUBYEAR >2009	6
Scopus	1-6-2022	(TITLE-ABS-KEY ((scaleup OR "scale up" OR "scale-up") AND ("start-up" OR startup) AND challenges)) AND PUBYEAR >2009	13
Scopus	1-6-2022	TITLE-ABS-KEY ((scaleup OR "scale up" OR scale-up OR "scaling up") AND (challenges OR bottlenecks OR hurdles OR cause W/5 failure))	47

A snowballing approach was used to find additional relevant literature based on the literature found using the queries. In addition, there was looked into the Valley of Death and the Growth Chasm, since these topics showed up in relation with scale-up challenges (see Table 12). Which among others provided Linton and Xu (2021); Kampers et al. (2021) and Schoonmaker and Rau (2014).

Table 12: Queries performed on the Growth Chasm and the Valley of Death for biotechnology

Database used	Date of Search	Query	Articles Found
Scopus	1-6-2022	TITLE-ABS-KEY ("growth chasm" OR "Valley of Death") AND PUBYEAR >2009	315
Scopus	1-6-2022	TITLE-ABS-KEY (("growth chasm" OR "Valley of Death") AND biotech*) AND PUBYEAR >2009	21

Besides, literature research was performed looking into scale-up support ecosystems (for industrial biotechnology) the facilities offered for technical scale-up support, its business models and stakeholder roles (Table 13). This resulted in for example, Stadler and Chauvet (2018); Guan et al. (2021); Bocken et al. (2014); Banc and Messeghem (2020); Djordjević and Mihić (2022); Hatvani et al. (2022); Hughes and Meckling (2018) The rest of the included literature was found using the snowballing approach (e.g., Bhatli et al. (2015); Delvigne et al. (2017); Hearn (2017)) or was supplied by Dr. Maria Cuellar-Soares on the topic (Biggs et al., 2021; Chen et al., 2022; Davison & Lievense, 2016; Efara et al., 2019; Humbird, 2021; Nielsen et al., 2022; Obloj et al., 2023; Smanski et al., 2022; Vankan et al., 2020).

A.3 Inclusion and Exclusion Criteria

Criteria of inclusion and exclusion were used to select the most relevant literature for the review (Table 14).

Table 13: Queries performed on scale-up support for industrial biotechnology or industries with similar characteristics, also looking into the technology readiness levels.

Database	Search Date	Query	Articles Found	Screened abstracts	Read papers	Included
Scopus	Feb 2023	TITLE-ABS-KEY ((scaleup OR ”scale up” OR scale-up OR ”scaling up”) AND (support* OR accelera* OR ecosystem OR hub OR incubat*) AND biotech*)	249	8	4	2
Scopus	Feb 2023	TITLE-ABS-KEY ((scaleup OR ”scale up” OR scale-up OR ”scaling up”) AND (support* OR accelera* OR ecosystem OR hub OR incubat*) AND ”economies of scale”)	20	3	2	2
Scopus	Feb 2023	TITLE-ABS-KEY ((scaleup OR ”scale up” OR scale-up OR ”scaling up”) AND (support* OR accelera* OR ecosystem OR hub OR incubat*) AND ”stakeholders”) AND (LIMIT-TO (SUBJAREA , ”ENGI”))	43	2	2	1
Scopus	Feb 2023	TITLE-ABS-KEY ((incubator OR accelerator OR hub) AND ”business model” AND (”type of support” OR focus))	84	23	15	2
Scopus	Feb 2023	TITLE-ABS-KEY (”technology readiness level” OR ”technology readiness levels” OR ”TRL” OR ”TRLs”) AND (LIMIT-TO (SUBJAREA, ”SOCI”) OR EXCLUDE (SUBJAREA, ”MEDI”)) AND (LIMIT-TO (SUBJAREA, ”BUSI”))	15	3	3	2
Scopus	Feb 2023	TITLE-ABS-KEY (techn* AND support OR ecosystem OR incubator OR hub OR accelerator AND facilit* AND (”technology readiness level*” OR trl*))	85	10	7	4

Table 14: Criteria of inclusion and exclusion of sources for the literature review.

Criterion	Inclusion	Exclusion
Publishing date	From 2010 till 2022	Before 2010, except when paper is fundamentally relevant or still highly cited
Language	English	Other languages
Study length	All	None
Research type	books (chapters), peer-reviewed scientific journals, other high regarded sources	Blogs, forums, non-journal websites, patents
Number of citations	credible or highly regarded articles (higher number of citations)	Uncredible articles and/ or low impact score article
Relevance	Related to scale-up requirements/ challenges, focusing on industrial biotechnology or related industries (4 characteristics)	Highly technical papers, unrelated sectors

The books that are included (Blank and Dorf (2012),Moore (2014), Harnish (2014)) kept coming back in relevant literature and are highly regarded in their field. Therefore, these are included in the review even though they did not occur in the SCOPUS database. There are also sources that were relevant, but did not meet the quality requirements, thus were not included. Another relevant article not included was on premature scaling, which is not a peer reviewed article and therefore not included, but gives insight into premature scaling. This literature research was more of an iterative process than previously described, with refining searches and finding literature via queries or indirectly via sources. Still, firstly creating a list of keywords (Table 10) and setting and refining the inclusion and exclusion criteria (Table 14) the literature research became more structured. The literature review resulted in the findings as discussed in section 2.1.

B Research Approach

B.1 Case study and interview process modelled using Business Process Modelling notation (BPMN)

The BPMN model of the conducted case study and interview process (see Figure 28)

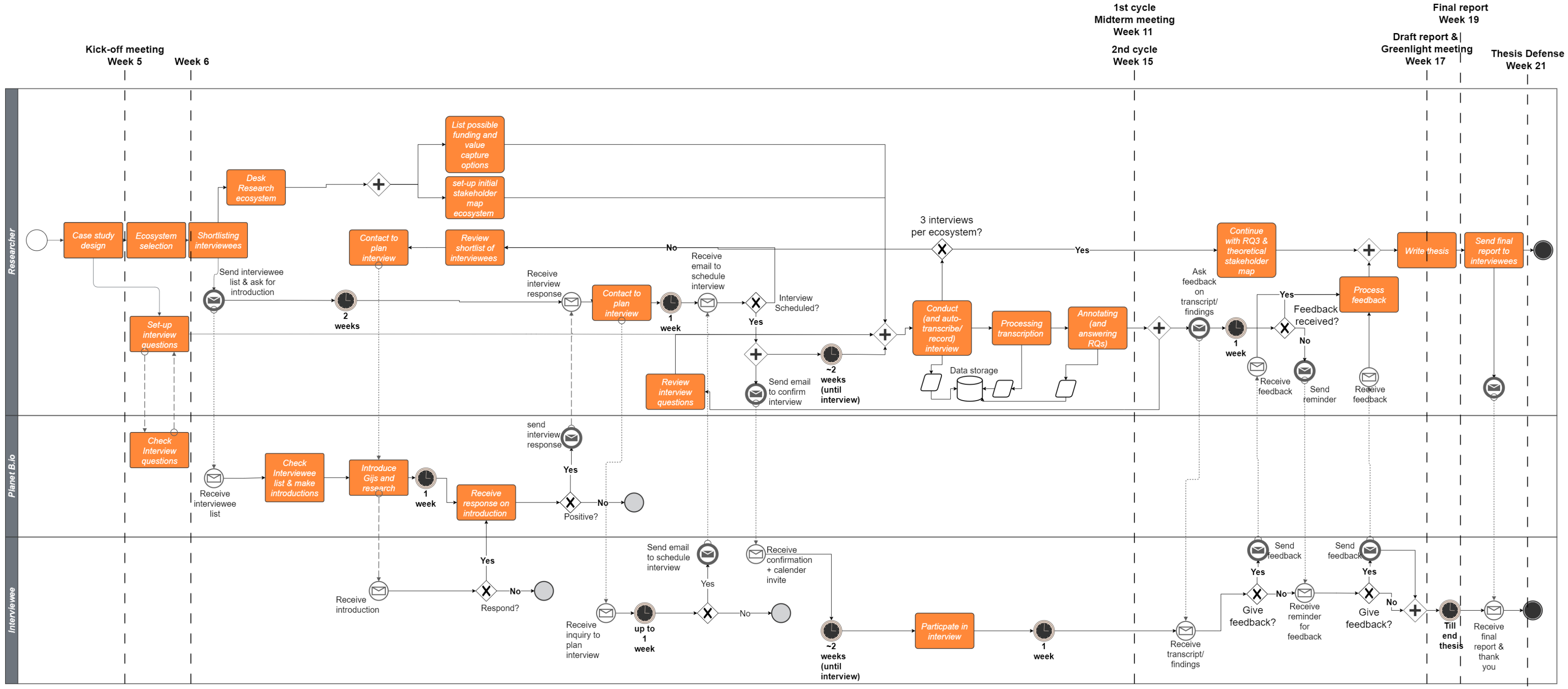

Figure 28: Overview of the case study and interview process modelled in a flowsheet, using business process modelling en notation (BPMN) modelling. The researcher (Gijs), the subject of study and research hosting organisation (Planet B.io) and the interviewee(s) have been visualised in separate swimlanes with their actions over time. Also, the project has been separated into milestones by dashed lines with the event and project week above. So, week 5 means that the study has been ongoing for 5 weeks.

B.2 Predefined interview questions for semi-structured interviews

Most important things to know about these scale-up supporting ecosystems based on the research questions. Essential questions to ask during an interview if not found through desk research.

Before interview:

- May I record and transcribe this interview?
- Can I publish your name and position in my thesis as an interviewee? I will publish the transcribed interviews anonymously and will ask permission to use specific quotes in my report.
- Will you sign the informed consent form? (see Appendix B.3, Figure 29)

Starting with an ice-breaker:

- What is your name?
- What is your background?
- What is your role at [name organisation]?
- NAME, can you tell me about [name organisation]?

Type of scale-up support:

1. How would you define technical scale-up support?
   - If needed, explain my definition: every service or facility offered to help scaling of the (bio)chemical process towards industrial scale.
2. How would you define an ecosystem?
   - If needed, explain my definition: network of organisations, individuals, and institutions that contribute to the creation and application of knowledge and technology in a specific industry and help with commercialising technology within this industry.

Technical requirements for scale-up support (facilities):

3. What is essential to be offered in terms of technical facilities or services for (industrial biotechnology) start-ups?
4. What (technical scale-up) support is currently offered within the [name organisation] ecosystem and how was this set-up?
   - Possible follow-up questions:
   - What is your Technology readiness level (TRL) focus/ from and until what scale (in liters) (of the scale-up facilities)? **Show list of TRLs** (see Appendix B.4, Figure 30).
   - Do you also provide human resources to the start-ups?
   - Which TRLs should be focused on initially when building a support ecosystem (and which later)?
5. What would an ideal scale-up support ecosystem have in terms of facilities/ support services and how would this be set-up?

Business models:

6. What are the type(s) of funding you obtain for the scale-up supporting facilities? and from which parties?
7. Are there any grants, VCs or corporate VCs that fund capital expenses? If so, which?

- **Evaluate list of funding options** (see Table 15), evaluate how likely (and how important) these are.

8. How is the income for the scale-up support (facility) generated/ secured?

- **Evaluate list of income models** (see Table 16), evaluate how likely (and how important) these are. What are possible ways of generating income for technical scale-up support?
  - For start-ups: Which business model would be attractive for you as a scaling company?

Stakeholders: (not for start-up interview)

9. What are the parties involved with the scale-up support ecosystem and what are their roles?

- Possible follow-up question:
  - Who are essential for the scale-up support facilities/ services and why?
- **Evaluate ecosystem maps**. Are these the parties and their roles in the (scale-up support) ecosystem of [name organisation]?

10. What stakeholders (and roles) would the ideal scale-up support ecosystem have?

Closing:

- Is there anything else?
- Can I send the worked out interview (and later the case study) to you for feedback?
- Are there any other people that you can refer me to that would be valuable to interview?

B.3 Informed consent form

Informed Consent Form

Title of Study:

Successful Scale-Up Support of Start-ups in Industrial Biotechnology and Similar Industries: A Multiple Case Study.

Researcher:

Gijs Brouwer, double degree master student Life Science & Technology and Management of Technology under supervision of Dr. Maria Cuellar-Soares of Planet B.io and Prof. Dr. Roland Ortt of the TU Delft

Introduction:

I am conducting research in collaboration with Planet B.io on scale-up in industrial biotechnology and similar industries. The aim of this study is to investigate the best role for ecosystems in scale-up support and how it can best be set up and organized. The study will focus on different ecosystems that support start-ups in scaling up to industrial scale, referred to as "scale-up support ecosystems." The focus of the research is mainly on "technical scale-up," as it is still seen as the biggest challenge at the moment.

Description of Interview:

The interview will take approximately 1 hour up to maximally 1.5 hours and will discuss the following points:

- The scale-up support currently offered within the ecosystem
- Hypothesize about the ideal scale-up support ecosystem
- Funding technical scale-up support
- Generating income for scale-up support
- The parties and their roles within a scale-up support ecosystem specifically and hypothesize about the ideal scenario

Recording:

The interview will be recorded for the purpose of accurately documenting the interview. Only the researcher (Gijs Brouwer) will listen to the recording. The transcript will be shared after the meeting for feedback, and the final report will be shared as well. All recordings will be deleted after the study is finished.

Withdrawal of Consent:

After the interview, you have 72 hours to withdraw permission to use certain answers. You can do this by contacting the researcher (Gijs Brouwer) through the provided contact information.

Date: Participant's paraph:

Confidentiality:

All information provided during the interview will be kept confidential. The data collected will be stored securely and only accessible to the researcher and research supervisors. No identifying information will be included in any reports or publications resulting from the study.

Contact Information:

If you have any questions or concerns about the study, please contact me (Gijs Brouwer) at gijs.brouwer@planet-b.io. If there are any complaints about the procedure or the researcher, you can contact Dr. Maria Cuellar-Soares (maria.cuellar-soares@planet-b.io) or Dr. Roland Ortt (J.R.Ortt@tudelft.nl).

Consent:

I **[NAME]** ________________ have read and understood the information provided in this consent form. I agree to participate in the interview and understand that my participation is voluntary. I understand that I have the right to withdraw my consent at any time during the interview.

Signature ___________ Date ____-____-______

Figure 29: Informed consent form as signed by every interviewee

B.4 TRL scale

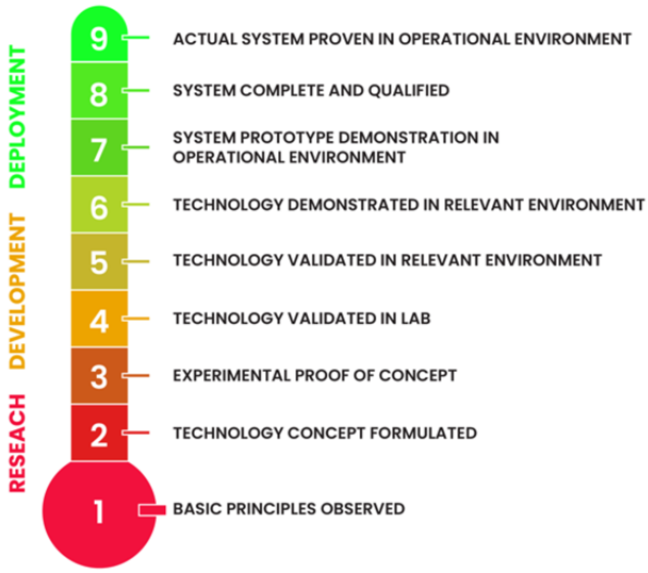

Figure 30: TRL scale used for the interviews, obtained from InnovoloGroup (n.d.).

B.5 Business models of scale-up support

B.5.1 Funding for scale-up support facilities

FUNDING SCALE-UP SUPPORT FACILITIES

1. Equity funding	2. Government funding (subsidies)	3. Corporate funding	4. Alternative funding	OTHERS?
Venture capital	Municipality	Corporate donations or sponsorship (membership)	Foundation grants	?
Angel investors (e.g., private investors, families)	Province	Corporate social responsibility funds	Endowments	
Investments from large companies (one, two or more?)	National government	Co-founding companies (one, two or more?)	Investment from educational/ research institute (e.g., university, TNO)	
Pension funds	EU	Investments start-up hosting hub (e.g., Planet B.io)	Crowdfunding	
Insurance companies			Crowdinvesting	

Table 15: Options investigated in terms of funding for a shared piloting facility

B.5.2 Revenue model for scale-up support facilities or services

LIKELIHOOD INCOME MODEL SCALE-UP SUPPORT FACILITIES

1. Services	2. Fees	3. Government payment	4. Payment options	5. Additional revenue streams	OTHERS?
Offer consulting services	Fee for access to specialized equipment and expertise	Government vouchers for scale-ups to use services/ facilities	Pay partly with equity	Events, workshops, or training programs hosted at the facility.	?
Offer customized research and development services	Corporates pay more than start-ups	Government subsidies (municipality, province or national?)	Pay in installments	Sale of by-products or waste materials from the scaling process.	
	Similar billing for all customers	EU subsidies	Pay part upfront rest when the next funding round is obtained	Licensing or selling intellectual property.	
	Membership model (for regular access to services or facilities) - corporates pay more?		Revenue sharing model	Research and education purposes at the facility.	

Table 16: Options investigated in terms of revenue model for a shared piloting facility

B.6 Case study protocol questions

The following are some case study protocol questions used during this study:

1. What are the research questions guiding the study?
2. What is the conceptual framework or theoretical perspective?
3. What are the cases being studied and why were they chosen?
4. What is the larger context within which the cases are embedded?
5. What is the rationale for using a multiple case study design?
6. What are the sources of data that will be used for the desk research, and how will the data be collected and analyzed?
7. Who are the participants for the semi-structured interviews, and how will they be selected?
8. What are the key questions for the semi-structured interviews?
9. How will the data from the interviews be collected, transcribed, and analyzed?
10. What are the potential biases and limitations of the study, and how will they be addressed?
11. What strategies will be used to ensure validity and reliability?
12. What are the ethical considerations and how will they be addressed?
13. What is the timeline for the study?
14. Who are the stakeholders and how will they be involved?
15. What are the expected outcomes and contributions of the study, and how will they be disseminated to relevant stakeholders?
16. How will the data be managed and stored to ensure confidentiality, privacy and security?

B.7 Ecosystems, hubs and piloting facilities considered but not included for the case study

B.7.1 Ecosystems/ industries/ hubs:

1. Watertechnology: Nederland, Leeuwarden, West, Noord; Wetsus, Royal HaskoningDHV, TNO, Stowa, IHE, TU Delft, WUR, RUG, UT, TU/e, UvA, VU en CEW, KWR, Deltares, Paques, CoE Watertechnology (piloting and demosites offered).

2. Quantum technology: QuTech (demonstrators), TU Delft, LION, Microsoft, SURF, AMS-IX, RUG, TU/e, UvA, TNO, Yes Delft, FET Quantum Technologies. Not a mature technology/ industry, thus mainly focused on research not on scaling of the technology.

3. Fotonica: photonhub europe, AMOLF NanoLab Amsterdam (facility, NanolabNL), Dutch optics centre (Delft), Lionex (contract piloting and manufacturing).

4. 3D printing, AddFab + brainport industries offer business and pilot-scaling when combined.

5. Automotive Campus Helmond met Altran testing facilities and small-scale production.

6. Robotics: Robovalley (robo house), unmanned valley.

7. The IAR Cluster (Industries and Agro-Resources), based in the Hauts-de-France and Grand Est regions (harder to find in depth info) (Stadler & Chauvet, 2018). Toulouse white Biotechnology was considered more relevant for industrial biotechnology.

8. Biomaterials: KCL pilot plant and labs, finland. Combination with Enter Espoo makes it a start/scale-up ecosystem.

9. Maritime engineering: Marin facility. Marine technology water simulation facility. Consortium based shared pilot facility, might offer interesting insights from the maritime engineering field. Marine technologies. R&I ecosystem: Rijnmond, Drecht-steden, Groningen, Friesland, Vlissingen, Hengelo, Nederland; TU Delft, Hogeschool Rotterdam, Marinebouw Cluster, Defensie, Damen, Oceanco, Veth Propulsion, Ampelmann, McNetiq, MARIN, Thales, TNO, IHC, Royal Huisman, Nederland Radarland.

10. Genopole, France: no technical scale-up facilities.

11. shakeup factory in France: only a start-up accelerator no technical scale-up facilities.

12. Wageningen University also has biobased products innovation plant, which is more a R&D facility than a technical scale-up facility.

13. Biopharma. Leiden BioScience park. No (shared) technical scale-up facilities

14. Biopharma. Pivot Park Oss. No (shared) technical scale-up facilities found.

B.7.2 Piloting facilities:

1. Bio Base Europe Pilot Plant, Ghent, Belgium. Only a pilot facility, no ecosystem. Can become a partner or a competitor for Planet B.io - Biotech Campus Delft in terms of piloting facilities.

2. Boku BioIndustrial pilot plant, for antibodies, plasmids etc (Austria, Vienna). Only technical scale-up facilities.

3. Bodec, Helmond, The Netherlands. Pilot facility, process development, optimisation and production for the food industry. Private company, only DSP.

4. Intertek. Chemical industry, Oil and gas pilot plant studies.

B.7.3 Industries and Agro-Resources cluster France: A Scale-Up Supporting Ecosystem for Industrial Biotechnology

The Industries and Agro-Resources (IAR) cluster, which was established in France in 2005 to promote innovation in the bioeconomy and develop industrial demonstration and feasibility platforms at TRLs 5 to 9 (Stadler & Chauvet, 2018). The IAR cluster focuses on agricultural and industrial biotechnology. IAR has a large network of more than 350 stakeholders, ranging from farmer cooperatives and research organizations to venture capital firms, start-ups, SMEs, large industries, and end-users. Their common goal is to optimise the valorisation of renewable resources through biorefining (Stadler & Chauvet, 2018).

Technical scale-up facilities
The IAR cluster has created an innovation ecosystem that fosters relationships between actors along the full value chain and has facilitated investments in new platforms and programs through public-private partnerships. The Biorefinery of Bazancourt-Pomacle is a good illustration of such a collective approach and focuses only on industrial biotechnology with the open innovation platform BRI (Bioraffinerie Recherches & Innovations). BRI has two components, public and private, that cover a significant part of the TRL scale, ranging from the lowest TRLs (ideas and proof of concept) to the highest TRLs (demo). The location of BRI within the biorefinery is also advantageous as it provides access to utilities and industrial substrates.

There are also public-private partnerships within the IAR cluster that bring together academic structures, financial, and industrial partners. There is a piloting facility set up in northern France that covers an area of 2300 m^2 and provides laboratory, pilot plant, and offices of 1200 m^2. An investment plan of 9 million euros over ten years will ensure the company's development, dedicated to purchasing laboratory and pilot equipment. All these tools have been selected with the support of INRA's experts, either for the process part or for the laboratory proteins characterization part. Synergies with their neighbor, EXTRACTIS (which has an industrial pilot with a scale-up capacity to handle several tons of material), were developed to reach TRL 8. Stadler and Chauvet (2018) highlights the importance of long-term strategy and support from regional and national public partners for a scale-up support organisation.

B.8 Interviews conducted and interviewee list of the multiple case study

In Table 17 the 8 interviews conducted with the respective 9 interviewees are listed with their respective ecosystem, role and expertise.

Table 17: Interviews conducted with the respective interviewees and interview length listed.

Interview #	***Scale-up support ecosystem***	***Interviewees***	***Date***	***Duration*** (hh:mm)
Interview 1	Planet B.io - Biotech Campus Delft	Interviewee 1, Managing director and founder Planet B.io	April 3, 2023	01:03
Interview 2	Planet B.io - Biotech Campus Delft	Interviewee 2, (ex) Manager Operations Bioprocess Pilot Facility (BPF)	April 18, 2023	01:21
Interview 3	Brightlands Chemelot	Interviewee 3 & 4, Commercial manager research facility services & Manager multi-purpose pilot plant of the Brightlands Chemelot Campus	April 21, 2023	01:01
Interview 4	Copenhagen Industrial Biotechnology	Interviewee 5 & 6, Professor of Biochemical Engineering at the Danish Technical University (DTU) & ex-advisory board member of Toulouse White Biotechnology (TWB) and the Co-founder and CFO of Biofynt, Copenhagen	May 1, 2023	01:32
Interview 5	Brightlands Chemelot	Interviewee 7, CEO and Co-founder of Vertoro which is also a Fellow Biomass Valorization into Chemicals and Fuels at TU Eindhoven	May 2, 2023	00:47
Interview 6	Planet B.io - Biotech Campus Delft	Interviewee 8, COO of Meatable	May 9, 2023	00:48
Interview 7	Copenhagen Industrial Biotechnology	Interviewee 9, Associate Business Development of BioInnovation Institute, Copenhagen	May 10, 2023	00:56
Interview 8	Toulouse White Biotechnology	Interviewee 5, Professor of Biochemical Engineering at the Danish Technical University (DTU) & ex-advisory board member of Toulouse White Biotechnology (TWB)	May 23, 2023	00:31

C Example transcript and interpretation

[00 : 19 : 59.970] - Interviewee 6 - Co-founder & CFO of Biofynt:
Yeah, but it's correct because in terms of scale, it makes a huge difference which product we are talking about. If it is the biotech, probably as John has said, piloting 2000 litres bioreactor or fermenter could be quite enough to show and to get a good amount of product for the validation or for production or for giving to customers. But definitely at the food level that scale increases quite a bit. At least when it is a product based company.

[00 : 20 : 47.230] - Researcher - Gijs Brouwer:
Yeah, then what I'm thinking about, is it possible to go from lab scale? So maybe in the end on lab scale you can go to like 50 litres maybe and then you need to transition to 2000 litres. Is that step something that could be viable?

[00 : 21 : 14.230] - Interviewee 5 - Professor Biochemical Engineering DTU & ex-advisory board TWB:
Yes, to me it seems that factors of ten would be okay. So we can talk about something in the lab and maybe ten litres or something like 15 litres. And then we could talk about the pilot plant which we have both in chemical engineering here, but also in BioSustain. Then that's at 300 litres. And so that's the kind of thing which we can do in the university. And then the next step could be another tenfold increase on that to let's say 2000 litres. And of course what goes with that is all the associated downstream as well. Because it's one thing to say well, that's the size of the fermenter. But of course there's a lot of downstream equipment that would need to go with this as well.

Interpretation:

- Piloting facility up until cubic meter scale ($\approx$ 2000 L bioreactor) is required, also to produce enough product for testing and validation
- Scale-up and piloting in industrial biotechnology should be done in steps of about x10 in terms of scale-up
- At the DTU technology transfer is done and piloting can be done up until 300 L bioreactor scale. Thus, a piloting facility is the next scale-up step.

D Initial findings on the Toulouse White Biotechnology ecosystem

- Heavily funded by the government (100 million), government ground from INSA which is a government organisation. However, gave TWB 7 years to match the funding with corporate investments (100 million in 7 years invested in start-ups from TWB). Macron (2018) wanted to create a start-up nation.
- A lot of different government organisations with different focus
- A lot of focus on fundamental research and experimenting
- Universities and CNRS (largest national research center) present in physical proximity
- All on the same campus
- Full on technology transfer
- Piloting till 300 L, they seem to have it all in place
- Contrast with Copenhagen:
  - centralised around TWB
  - direct government funding from several institutions instead of from one foundation
  - Copenhagen is focused on scale, whereas TWB is focused on fundamental research and creating products from that.
- Where are all the engineers who understand how to get to scale, Interviewee 10, maybe the problem of scaling is already with education and is this too traditional and not suited to create the experts required to help biotechnology flourish.

D.1 Desk research: Toulouse White Biotechnology services and facilities

TWB offer includes:

- the setting up and management of collaborative R&D projects;
- the realization of service provision;
  - iMEAN delivers a technology that can produce very high-quality mathematical representations of living organisms. These can be used to generate predictions in terms of metabolic engineering and drastically reduce research time and costs by targeting the sticking points that are delaying scale-up.
  - Processium offers technical and economic studies to verify the viability of a project before its development. These studies aim to establish a purification process for a target molecule resulting from bioproduction and to estimate the production costs of a complete process.
  - Syngulon develops original genetic technologies to increase the efficiency of microorganisms used in industrial biotechnology. These technologies are based on synthetic biology, which revisits microbial genomes to make them more in line with industrial demands in terms of efficiency and environmental compatibility.
- supporting start-ups.

Activities

TWB plays its role as an innovation transfer accelerator. TWB is a demonstrator forging links between basic research and industry. On the one hand, it offers collaborative public/ private R&D projects and services. On the other hand, it supports start-ups in order to accelerater their launch development.

Expertise

TWB covers a wide range of skills, from biological engineering to the development of processes at the pre-industrial pilot scale. Build up:

- Public research laboratories as the Toulouse Biotechnology Institute (TBI), Bio& Chemical engineering at the university of Toulouse (research and application), and other national units of INRAE and CNRS.
- The Centre de Ressources Techniques (CRT) CRITT Bio-industries Midi-Pyrénées (Toulouse). This organisation offers scientific support in microbiology, biocatalysis and industrial separation (design, improvement, implementation and qualification of production procedures of simple or complex molecules by microorganism or enzymes from raw or processed material). Also, it is **qualified for all funding types for innovation** (direct contract, CIR certification (tax refund for research), call for funded research project, unique interministerial fund, National Research Agency, EU project H2020, Strategic industrial innovation program, Network technological services financial aid. Equipment from 500 mL up to 300L fermenter (TWB property) and enzymatic reactor up to 150L, solid/liquid separation equipment, cell breaking equipment, purification equipment and asset stabilisation equipment (evaporators/ dryers), analytics: chromatography (HPLC, IC, GS), spectrophotmetry (UV/VIS, halogen, microplate reader), microscope, gas analyzers, viscometer, dessicator, AWmeter (see: https://www.bioindustries.net/equipements-traitement-biomasse-purification/)

Support

- Investissements d'Avenir French program
- Local authorities: Région Occitanie/Pyrénées-Méditerranée, Toulouse Métropole, SICOVAL
- European Union (FEDER program)

Platforms/ facilities/ services offered by TWB:

1. The TWB offers a cutting-edge microbial strain engineering platform that provides access to automated equipment and devices for genetic and metabolic engineering, synthetic biology, and optimization of protein expression. The platform is equipped with various automated liquid transfer devices, high-throughput analysis equipment such as capillary electrophoresis systems, spectrofluorometer, and luminometer, and an automated colony picker. TWB offers services on this platform and can be used in its entirety or for independent steps. A global approach from gene to process is available, including the construction of strains and the selection of more efficient cultures, and process optimization. As well as services are offered on this platform.
2. The TWB's Biotransformation and Culture platform offers access to a range of instrumented bioreactors (batch, continuous, enzymatic) with capacities from 50 mL to 300 L, for pure strains or mixed-cultures (consortia), coupled with at-line or on-line analytical systems for monitoring biotransformations. The platform includes equipment for

placing micro-organisms in pure or mixed culture, and for characterizing and sorting microbial populations using flow cytometry. The platform also has a culture robotic device equipped with 24 mini-bioreactors (50 mL) for in-depth characterization and culture optimization. The equipment is designed to maximize the potential of other technical platforms, without compromising speed or capacity. TWB offers services on this platform, and the start-up Altar's technology is integrated into the platform for developing new microbial strains without genetic modification. The development of this platform was supported by **local and regional authorities** (Conseil Régional Occitanie / Pyrénées-Méditerranée, Toulouse Métropole, Communauté d'Agglomération du SICOVAL), **the European Union** (2007-2013 FEDER Program) and the **French National Research Agency (ANR)**.

3. The TWB's Analytical platform offers a host of "joint" central analytical tools for research teams collaborating with TWB and other platforms, including chromatographic separation devices (liquid, ion, gas, and size exclusion), total organic carbon (TOC) analyzer, rheometer, flow cytometry cell sorter and analyzer (FACS), and the possibility of coupling with a range of conventional and new-generation detectors such as mass spectrometry and multi-angle light scattering. The platform also offers high-performance and high-speed (UHPLC) analyses and access to cutting-edge analytical tools such as heavy **mass spectrometry** and **NMR** solutions in collaboration with external support platforms (e.g., **MetaToul**). TWB also provides services on this platform.

4. The Unitary Operation platform at TWB provides **solutions for processing and standardizing operations both upstream and downstream of the bioprocesses developed to facilitate their industrial integration**. It also provides solutions for protein purification and the implementation of separation processes based on the use of biomembrane systems. The platform collaborates with **CRT/CRITT Bio-Industries Midi-Pyrénées** in this activity.

So, only the cutting edge microbial strain engineering there is no help or partner mentioned for setting it up or providing equipment/ services.

Services are executed by high-level scientists using high-technology and massively robotised equipment. Eight services offered:

1. High-throughput colony picking
2. Plasmid and strain engineering
3. Single cell characterisation and high throughput screening of microbial cells by cytometry
4. Rapid optimisation of microbial and enzymatic processes
5. Scale-up of the microbial culture process
6. Amino acid quantitative assay
7. Determination of the average molar mass of polymers in solution
8. Ethics and society

Furthermore, access to equipment, hosting teams and activities, and professional training (by INSA Toulouse)

TWB provides support to startups from their creation to their development by offering workspace, services, and access to equipment. This support includes strategic and financial advice, scientific and technological support, administrative support, and introductions to contacts in the TWB ecosystem. The startups hosted by TWB include Aviwell, BioC3, iMEAN, Lantana Bio, and PILI. TWB also partners with national players such as French Tech and AgriO to encourage entrepreneurship and support business creation. To learn more, visit their website.

The support offered by TWB can be summarised as follows:

- Hosting of startups in laboratories and offices
- Strategic and financial advice
- Scientific and technological support
- Access to leading edge equipment
- Administrative support
- Introduction to a wide range of contacts in the TWB ecosystem
- Partnership with national players such as French Tech and AgriO to encourage entrepreneurship and support business creation

D.2 Desk research: Toulouse White Biotechnology ecosystem:

Campus de l'INSA, physical proximity on the campus hosting:

- TBI, Toulouse Biotechnology Institute, Bio & chemical engineering (research and application)
- INSA Toulouse
- CRITT Bio Industries
- TWB

In order to expand TWB range of skills, other partnerships are also developed: Genopole Université d'Evry, ESPCI Paris Tech, MICALIS Jouy-en-Josas, BBF Marseille. Depending on the needs, TWB also collaborates with complementary life science platforms such as the Genotoul Toulouse network.

Suppliers of Technology and Services:

- iMEAN
- Processium
- Syngulon
- MetaToul

Technical development and services:

- Centre de Ressources Techniques (CRT) CRITT Bio-industries Midi-Pyrénées (Toulouse)

Universities & research Institutes:

- Toulouse Biotechnology Institute (TBI)
- Bio & Chemical Engineering at the University of Toulouse
- INSA (TWB supervisory body, core)
- INRAE (TWB supervisory body, core)
- CNRS (TWB supervisory body, core)

Tech transfer structures:

- INRAE transfer
- others also?

Funding and Support:

- Investissements d'Avenir French program
- Local authorities: Région Occitanie/Pyrénées-Méditerranée, Toulouse Métropole, SICOVAL
- European Union (FEDER program)
- A lot of large corporations such as Total energies in the region

Other Partnerships and Collaborations:

- Partnership with national players such as French Tech and AgriO to encourage entrepreneurship and support business creation
- Collaborations with other research institutions such as Genopole Université d'Evry, ESPCI Paris Tech, MICALIS Jouy-en-Josas, BBF Marseille
- Collaborations with complementary life science platforms such as the Genotoul Toulouse network
- Collaborations with the partners of technological infrastructures from IBISBA (Industrial Biotechnology Innovation and Synthetic Biology Acceleration) programme.

E Scale-up support ecosystem comparison overview

Table 18: Scale-up support ecosystem comparison on the completeness of the scale-up support elements based on the identified scale-up support requirements

Scale-up support ecosystem	Planet B.io – Biotech Campus Delft	Copenhagen Ecosystem	Brightlands Chemelot Ecosystem
1. Technical facilities & services	Incomplete* (was partially complete with piloting facility)	Partially complete	Partially complete
Piloting facility, model and room for growth (success factor: pilot where you operate, Sanford et al., 2016)	No piloting facility (bankruptcy BPF), was offering fully-serviced piloting until TRL5-6 (2000 L). Also, room to build own pilot plant or industrial-scale plant	Several facilities offered, under development, pre-piloting facility DTU until TRL5 (300 L). No local fully serviced piloting facility present (yet), (Ferm Hub Zealand and 21st Bio working on this). Locally, not a lot of room to grow and build own facilities.	Multipurpose pilot facility (fully serviced until 300 L, TRL5-6 for sustainable chemistry). Also, a lot of room to grow and build own pilot plants or industrial-scale plant.
Technical support lab to pilot scale and planning towards industrial scale	No, some help was offered by the BPF	No, DTU does help with this also when translating their research to their pre-piloting facility	No, does do safety analysis of the process before piloting and consultancy firms available but expensive.
Flexible pool of experts (e.g., operators)	No, BPF was operated by its own operators, but not flexible.	Some, mainly just facilities offered. Maybe Ferm Hub Zealand and 21st Bio will offer this with their facilities.	Yes, different flexible pools of different types of experts (e.g., operators, contract R&D).
2. Funding & business services	Incomplete	Partially complete	Partially complete
Availability of funding	Some funding. From government and DSM possible within the ecosystem.	A lot of funding available from the Novo Nordisk Foundation and additionally some from the government.	Mostly funded by regional government, also a lot of corporates with funds present within the ecosystem. However, main corporate stakeholder left the ecosystem.
IP strategy support	No, not formally within the ecosystem.	No, not actively present within the ecosystem.	Yes, IP firm within the ecosystem.
Investment planning support	No.	No, not for scaling up. However, this might be offered by investors within this decentralized scale-up support ecosystem.	Yes, from Brightlands Chemelot and only billed when start-up leaves the ecosystem.
Grants, subsidies and investment application support	Little. Some indirect benefits from grants and subsidies applied for by Planet B.io	No.	Yes, partner available that can help with writing grant and subsidy proposals. However, might be expensive since it is not offered by Brightlands Chemelot itself.
3. Network formation & coordination	Partially complete	Incompatible	Complete and compatible
Network organisations	Yes, a lot of network organisations connected to the ecosystem, most of them not directly focused on scale-up support.	No. Only one network organization within the ecosystem but that is not actively coordinating the scale-up support ecosystem.	Yes, but no other network organisations identified within the ecosystem.
Ecosystem completeness	No. Missing roles within the ecosystem	No. Uncoordinated ecosystem	Yes, seems to be a complete ecosystem in terms of actors and roles
4. Knowledge & talent	Incomplete	Partially complete and compatible	Complete and compatible
All education levels present	No, vocational level missing.	Not aligned, due to the decentralized nature of the ecosystem.	Yes, and all education levels are locally present within the ecosystem.
Active translational activity	No, translational activity is lacking compared to other ecosystems.	Yes, DTU even has pre-pilot plant until TRL5.	Yes.
Knowledge & talent is aligned with scale-up requirements	Partially, lack of talent and experts required for scale-up. Link with the TU Delft Engineering Doctorates which can do an internship at the start-ups which is very useful for helping start-ups to "start with the end in mind"	Partially, due to the scale-up and translational activity of the DTU.	Yes. Flexible pools of human capital available, as well as an internship and recruitment office.

Legend

Scale-up support factor is incomplete or incompatible
Scale-up support element is partially complete or compatible
Scale-up support factor is complete and compatible