

# From Lab to Fab

Navigating scale-up challenges of biomass and precision fermentation processes for microbial protein production

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# Executive summary

The **protein shift** is accelerating as we face the environmental and resource challenges of traditional proteins. Animal-based production and massive soy imports carry a heavy ecological footprint, driving greenhouse gas emissions, deforestation, and biodiversity loss. To feed a growing population and supply industries beyond food, including feed, cosmetics and materials, we need solutions that are sustainable, scalable, and innovative.

**Microbial proteins** offer exactly that. By harnessing the power of bacteria, yeast, or fungi, alternative proteins can be produced using fewer natural resources. The key approaches leading this transformation are **biomass fermentation**, in which microbial cells are used as a rich source of protein (single-cell protein), and **precision fermentation**, utilizing programmed microbes to produce specific functional proteins.

To unlock the potential of these innovative technologies, microbial proteins need to be produced at commercial scale. Yet, the journey **from lab bench to large-scale production** is far from straightforward and often requires as much efforts as developing the processes and strains itself. Each stage of **scale-up** introduces new challenges, but overcoming these is critical to achieving **cost-effective** microbial protein production. This report aims to bring clarity in the most significant **bottlenecks along the upscaling journey** and which routes to consider to **de-risk the path to commercialization**.



These **key challenges for scale-up** of microbial proteins are summarized in Figure 1. At the level of the microbes, several issues can arise when dealing with limited strain robustness, including low product yields or increased risks of contamination. In addition, strains with intracellular protein production can require complex and costly downstream processing steps. Specific technical challenges, related to the functional properties of microbial proteins, can also prove to be challenging. For instance, egg white proteins desired for their excellent foaming properties or viscous single-cell protein fermentation may cause significant processing related hurdles. Furthermore, scale-up of microbial protein production demands substantial investments, both in terms of equipment and expertise, and is greatly influenced by the upstream and downstream processing requirements. Finally, bringing the novel proteins to the shelf is constrained by regulatory approval pathways, consumer perception, and market uptake.

The difficulties faced when addressing these challenges often stem from their interconnected nature. Biological factors can shape the required processing steps and associated costs, as well as the regulatory considerations, which in turn affect the market viability of these alternative proteins. **Fortunately, several strategies exist to expedite and support this upscaling journey.** Firstly, building upon a robust business plan enables to identify these interconnections early on, and to approach them with structured preparation. It should define the preferred market position and long-term goals, anticipating the necessary and possible CAPEX investments, operational costs and key process risks. Secondly, scaling-up can be approached by scaling-down. By mimicking large-scale restrictions or applying intentional process perturbations, valuable information to guide further process design is gained. Moreover, such datasets are increasingly valuable for digital, data-driven development tools, including digital twins, which support process monitoring and virtual testing of operating scenarios. In this context, advanced sensing technologies and real-time analytics play a pivotal role in delivering high-quality data. Further opportunities lie in continuous fermentation strategies and innovative downstream processing techniques, both aimed at improving productivity and reducing costs. Finally, a successful scale-up strategy includes a pilot-scale plant to bridge the gap between lab and industrial production, allowing to test processes under industrial conditions, refine process or plant design, and “fail small” before full-scale investment. Beyond technical validation, these facilities foster partnerships, generate reliable

techno-economic data, support regulatory and customer evaluation through representative samples, and strengthen investor confidence.

In essence, scale-up is not a single step but a **multidisciplinary journey**. Those who manage its biological, technical, and market complexities holistically will be best positioned to accelerate the transition from concept to profitable commercialization and shape the future of microbial protein manufacturing.

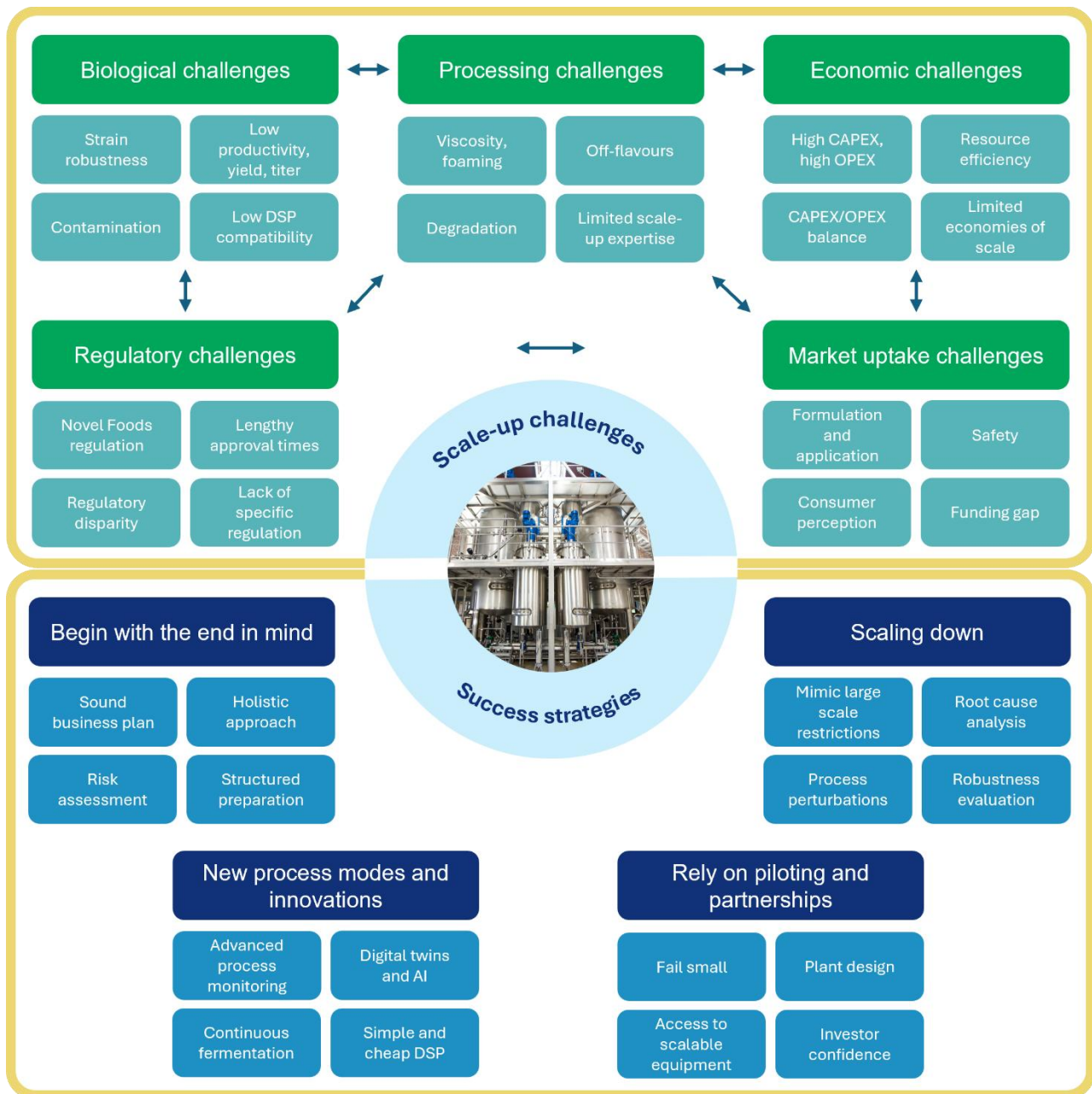


Figure 1. Key challenges and solutions towards successful scale-up of microbial proteins

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# Introduction

**Fermentation** has been integral to human civilization for millennia. Some of the earliest and most widespread applications of fermentation include bread and alcoholic beverages, dating back thousands of years. This ancient technique, once primarily used for food preservation and flavor enhancement, has now evolved into a cutting-edge method for creating sustainable, nutritious, and environmentally friendly protein sources.

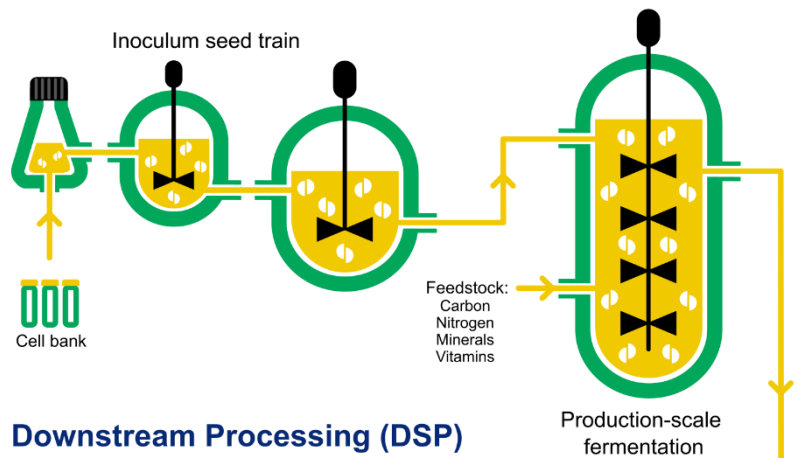
During fermentation, microorganisms, including bacteria, yeasts, or fungi, break down complex organic compounds into simpler molecules. In bread making, for example, yeast ferments sugars derived from the starch in flour, producing carbon dioxide. The CO<sub>2</sub> forms bubbles within the dough, causing it to expand and rise. This technique dates back to ancient Egypt, at around 3 000 BCE. In the 19th and 20th centuries, scientific understanding of fermentation processes grew significantly, thanks to the work of scientists like Louis Pasteur. This knowledge paved the way for more controlled and sophisticated applications of fermentation in various industries, including pharmaceuticals, industrial chemicals, biofuels, food additives, and enzymes. In recent years, fermentation has emerged as a key technology in the **alternative protein sector**. It is now being used to create meat analogues with improved texture and flavour, dairy alternatives, egg substitutes and novel protein ingredients.

These alternative proteins are becoming increasingly vital due to their ability to address **global challenges in food security and sustainability**. As our population grows, traditional agriculture struggles to meet protein demand, whereas fermentation offers scalable production in smaller spaces, customizable nutritional profiles, and resilience against climate-related risks. Beyond food security, fermentation delivers significant environmental benefits, including a lower carbon footprint, reduced land and water use, and the ability to repurpose agricultural by-products, supporting a circular economy. Economically, microbial proteins have the potential to become more cost-effective than animal-based proteins as the technology scales up and becomes more efficient.

A process scheme of a typical industrial-scale fermentation process for alternative protein production is given in Figure 2. First, **upstream processing (USP)** includes all steps involved in supplying microorganisms with a nutrient feedstock and their growth to produce microbial biomass or the protein of interest. Such growth is often performed in a stirred tank reactor (STR). To first generate the required quantity of microbial cells to start a large-scale fermentation, cells are propagated in a seed train. This entails growing microbes from a cell bank in reactors with increasing size. After sufficient biomass is reached, the fermentation process is initiated in a large-scale bioreactor, in batch, fed-batch or continuous mode (see below). Here, parameters including the temperature, pH, pressure, mixing, nutrient and cell concentration can be tightly controlled.

After successful fermentation comes the collection of purification steps to obtain the isolated protein of interest. These **downstream processing (DSP)** steps can significantly differ depending on the type and purity of the desired end product. In addition, a variety of techniques can be employed to this end. A typical first step after fermentation is a cell harvesting step, in which the grown microbial cells are separated from the fermentation broth via centrifugation or filtration techniques. For biomass fermentation products, these cells are often dried directly afterwards using for instance spray drying or drum drying techniques. For precision fermentation products, the produced proteins are either secreted in the fermentation broth or remain

### Upstream Processing (USP)



### Downstream Processing (DSP)

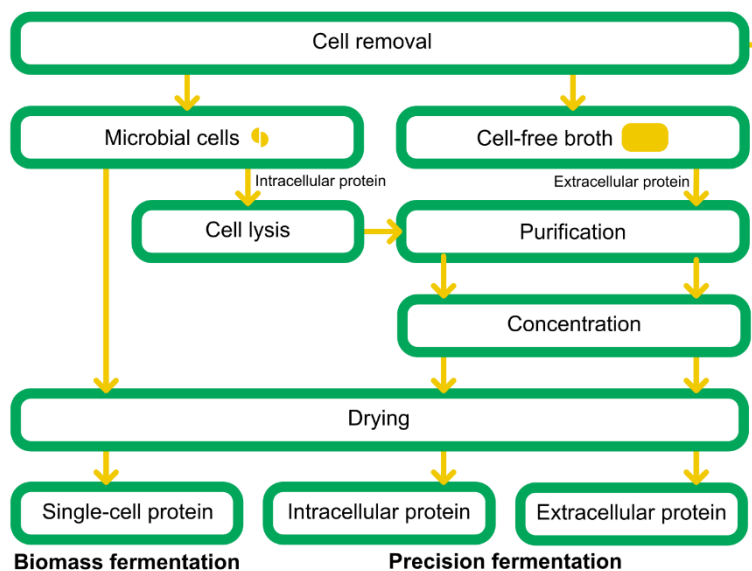


Figure 2. Process flow diagram of industrial biomass and precision fermentation processes.

intracellular, depending on the production microorganisms used. In the latter case, the protein of interest needs to be extracted via lysis of the biomass, after which the cell debris is separated from the soluble protein. This can be mediated via centrifugation or filtration techniques, including for instance tangential flow filtration. Similar filtration techniques can be used to purify secreted proteins from the fermentation supernatant, and additional polishing steps can be included if a high purity end product is desired. A final drying step ensures the shelf stability of the final protein.

Depending on the desired end products, used feedstock and microorganisms, **different fermentation processes** can be employed. During liquid fermentation, microorganisms are cultivated in a liquid medium, where the nutrients are dissolved in water. This allows for precise control over the fermentation conditions such as pH, temperature, or nutrient concentration, while facilitating easy mixing aeration and harvesting of products. Some key applications of this technique include the production of enzymes or single-cell protein. In contrast, solid-state fermentation involves the growth of microorganisms on a solid substrate, mimicking many natural microbial processes. This technique is often used for growth of fungi, given their ability to thrive in low moisture environments. Finally, gas fermentation is an emerging technology in the alternative protein space, utilizing gas-consuming microorganisms to produce proteins and other valuable compounds. It uses gas mixtures, including carbon dioxide, carbon monoxide, or methane as primary carbon source for microbial growth. Hence, industrial waste gases can be utilized for single-cell protein production, contributing to carbon capture and utilization.

Additionally, fermentation can operate under **different process modes** depending on the production needs. Batch fermentation is one of the simplest and most flexible set-ups used. In this closed-system process, all nutrients are added at the start, and the fermentation ends when these are depleted. With the semi-open fed-batch process, nutrients are incrementally added during the fermentation, giving more precise control over microbial growth and therefore allowing optimization of the product yield. Finally, continuous fermentation is a highly efficient process mode, allowing constant output over extended periods of time. It operates as an open-system process where fresh nutrients are continuously added while broth containing cells or products are simultaneously removed. This creates a steady-state system, reducing downtime by eliminating batch-to-batch transitions.

# Why is scale-up difficult?

The central reason scale-up of microbial protein production is so challenging is that biological, processing, economic, and regulatory factors all interact in complex ways, making the process far from straightforward. In this section, we discuss the key hurdles encountered during upscaling and highlight how these bottlenecks are interconnected.

## Biological challenges

At the heart of any biomass or precision fermentation process lies the microbial production strain. Given this, it can only be expected that one of the first bottlenecks that pops up during the scale-up process is a **lack in microbial strain robustness**. Microorganisms that perform well under lab conditions may fail to maintain their productivity or genetic stability when employed at industrial-scale conditions. In addition, it is often difficult to predict how a lab-tested microorganism will perform in these larger environments, of which the conditions are often less accurately controlled.

As a result, one may face **limitations in the productivity and final yield** when scaling the production of microbial protein. This may require further microbial strain optimization to reach commercially viable titres or to reduce the production of by-products. Also, **inefficient feedstock utilization** can be a bottleneck that threatens cost-efficient production. This can be addressed at the level of the strain but may also need to be resolved by modifying the nutrient medium composition or feeding regime in the case of fed-batch or continuous fermentations.

Producing microbial proteins at larger scale also increases the risk for **contaminations** to take over the bioreactor, drastically reducing or eliminating the yield. While some production strains are more prone to contaminations than others, maintaining sterility of large bioreactors becomes more complex with increasing scale, and poses a significant engineering challenge.

Finally, several biological properties of the production strains may cause **limited compatibility with subsequent DSP**. For instance, the grown biomass may have a high viscosity, while some strains for precision fermentation produce their proteins intracellularly, both complicating harvest and purification at larger scale. These biological pitfalls may hinder the scalability of the production process.

## Processing challenges

To ensure optimal functionality of the microorganisms at large scale, they must be cultivated within a carefully engineered production line. Designing this setup effectively is not a matter of simply scaling the individual unit operations and linking them together, as a commercial-scale process is never a simple one-to-one translation of that developed in the lab.

As mentioned above, various biological bottlenecks can be addressed through genetic or metabolic engineering efforts. Microbial strains can be improved via synthetic biology, and optimization of the medium composition can improve the overall feedstock utilization and growth rates. In addition, optimal design of the seed train may depend on the strain's growth rate or cryopreservation strategy. **At the level of the bioreactor**, several process parameters become more essential to optimize with increasing scale. For instance, ensuring sufficient oxygen transfer during aerobic fermentations may be challenging, and will be steered by trade-offs between operating pressure, mixing speed, and the level of aeration. Compared to lab-scale systems, the reduced surface-area-to-volume ratio and therefore **longer mixing times** at larger scales limit the ability to supply oxygen and remove metabolic heat uniformly. As a result, spatial gradients in dissolved oxygen, substrate concentration, pH, and temperature can develop, which can affect the microbial metabolism and therefore lower the protein yield. These heterogeneous conditions are further exacerbated at high cell densities, where increased broth **viscosity** impairs mass and heat transfer, and elevated agitation and aeration rates required to meet oxygen demand introduce additional **shear stress** and **foaming**. Consequently, deviations from ideal, well-mixed conditions that are negligible at lab scale become significant and difficult to avoid at industrial scale.

Specific technical processing challenges for microbial proteins often arise from the exact **functional properties that make them desirable**, including emulsification, gelation, viscosity, or elasticity. For example, many alternative proteins produced by precision fermentation are desired for their foaming or emulsification properties. Egg white proteins such as ovalbumin are specifically produced for their exceptional emulsification and **foaming** properties, enabling the formulation of animal-free dairy or bakery products. However, these same properties must be carefully considered during process optimization, as excessive foaming may interfere with

bioreactor operation, potentially causing overflow, limiting the oxygen transfer, or causing filter fouling in later DSP steps.

Furthermore, their **proteinaceous nature** gives microbial proteins several additional scale-up challenges to consider. The conformation of the protein will determine its properties and therefore its final value. Yet, this conformation, such as its quaternary structure or stretchiness, is often difficult to determine at intermediate steps of the process line and can hence only be tested in the final application. In addition, it may be impacted by the nutrient medium composition or process parameters. Moreover, proteins can be particularly sensitive to denaturation, degradation, or precipitation. This can be induced by harsh process conditions, including strong pH, shear stresses or the use of solvents during DSP. Also, the presence of native proteases originating from the production host can lead to breakdown of the target protein. Such proteolytic activity may generate peptides or free amino acids that contribute to **off-flavour** formation in food applications or can result in increased Maillard reaction with reducing sugars, ultimately reducing product quality and overall yield. Finally, these proteins may have allergenic properties, requiring extensive risk assessments and correct safety precautions for the involved personnel.

Similar challenges will arise **at the level of DSP**. Firstly, and especially relevant for precision fermentation proteins, separation from impurities of similar size such as DNA, endotoxins, or cell debris, may generally be difficult. Moreover, for end products desired at high purity, chromatography steps may be required. These techniques rely on expensive resins and therefore limit the process **scalability**. Avoiding contaminations may also be more difficult for scaled microbial proteins. Heat sterilization is generally not possible given the heat-sensitive nature of most proteins, while sterile filtration to remove the microbial load can be hampered due to high viscosities of the protein preparation. Overall, the general complexity and diversity of fermentation-made proteins make the scale-up journey difficult to predict and model.

Finally, a general hurdle frequently encountered by early-stage companies during upscaling is the **limited availability of in-house process engineering expertise**. Tackling the aforementioned challenges requires substantial technical know-how and a large team of engineers and technicians with experience in biomanufacturing scale-up. Early-stage companies typically operate with smaller teams that often lack dedicated scale-up expertise.

As a result, bridging this gap becomes a critical factor for successful commercialization, underscoring the importance of **access to pilot-scale infrastructure** and **external engineering support** to de-risk scale-up.

## Economic challenges

Beyond technical hurdles, scale-up of microbial protein production is also associated with significant economic challenges. Achieving **cost-competitiveness** with animal or plant-based proteins poses a significant hurdle, yet is essential for successful commercialization.

These economic pitfalls are largely driven by the substantial **capital expenditures (CAPEX)** required during upscaling. Significant investments are needed for the acquisition and installation of large-scale fermentation and downstream processing equipment, as well as for the construction or retrofitting of dedicated production facilities. In addition, uncertainty surrounding the optimal process design often necessitates testing and validating multiple types of industrial equipment and unit operations, further increasing capital risk. Microbial proteins are also associated with distinct CAPEX challenges. Biomass and precision fermentation batch processes rely on large production volumes to achieve economic viability, requiring substantial investment in large-scale fermentation capacity and high-throughput harvesting infrastructure. Moreover, production of precision fermentation proteins, especially for food applications, entails more expensive equipment per unit of product as they require food-grade fermenters and more complex processing to achieve the desired purity and functionality. The lower yields of precision fermentation processes, compared with biomass fermentation where the biomass itself is the final product, also represent a significant cost driver. For early-stage companies, **the limited economies of scale** achievable during initial deployment further exacerbate these challenges, as early production is too limited to offset the high initial costs. Consequently, committing to fully owned industrial infrastructure at an early stage represents a substantial financial burden, further highlighting the **potential value of pilot facilities** to validate process design, reduce capital risk, and inform subsequent investment decisions.

Additional to these capital investments, scale-up must also deal with larger **operational expenditures (OPEX)**. These include the day-to-day costs of running microbial protein production, such as energy use, raw materials, processing, and labour. At lab scale, **resource efficiency** is often not a major concern. Water, energy, and feedstock are consumed in small

amounts, and their cost or sustainability impact is negligible. At industrial scale, however, inefficiencies in media use, energy consumption, or water management can have significant economic and environmental consequences, making process optimization essential for both cost-effectiveness and sustainability. This is particularly evident in biomass and precision fermentation, where the quickly increasing viscosity upon dewatering of protein solutions leads to high drying costs, and therefore poses a major economic challenge. Finally, it is important to recognize that operational efficiency is intrinsically linked to the capital decisions made.

## Regulatory challenges

Even if all intertwined biological, processing, and economic bottlenecks have been addressed, commercialization of microbial proteins may still be constrained by **regulatory hurdles**. In the European Union (EU), the regulatory framework governing these products varies depending on their intended use, the production process involved, and whether genetic engineering is utilized. Innovative foods and food ingredients are subject to stringent rules, particularly under the **Novel Foods Regulation** (EC 2015/2283), which governs products not significantly consumed before May 1997. Both biomass fermentation and precision fermentation proteins for food applications typically require novel food authorization, including a comprehensive safety assessment by the European Food Safety Authority (EFSA).

These regulatory requirements pose several challenges. **Lengthy approval processes** can delay market entry, as novel food applications often take two years or more for evaluation. Also **harmonization issues** can further complicate commercialization. While EFSA provides centralized risk assessments, individual member states sometimes impose additional requirements or restrictions that delay or restrict market access. The lack of clear and transparent standards and guidelines at both national and international levels, coupled with incomplete safety assessments, adds further uncertainty for the food industry and slows progress. Collectively, these regulatory factors underscore the importance of **early engagement with authorities** and careful planning of commercialization strategies for microbial proteins in the EU.

## Market uptake challenges

**Reaching the shelf** remains a significant challenge for microbial proteins, specifically for food applications, and is again shaped by a complex interplay of above-mentioned factors. From a technical perspective, product **formulation** and application pose significant hurdles: achieving **nutritional quality** and **sensory profiles** comparable to conventional animal-derived proteins remains challenging, particularly due to deviations in techno-functional properties. This often results in the need for complex formulations or protein blends. Moreover, additives such as artificial flavorings or colorants may be needed to overcome unpleasant flavors, odors, and tastes, but raise clean-label and “naturalness” concerns.

These technical uncertainties also intersect with **safety considerations**, including contamination risks or potential allergens that originate from feedstock or toxic microbial by-products, all of which require thorough assessment. Ultimately, however, a key bottleneck toward commercialization lies with **consumer acceptance**. Foods derived from genetically modified microorganisms may be perceived as unfamiliar or unnatural. While many consumers express interest in novel foods, for environmental or health considerations, purchasing decisions remain strongly influenced by cost, sensory quality, availability, and perceptions around healthiness or ultra-processing. Together, these intertwined challenges also reduce the attractiveness of microbial proteins to investors, creating a **funding gap** that further slows progress toward large-scale commercialization.

# Success strategies to tackle scale-up

While the challenges associated with scale-up of microbial proteins are substantial, several strategies can be adopted to mitigate these barriers on the path towards commercialization successfully.

## Begin with the end in mind

A general successful strategy is to **begin with the end in mind**. Firstly, this entails developing a **sound business plan** prior to starting with scale-up. Such a plan should be grounded in the intended market position of the final product and be informed by key strategic questions, including who the end users or customers are, what commercial model will be pursued, who the potential competitors and collaborators are, and what the long-term vision for success entails.

Establishing a clear and well-defined business plan early on enables to make **informed decisions throughout the upscaling journey**. For instance, it will guide the critical capital investments needed, by aligning the industrial equipment selection and facility design with the targeted annual production capacity and the intended market application. The required production scale influences the size and configuration of fermentation and downstream equipment, while the final product application determines the necessary technical and regulatory specifications, particularly for food-related products that must comply with strict food-safety standards. In addition, specific process conditions, such as high salt concentrations or the use of solvents, may further necessitate specialized materials, equipment, and safety measures. Furthermore, a clear definition of the required product purity can inform DSP design, where simplified schemes may be sufficient for certain applications, thereby reducing overall capital costs. Finally, having a clear view of the market entry strategy allows to prepare for regulatory approval, for instance by motivating production of early product samples for safety evaluation and market testing.

Secondly, beginning with the end in mind can entail to **approach scale-up in a holistic manner**, where the entire production chain is considered at each stage. Decisions made at early stages, including for instance the medium composition or bioreactor composition can

greatly affect the DSP complexity, the resource efficiency, and the overall economical viability of the process. Optimizing individual unit operations may therefore lead to suboptimal outcomes at the process level. Instead, successful scale-up depends on striking an appropriate balance between capital investments and operational costs. For example, incorporating additional unit operations will mean higher upfront CAPEX, but may, in some cases, increase the resource efficiency downstream, effectively lowering the OPEX over the lifetime of the process. Adopting such a **system-level perspective** is essential to managing trade-offs, minimizing inefficiencies, and ensuring robust and economically viable microbial protein production at scale.

Finally, foreseeable process **bottlenecks should be addressed early** in the upscaling journey. For example, production strains with low productivities or that are particularly sensitive to contamination will not deliver sustainable or cost-effective large-scale processes. Similarly, lab scale productions relying on expensive and unscalable purification steps are destined to encounter problems. Iteratively addressing these hurdles through further process development and optimization at smaller scales is essential for scale-up success. Furthermore, approaching scale-up with **structured preparation** is key. Defining clear objectives, performing the necessary safety risk assessments, and having strong mitigation options ensure that scale-up can be executed with confidence.

## Scaling down

Scale-up campaigns traditionally follow an iterative strategy of developing and validating the process at successively larger scale. Hence, any pitfalls or problems encountered at a certain scale are resolved before moving to the next. In practice, this often results in similar problems that continuously must be solved in new ways, or serious problems only arising at later stages. One way to foresee these issues is by applying a **downscaling** strategy. This works by identifying the restricting process conditions at large scale and mimicking these at lab scale. Such constraining factors to test can include many of the challenges described previously, such as increased mixing times or gradients in substrate concentration, pH, and temperature. Other downscaling approaches include testing intentional process perturbations, such as over- or underfeeding schemes or strong pH changes, which enable the evaluation of the overall

process robustness. In general, these smaller scale runs are much cheaper and provide valuable information for further process design choices.

Downscaling can also involve deliberately **stepping back to a lower production scale**. Reducing the production scale to enable targeted process optimization, particularly at the DSP level, may be necessary when complex or unexpected issues arise. Performing a **root cause analysis** always proves to be a successful strategy in this regard. Such analyses may be adopted following unexpected events or failures, including contamination incidents or process runs with low productivities. Emphasis could be laid on thorough post-run debriefing and reflection, strengthened by gathering sufficient and **high-quality process data**. These ensure to actively find the learnings or strongly prepare for the next production campaign.

## New process modes and innovations

In parallel with such strategic and practical approaches, the recent advances in process modes and technological innovation can offer important opportunities for more sustainable and efficient production processes or to **address scale-up challenges in new ways**.

**Digital data-driven process development** is increasingly recognized as a key strategy to support biomanufacturing scale-up, a transformation referred to as Bioindustry 4.0. By combining **advanced sensing technologies and real-time analytics**, fermentation processes could be monitored and controlled with unprecedented resolution. With these tools, offline and even online (real-time) data is gathered, including the biomass concentration, substrate and metabolite levels, or off-gas composition.

Such extensive data acquisition **reduces the “black-box” nature** of large-scale fermentation and enables faster detection of deviations, including contamination events or metabolic shifts. In biomass fermentation, for instance, online biomass and viscosity monitoring can help manage high cell densities and rheological changes, while in precision fermentation, real-time tracking of product formation and host metabolism can support tighter control over expression and downstream processing requirements. Moreover, novel sensors or volatiles analysis tools can monitor sensory or flavour parameters throughout the production process, which can lead to better product formulation and increase its overall consistency in the microbial protein field. Finally, the integration of advanced process control and automation could reduce the

necessary manual intervention, thereby improving the reproducibility and lowering the labour demands.

Moreover, digital tools such as **digital twins** are increasingly being adopted for fermentation-based biomanufacturing and can be particularly valuable during scale-up. Digital twins are dynamic, data-linked models of the fermentation process that mirror its real-time operation, and can be combined with artificial intelligence and machine learning algorithms to enhance predictive capabilities. As such, these tools enable virtual testing of different operating conditions and can predict how upstream changes may impact downstream requirements. These methods also allow evaluation of various scale-up scenarios before committing to any capital expenses. Together, these data-driven approaches support more robust, scalable, and resource-efficient upscaling fermentation processes.

A process mode that holds particular promise for achieving cost-effective microbial protein production is **continuous fermentation**. In this mode, fresh nutrient medium is continuously supplied to the bioreactor while a similar volume of fermentation broth containing cells and product is simultaneously withdrawn, resulting in a steady-state operation. This enables sustained production over extended periods, leading to high volumetric productivities, reduced reactor downtime and consequently reduced cleaning and sterilization costs. Higher productivities also allow the use of smaller production and processing equipment with lower CAPEX costs. Moreover, continuous operation can be especially advantageous for processes affected by product inhibition, as the ongoing removal of product limits inhibitory effects. In addition, the integration of cell retention or recycling systems allows for high cell density fermentation, reducing the cost of inoculum preparation and further enhancing productivity.

Despite these advantages, industrial adoption of continuous fermentation remains limited. Key challenges include genetic instability of production strains over prolonged cultivation times and an increased risk of contamination in these long-running systems. Furthermore, DSP technologies with compatible continuous throughput are often lacking, complicating complete process integration. Nevertheless, the potential benefits of continuous fermentation are substantial, and ongoing advances in strain engineering, real-time monitoring, automation and contamination detection technologies are expected to improve system robustness and facilitate broader industrial implementation.

**Downstream processing** remains one of the **most significant cost drivers** in microbial protein production, particularly for precision fermentation processes that require high purity and functionality. In addition, DSP costs and complexity increase disproportionately with scale. As a result, the development of **simplified, robust, and inexpensive DSP technologies** is critical for enabling successful and economically viable scale-up. Such novel approaches can include intensified and integrated unit operations that reduce the number of processing steps, such as in-situ product removal, membrane-based separation or aqueous two-phase systems. Compared to conventional chromatography, these techniques can offer lower capital and operating costs, higher throughput, and improved scalability. In addition, advances in continuous and semi-continuous DSP can enable smoother material flow and reduced buffer, water, and energy consumption.

## Rely on piloting and partnerships

A final scale-up strategy destined for success is to bridge the valley between lab and industrial scale with a **pilot scale plant**. This intermediate step allows companies to test processes under industrially relevant conditions before committing to full-scale implementation.

**Piloting facilities or CDMOs** can play a crucial role in de-risking the scale-up journey by enabling companies to “**fail small**”. They provide access to the right expertise and scalable infrastructure, and hence allow to test and select the appropriate unit operations and industrial equipment. Also the evaluation of alternative process configurations and optimization of overall plant design can be supported by such facilities. In addition, pilot testing at intermediate scale supports further process development and validation by generating detailed data on mass balances, side-stream composition, and product quality. This hands-on production experience is essential for training operational teams and for preparing the technical groundwork required to design, operate, or outsource production to an industrial facility.

In parallel, **building strong partnerships** is a key success factor for scaling microbial protein production, and engagement with pilot facilities can play an important role in this process. Pilot plants or CDMOs often function as **collaborative hubs**, bringing together technology providers, industrial partners, end users, and researchers, and thereby facilitating interaction across the value chain. Through these collaborations, companies can test different product applications and generate representative **product samples**, which are frequently required for

regulatory approval and customer validation. Early access to such partnerships can also help to access or build market demand and establish customer relationships. In addition, pilot-scale activities generate reliable technical and economic data, including validated production capacities and realistic cost-of-goods estimates, which can significantly strengthen **investor confidence**. Finally, participation in matchmaking and networking events further enhances access to strategic partners, funding opportunities, and intellectual property expertise, all of which are critical towards commercialization.