Reduce risk from concept to commercialization: a comprehensive roadmap for bioprocess development

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Disclaimer

This white paper has been compiled through collaborative efforts of experienced engineers and experts in the field of process development and scale-up. However, it is essential to acknowledge that every project is unique, and the complexities of process development and scale-up cannot be fully captured in a single document.

The guidelines, recommendations, and best practices outlined in this document are intended to provide general guidance and should not be considered exhaustive or foolproof. Users of this document must exercise their own judgment, expertise, and due diligence when applying the principles and advice contained herein.

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It is recommended that users consult with qualified experts and conduct their own thorough ana-lysis before making decisions or taking actions based on the information presented in this document.

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Introduction

A recent study by the EU (European Commission, 2025), revealed a substantial shortage of skilled professionals capable of scaling up bioprocesses from conceptual to commercial scale. This gap threatens to hinder the growth of the bioeconomy, not only in Germany but globally.

Why do projects fail?

Experience has shown that projects aiming to scale-up processes into commercial scale fail due to the following three reasons:

- Underestimating the complexity of the process – it is extremely tempting to skip the pilot and/or demonstration steps in an attempt to save time and money, but this leads to large scale failures that are usually unrecoverably expensive.
- Poor communication with stakeholders – it is of utmost importance that investors are fully aware of the complexity of the process and that they have a realistic expectation of the cost and timeline of such a project. If not, they lose confidence and pull out of the project, taking their investment with them.
- Acquired funding does not endure the development stages – If all the needs and costs of development and scale-up are not identified and planned for by the conceptual phase at the very latest, funds run out before returns can be made.

Good project management

Project management requires understanding business needs, a well-defined business plan, the ability to identify and exploit opportunity, applying front end loading (FEL) principles, strong communication skills, a clear understanding of market behavior, acquiring funding, etc. In an economic, political and legal environment characterized by volatility, uncertainty, complexity and ambiguity, one must think and behave with agility, clear, visionary goals and a good understanding of the process and the environment to achieve success. This can be ensured through continuous monitoring and analysis and subsequent updating of predictive models, sensitivity analysis, and applying expert judgement.

Successfully developing and commercializing a complex process such as a bioprocess requires a diverse team of experts and extensive planning. Involve members from each field of the business from the beginning so that the cumulative understanding of the project scope does not fail to identify all needs and restrictions. (Sauer and Wachsen, 2025) In this document, color coded symbols are assigned to the different disciplines involved in each step to help provide some clarity, as shown on page 3.

The levels of flexibility and uncertainty decrease throughout the project and costs increase; therefore, it is advised to apply FEL and spend the necessary time, effort and money to precisely characterize and design the process in early stages rather than during or after the commercial phase. Research has shown FEL to reduce the likelihood of over-expenditure in the commercial phase (Weber, 2016).

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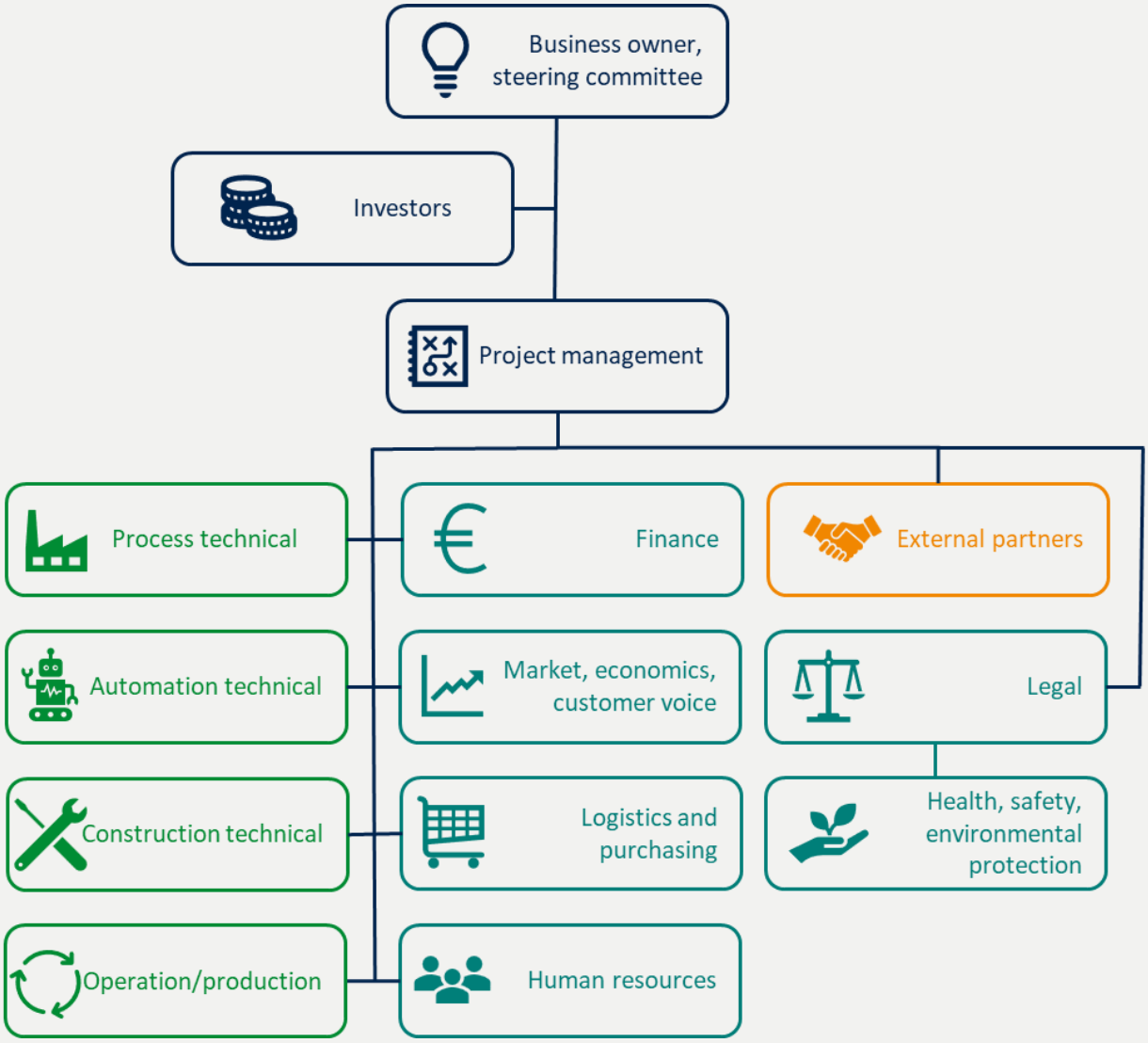

Scale-up Roadmap

This white paper provides a comprehensive roadmap for scaling up bioprocess concepts to industrial scale. The guide outlines essential steps, considerations, and best practices for each stage within the technical aspects of project management, supplemented by additional information, resources, and expert insights from within the TransBIB network. Intended for bioprocess developers, entrepreneurs, and industry stakeholders, this practical guide aims to equip readers with the knowledge and resources necessary to overcome the upscaling challenges, to not repeat common mistakes, and to unlock the full potential of the bioeconomy. The document is not an all-inclusive guide to save all projects, but it provides the reader with a roadmap that includes all the important steps for successful commercialization. The process is divided into five phases as shown on page 4.

An increase in the technology readiness level (TRL) of the applied technologies occurs within each phase. It is extremely important to verify that this TRL has been reached before continuing with the next scale-up phase. If not, the use of immature technologies is likely to result in unfulfilled targets as well as losses in funds, time and reputation. Pay attention to the details.

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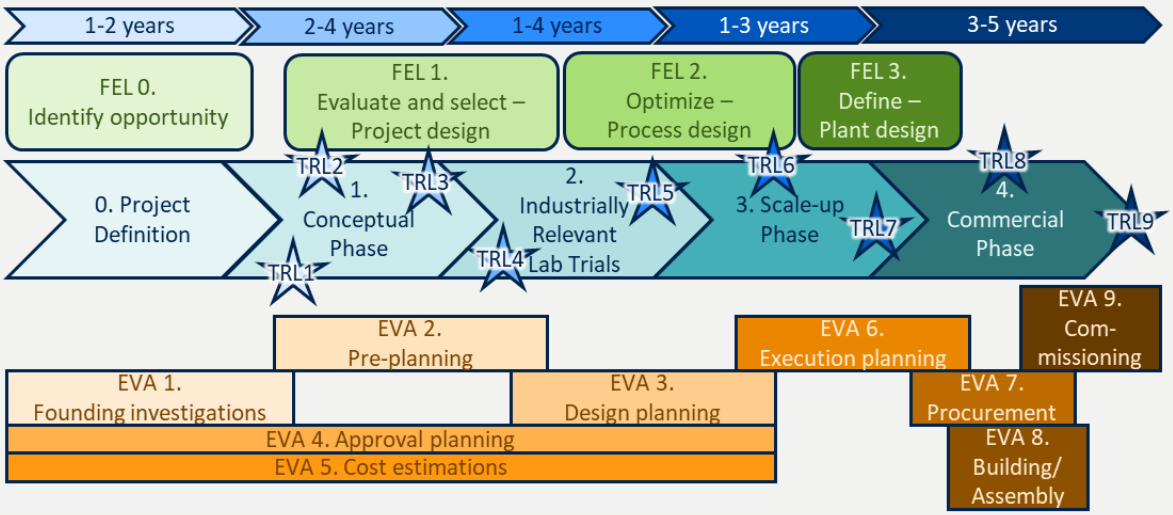
The roadmap - overview

The process of developing and commercializing a bio-process is divided into five phases within this roadmap. The diagram below**Error! Reference source not found.** show these five phases and how they correspond to the phases discussed by Weber (Weber, 2016). In the diagram, it is also shown when the different FEL levels are to be applied and when certain TRLs are to be achieved. FEL and the guidelines described in Weber's Engineering verfahrenstechnischer Anlagen (EVA) are effective tools used to achieve the relevant TRL goals.

Each phase starts with a kick-off meeting, in which clear deliverables are set for the stage, guided by the business boundaries. The phase ends with a stage gate meeting, in which the deliverables are reviewed and their achievement confirmed. Before moving on to the next phase, it is necessary to ensure that all key performance indicators (KPIs) (or stage gate criteria) have been completed and that the suitable TRL has been achieved. The diagram also shows common timeframes to be expected for each phase.



Project definition

This phase sets the scope for the entire project. Select the target product and application. Start with the end in mind. This phase roughly corresponds to phase 1 as described in Engineering verfahrenstechnischer Anlagen (EVA) phase 1 (Weber, 2016) and this is where FEL 0 is applied.

The conceptual phase

In this phase FEL 1 is applied and TRL 1 to 3 is to be achieved. It also roughly corresponds with the EVA phase 2. In this phase, a proof-of-concept is developed. This is supported by literature, experiments, computer models and feasibility calculations. Patents may also be registered in this phase.

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The ”valley of death”

While “the valley of death” may sound quite ominous, the name is rather misleading. It is true that this is where most projects fail, but this is also where the idea becomes reality. One could compare the challenges faced during the valley of death with the money, frustration and effort required to support and guide your teenage child or the stringent pruning and constant care required for a newly planted orchard. It requires real dedication, particularly from the project owner, to push through the valley of death, continually spending money without receiving income, to finally achieve the reward at the end. The intention should not be simply to survive the valley of death, but to grow, develop and build the best process through lessons learned.

Industrially relevant lab trials

This phase corresponds roughly to EVA phase 3 and is considered the start of the “valley of death”. TRL 4 and 5 are to be achieved in this phase through applying FEL 1 and 2. Process steps and systems are developed and optimized in the laboratory considering conditions that are to be expected in full commercial scale. In some cases, this may already include isolated pilot scale tests. Models and artificial intelligence (AI) need to be constantly updated to include new findings and guide decisions. Findings from this phase are the basis for decisions to be made for expensive and time-consuming steps in the next phase. To survive the valley of death, it is therefore of utmost importance to obtain statistically relevant results from experiments conducted under conditions that are realistic for industrial production scale.

The scale-up phase

This phase roughly corresponds to EVA phase 6. It is the second half of the “valley of death”. In this phase, FEL 2 and 3 are applied and TRL 6 and 7 must be achieved. Here, the process is scaled up incrementally with the aim of discovering and solving any and all potential problems that can arise at commercial scale, but at much reduced costs and volumes. It is very tempting to neglect piloting and demonstration due to its costly and time-consuming nature, but this would be a fatal mistake for the project, because piloting and demonstration show real process behaviours such as blockages, corrosion, erosion, accumulations, response to fluctuations, machine errors, operator errors and -initiatives, etc., all of which would be entirely unknown without piloting and demonstration. These unknown process behaviours are potentially dangerous and extremely costly at commercial scale. Risks of neglecting piloting and demonstration include poor performance, inconsistent quality, high costs, process instability, health and safety complications, etc. To survive the valley of death, do not skip or neglect any step in piloting and demonstration.

Commercial phase

This phase corresponds roughly to EVA phases 7 to 9. In this phase, the process is brought into full commercial production scale and operated continuously. TRL 8 and 9 are to be achieved in this phase. Skilled project management is required during construction and commissioning to avoid unnecessary costs and delays. During operation, continuous improvement must be applied to remain competitive in the market.

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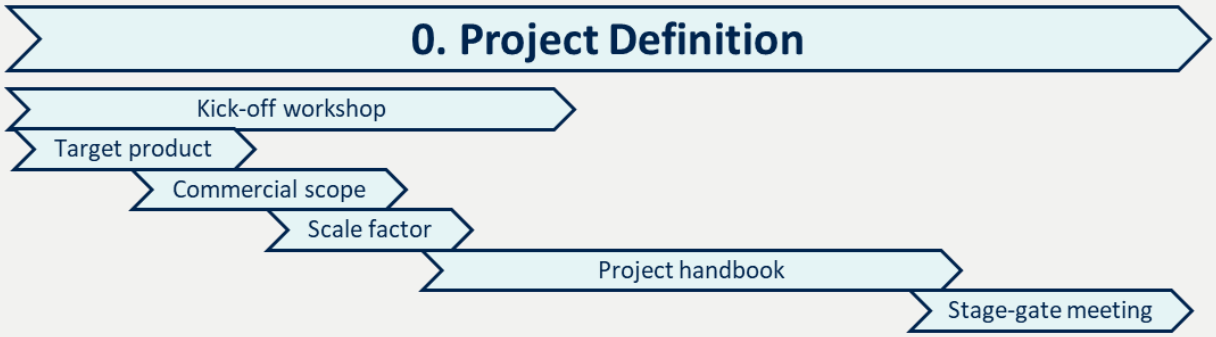
The roadmap – Project definition

This is where the project comes alive and develops an own identity. Apply FEL 0.



Kick-off workshop

At the beginning of every project phase, a kick-off workshop is needed in which the required KPIs are set, project boundaries and goals are reviewed and the project planning is refined. In this workshop, do at least the following:

• Align targets and priorities with all stakeholders. Ensure that all stakeholders understand the complexity of the process.

•Define the scope of the project. What is in scope, what is out of scope, what is "potentially in scope if necessary".

•Define the purpose of the project. What value does it add to the world?

•Determine what resources would be needed by when and plan how to acquire it. Set funding milestones.

•Draw up a RASCI chart (Responsible, Accountable, Supporting, Consulted, Informed) in which responsible and accountable persons are allocated to each action item to ensure clear understanding of roles and completion of tasks. Define deliverables and resources dedicated to the tasks. Do not over-dedicate personnel resources to a variety of tasks, because this will result in diluted efforts. Rather dedicate specific persons and resources to as few tasks as possible per person, to ensure adequate dedication and focus.

•Conduct a SWOT analysis (Strengths, Weaknesses, Opportunities, Threats) on the envisioned project.

•Generate a realistic Gantt chart for the project.

•Set relevant KPIs to be achieved in the project as a whole, in the project definition phase specifically and later also in the other phases.

•Create a communications and reporting plan. Consider and define plans for deviation management and project governance.

Clearly defined targets, well defined communication strategies and a good understanding of one's limitations and strengths are of utmost importance. It gives decision makers the freedom to act and decide with reduced risk and gives clear direction to those who must perform tasks. Without it, expensive mistakes are made that could have been avoided.

The target product

One material can be used to create a multitude of products and one product can serve many applications, but in order to make it into the market, the product must have its own niche that makes it attractive to the target consumer. It must therefore be manufactured with a

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specific set of properties that fulfil the needs of a specific application better than any competitor. This cannot be done if a product (or several products) is to be manufactured to serve many different purposes. Each application requires slightly different attributes (price, quality, texture, purity, etc.). Attempting to produce for different applications will therefore always introduce compromises, which undermine the applicability of the product in one way or another for all of the different applications. Select the target product and application which is the most realistic and focus all project efforts on this. Define the product specifications based on the customer's needs.

Feedstock vs. Product value

Is the selling price of your product and byproducts more than the cost of your raw materials and waste disposal? If not, the process cannot be viable. Find cheaper alternative raw materials, eliminate unnecessary inputs, find ways to sell side streams and improve the planned product for a higher selling price. Produce your own input. The aim is to create value.

The price of some publicly traded chemicals and materials are publicly available, including the price trends over time. It is advised to request quotations from industrial suppliers to obtain reasonable estimates for privately traded compounds. For new market entries, several interviews are to be conducted to determine a reasonable selling price and the size of the potential market.

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Consider that a certified environmentally friendly product may sell at a slight premium and that waste streams from other processes or industries may serve as a cheaper and greener alternative raw material feedstock.

Set commercial scope

"Start with the end in mind"

Determine the commercial production volume that will be produced. This must be informed not only from market capacity, but also from the capacity of existing industrial equipment, supply chain capacity, raw material availability, the impact of economies of scale, different locations with different laws, etc.

Decide what auxiliary processes will be included within the project scope and which will be outsourced. This sets the process design boundaries for the entire project.

Determine the scale factor

Depending on the project type and complexity, company structure and regulatory requirements, the level of project management discipline, documentation and resources should be adjusted. Less complex projects do not require overly formal bureaucratic systems which would slow down progress and introduce unnecessary costs. Do not, however, underestimate the scale of the project. Even "simple" projects require some system for proper control and management. Larger, more complex projects, however, may be impossible to control without very specific formal structures and procedures in place and without sufficient project management resources allocated. Determining the correct scale factor sets the stage for successful and efficient management throughout the project.

Create a project handbook

Create a central document detailing the project scope, boundaries, goals, vision and mission, organogram, etc. and providing guidelines as to

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how work is to be conducted and reported. Read and apply the principles in the book, "*Engineering Verfahrenstechnischer Anlagen*" (Weber, 2016), which gives a clear and in-depth guidance on the requirements during the design and scale-up of commercial (bio-)chemical production plants.

Stage-gate meeting

At the end of each stage, hold a stage-gate meeting with all stakeholders. Also include project-external subject experts to provide a multi-perspective view. Do at least the following:

- Review the documents, policies and boundaries established in the kick-off workshop (e.g. scope and purpose; Gantt chart, communication plan, etc.). Ensure that they are still valid and applicable. Update if necessary.
- Review KPIs for the project definition phase. All KPIs must be met before the Conceptual phase may be commenced.

Reviewing the original documents allows realignment with the original idea and refreshing one's awareness of important factors. This is to be done at every stage-gate meeting at the end of every phase of the project. It also allows updating the documents in case this becomes necessary due to changing technology and political- and economic conditions.

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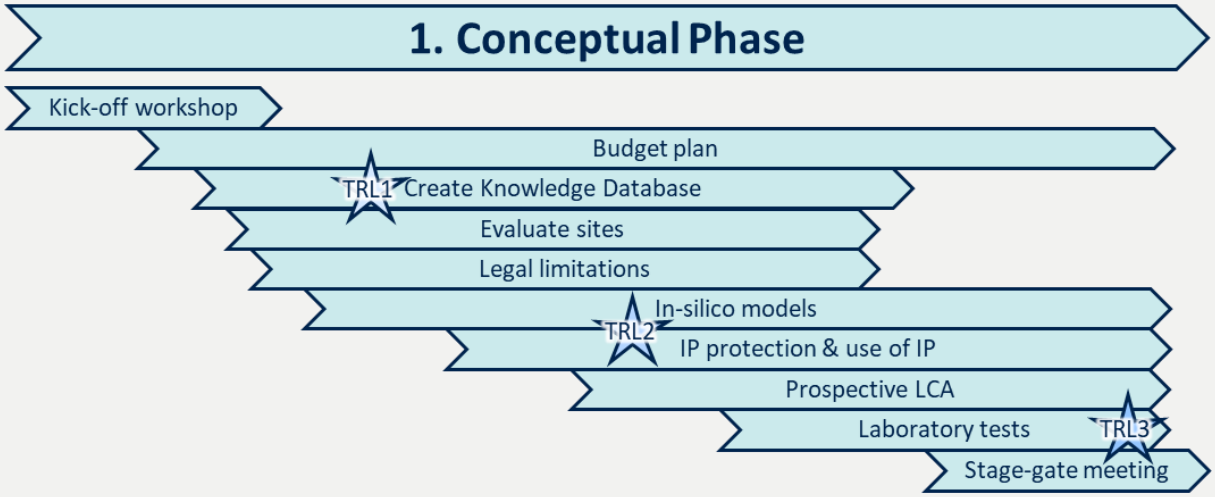
The roadmap – Conceptual Phase

In the conceptual phase, the production process structure is developed and becomes clearer. Along with the production volume defined in the project definition phase, the legal framework and the scope for energy, raw material, staff and logistics demand also become more defined. Apply FEL 1. TRL 1 to TRL 3 must be achieved in this project phase.



Kick-off workshop

Hold a kick-off workshop with all stakeholders. Do at least the following:

• Align targets and priorities with all stakeholders. Ensure that all stakeholders understand the complexity of the process.

• Determine what resources would be needed in the conceptual phase and plan how to acquire it.

•Expand the RASCI chart with detailed conceptual phase-specific action items to ensure that the required TRLs will be achieved with sufficient statistical confidence. Define deliverables and resources dedicated to the tasks. Do not over-dedicate personnel resources to a variety of tasks, because this will result in diluted efforts. Rather dedicate specific persons and resources to as few tasks as possible per person, to ensure adequate dedication and focus.

•Expand the Gantt chart for the conceptual phase with more detail. Set realistic timeframes.

•Set relevant KPIs and clarify existing KPIs to be achieved in the conceptual phase.

Create a knowledge database

Collect and index knowledge from literature, own work or elsewhere that is relevant to your project. This includes everything from fundamental properties to processes, prototypes, state-of-the-art, interactions and environmental impact studies. Also, relevant laws, regulations and standards. Refer to the European Union (EU) “blue guide” for product conformation legislation. Make use on an interdisciplinary team. Collaborations with universities, networks, customer representatives, clusters and/or IBISBA is advised. Relevant standards may include: Food safe, FAMI-QS or GMP+ feed certification, REACH, ISO 14001, ISO 15001, ISO 9001. Potentially relevant laws and risk assessments are listed on page 27 of this document. This database must be able to manage the project complexity comprehensively. Keep the database up to date throughout the entire project.

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The budget plan

Draw up a budget plan for the project. Understanding the costs of process development activities, why they are required, and when to expect certain cash flows is important for financial management, investor communication and defending one's expenses. Include spending curves, risk adjusted net present value (NPV), market trends and development in the budget plan. Understand that the "valley of death" has earned this name due to the high costs and long timelines related to process development and scale-up. Plan accordingly to bridge the gap and reach commercial scale.

Continually apply to suitable government support programs for sustainable innovation. Government support not only provides financial support, but may also include political support in product market entry. However, do not make the project entirely dependent on public funding. Public funding is slow to be approved and may fail due to political changes. Apply own funds, bank loans and private investor money to avoid project delays.

Evaluate sites

Shortlist potential sites for the full-scale processing plant. Consider brownfield or greenfield options. Consider feedstock availability and customers for your product in the region as well as infrastructure to transport feedstock and product, to supply utilities and to process waste streams. A lack of adequate logistics will prevent operating at full capacity. The effects may even be so extreme as to prevent commercial viability.

Consider environmental and weather conditions. Extreme weather conditions may also affect operability if the process and the structures are not designed to withstand the conditions.

Research building regulations, business operation- and tax regulations and environmental regulations applicable to potential sites for the full industrial scale process plant. (See non-exhaustive list on page 27) Also consider import and export regulations (e.g. CBAM) if they apply to the planned business model. Prepare documents for permit applications. Projects can be significantly delayed as a result of not adhering to some or other applicable laws or regulations. Non-adherence also often results in heavy fines. Adherence to building or business operation may require applying for permits, which can take years to be issued. Adherence to environmental regulations may require significant process changes as well as applications for certain permits. It is therefore important to understand the full scope of applicable laws. It is advised to consult with an expert in the field. Consider when and how the laws and regulations apply and when they do not. Act accordingly.

IP protection and use of IP

One may already consider protection strategies for intellectual property (IP). Protection of intellectual property not only prevents others from using your IP without your permission, but it prevents others from registering your IP as their own and limiting your use of it. Many strategies exist, which do not all include patenting the IP. Decide on an IP roadmap: what will be needed by when? How to keep up to date on newly filed and registered relevant patents. Consult with an expert. This is an ongoing task that requires continuous monitoring throughout the life of the project. Research legal requirements related to IP and use of patents. Conduct a thorough patent search to ensure that you do not accidentally infringe on a registered patent. Find legal solutions as soon as possible. Either develop something that has not been patented and protect the IP yourself, or pay for the use of a registered patent.

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Patents may only be used without the owner's permission after they expire. Patent infringement may result in heavy fines and/or a legally binding order to stop operations completely. Consider the Nagoya protocol.

In-silico models

Create a computer model of your proposed process at the intended industrial scale. It is important to design and test based on industrial scale because costs, safety and feasibility of equipment and processes vary significantly over scale.

Modelling provides several advantages:

•Process modelling software automizes and speeds up mass and energy balances. It also allows investigation into the financial and quality effects of stream recycling, different processing options (e.g. downstream processing routes) and heat integration.

•Most process modelling software generate an initial capital cost estimate and economic indicators to allow easy evaluation of the process economic viability. Environmental im-pact factors and stream summaries are also generated. These are important prospective life cycle analysis (PLCA or P-LCA) inputs.

•Changes in the process can be simulated in minutes, and a Monte-Carlo type analyses can be performed on a simulated model to give insights into the likelihood of a process being economically viable and to identify the major cost drivers that require development and optimization.

•Modelling processes in silico costs only limited time and a license fee, as opposed to much more time in the laboratory, higher costs due to the use of consumables and some safety risks. After modelling, lab work can be done more targeted and efficiently to improve the model fidelity.

Many different simulation packages exist, each with their own advantages and disadvantages. Mechanistic models, based on first principles, predict behaviour taking into account a large amount of proven scientific and engineering knowledge. This is useful when you do not have much information available yet. On the other hand, data-driven machine-learning models can accurately predict behaviours of your specific system, but needs a large amount of training data from the same system to do so. It is advised to consult with an expert and to spend time to get to know the chosen software yourself. The choice of software and of modelling style will be influenced by the type of process and available information. The important consideration is to ensure that the input is as accurate as possible and the simulation resembles reality as close as possible. This requires an understanding of both the process and the software, taking responsibility for the models, as well as continuously updating and improving the simulation design and inputs with accurate new information.

While creating a process simulation model, assumptions are to be made when data is not available from literature or other sources. Modelling therefore generates a guide as to what information must be generated in the laboratory to improve the model fidelity. It is important to validate assumptions through experimentation, not just accept assumptions as reality.

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Laboratory tests & risk assessment

Conduct initial laboratory tests to collect or confirm information required for proof of concept and to improve the validity of the simulated models. Laboratory experiments in this phase are aimed at validating the concept and providing estimates for reaction rates, yields, selectivity, etc. Always update the model and your research inventory with real, validated lab data. This may require several iterations. The conceptual phase is the least expensive and allows the highest degree of freedom in your process development. Therefore, conduct these steps diligently. Do not skip steps. Do not ignore minor issues. Conduct negative controls, Apply DOE, understand the governing mechanisms. Acquire statistically relevant information. Ensure minimal uncertainty. Collaborate with universities or research institutions and consult with your own engineering and operations experts if you already have them on the team.

If you already have employees at this point you are legally required to have a risk assessment in place.

Legal limitations on the process

Research legal requirements for the cultivation and use of organisms, chemicals and energy sources in your process. If you are developing a product for medical application (or food/cosmetic/feed/food contact), you must already consider the legally required steps in the process, limitations on raw materials and microbial strains and the costs of these steps and limitations, e.g. clinical trials, water for infusion. Best practice would be to avoid genetically modified organisms (GMOs) and toxic- or explosive chemicals as far as possible. Make use of safe strain lineage organisms wherever possible to enable easier approvals for industrial application. Consider operating in different countries or regions where different laws may apply. Conduct a freedom-to-operate analysis on the different options under consideration.

Prospective LCA

A prospective LCA already gives an indication of the environmental impacts of different production routes. This is valuable information for deciding on which processing routes to pursue (Cucurachi et al., 2022).

Stage gate meeting

Hold a stage-gate meeting with all stakeholders. Also include project-external subject experts to provide a multi-perspective view. Do at least the following:

•Review the project documents, policies and boundaries established in the project definition phase as a reminder of the project guidelines and goal. Ensure that they are still valid and applicable. Update if necessary.

•Review KPIs for the conceptual phase. All KPIs must be met before the industrially relevant laboratory phase may be commenced. This is extremely important because it prevents unnecessary expensive and time-consuming rework of experiments and designs.

•Prepare for the Industrially relevant laboratory trials phase. Ensure that all information and resources required will be available.

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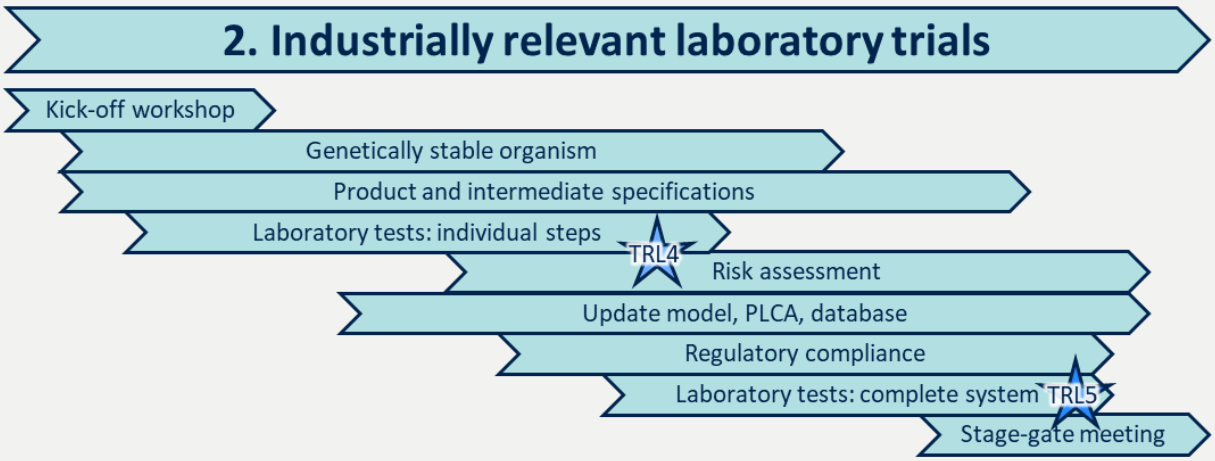
The roadmap – Industrially relevant laboratory trials phase

In this phase, the concept becomes reality. The ideas and knowledge collected and created in the conceptual phase must now be combined and tested in a way that resembles industrial behaviour without industrial scale or costs. Laboratory trials in this phase aims to simulate real conditions that may be expected in industrial scale operations, and optimizing controllable conditions for the best possible outcome that aligns with the business goals set in the project definition phase. Experiments and designs should consider safety and sustainability at commercial scale. Findings from this phase are the basis for decisions to be made for expensive and time-consuming steps in the Scale-up phase. To create the most suitable process and survive the valley of death, it is therefore of utmost importance to obtain statistically relevant results from experiments conducted under conditions that are realistic for industrial production scale. Apply FEL 1 and 2. TRL 4 and TRL 5 must be achieved in this project phase.



Kick-off workshop

Hold a kick-off workshop with all stakeholders. Do at least the following:

• Align targets and priorities with all stakeholders. Ensure that all stakeholders understand the complexity of the process.

• Determine what resources would be needed in the industrially relevant laboratory trials phase and plan how to acquire it.

•Expand the RASCI chart with detailed phase-specific action items for the industrially relevant laboratory trials phase to ensure that the required TRLs will be achieved with sufficient statistical confidence. Define deliverables and resources dedicated to the tasks. Do not over-dedicate personnel resources to a variety of tasks, because this will result in diluted efforts. Rather dedicate specific persons and resources to as few tasks as possible per person, to ensure adequate dedication and focus.

•Expand the Gantt chart for the industrially relevant laboratory phase with more detail. Set realistic time-frames.

•Set relevant KPIs and clarify existing KPIs to be achieved in the industrially relevant laboratory trials phase.

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Genetically stable organism

In production scale, antibiotics are prohibitively expensive. Antibiotic resistant DNA is also not allowed outside of a controlled laboratory environment in most countries, including Germany, posing problems for the approval to use the strain in industrial scale. Additionally, plasmids place a high metabolic burden on the organism, limiting its growth rate and general health.

If you have so far been using a GMO with a plasmid, develop an antibiotic-independent strain with the relevant genes included in the organism's genome to prevent problems related to plasmid loss. Test genetic stability at the same generation number as expected in industrial scale. Genetic drift can occur even without a plasmid due to the additional metabolic load in an engineered strain.

Risk assessment

If you have not done so already, conduct a risk assessment, including an evaluation of the potential impact severity before and after mitigation measures. Follow the hierarchy of controls to mitigate impact severity and implement the mitigating measures.

Product and intermediate specifications

Define product specifications and analysis methods. Define parameters to be monitored in intermediate steps or streams. Consider the requirements and certifications needed for certain target markets, e.g. Food safe, FAMI-QS or GMP+ feed certification etc. Consider packaging laws, the EU blue guide, and characterization tests for certifications and material safety data sheets.

Interview potential customers to determine which properties and certifications are important and to evaluate the value of these properties. Compare with competitor product specifications. Choose properties in intermediate steps or streams that are likely to influence cost drivers such as energy consumption, downstream processing, yield and product quality. Consider ISO 9001 quality management standards. Consider which certifications are mandatory and which are nice to have. What value do they add to the product?

Laboratory tests: Individual steps

Design experiments to test individual steps in the designed process. Consider the holistic view, how the steps are interconnected and how they are expected to interact. This includes testing different step options. Test the process steps in equipment and conditions that are equivalent to industrial scale equipment and conditions. This is particularly complex when testing the fermentation step. Process parameters (such as pressure, component gradients, shear stresses, heat and mass transfer, etc.) do not scale linearly in a fermenter (Cleaver, 2023). For this reason, it is important to consult with an expert in industrial fermentation, to understand the fermentation organism's response to process variables and to select the most suitable scale-up parameter to be kept constant in order to achieve the targeted result.

Make use of existing research institutions with well-equipped laboratories and experienced staff. Experienced staff have developed an intuition for processes and can often solve technical

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problems easily. Also include fresh, inexperienced persons such as students or interns. These people will ask the questions and notice behaviors that seem obvious, but may be specifically important for the process. The students/interns also pose an opportunity for you to identify potential personnel that you may employ for scale-up and commercial operation.

You may also consider consulting with providers of flexible, modular experimentation platforms, which may speed up runs through automation, simplify simulations, assist in experimental design, and improve data collection.

Design your experiments to investigate the following:

•Is the process step realistic? Does it work?

•Is the process step viable? Does it work well enough? Will it be safe in industrial level? Is it cost-effective? How does it compare to other options? Is it compatible with upstream/downstream steps and recycling?

•What is the governing/limiting mechanism? Can this be manipulated or optimized?

•How can the step be optimized to cost less, yield more, be safer, last longer, waste less? Test and prove it.

Consider feedstocks that are commonly available in excess and consider environmental and weather conditions of the regions where these feedstocks are available. Designing and optimizing a process for an inadequately available feedstock or for non-applicable environmental conditions will result in a non-viable large-scale process.

Conduct these steps diligently. Do not skip steps. Do not ignore minor issues. Conduct negative controls, Apply DOE, understand the governing mechanisms. Acquire statistically relevant information. Ensure minimal uncertainty. Collaborate with universities or research institutions and consult with your own engineering and operations experts if you already have them on the team.

Laboratory tests: Complete system

Select the process steps/equipment that performs best in terms of the final industrial goal and create a lab scale process plant as complete as possible to test the process as a complete system (end-to-end). Determine where the process bottleneck is and optimize accordingly. Make use of a “microplant” or “miniplant” setup (ProcessNet, 2016) if applicable. Results should be statistically relevant.

Depending on the complexity of the system, you may already consider applying automation and control strategies to help regulate process behaviour.

Also consider the potential effects of recycling process streams, waste avoidance or waste treatment. Recycling process streams tend to increase plant yield and recovery and decrease waste, but may also accumulate contaminants and increase equipment cost due to an increasingly complex and sophisticated design (Heinzle et al., 2006). It is important to investigate the effects and find the optimum operating conditions for recycling. This can only be proven on larger scale, but a few complete system runs in lab scale will already provide valuable insights as to the system's behavior.

Update the model, PLCA, database

Continually update your simulation model(s), PLCA and research inventory with new proven information from measured results. Maintaining an up-to-date model of your process design allows one to decrease technical uncertainty and therefore also economical risk. The model can quickly predict expected technical and economical outcomes at minimal cost and, through Monte-Carlo analysis, can pinpoint the

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major cost drivers in a process. This provides guidance as to which areas deserve development focus.

Creating and updating computational fluid dynamic (CFD) models may also be advantageous for steps that display complicated flow behaviours that influence process performance.

Regulatory compliance

Draw up a regulatory gap analysis and develop an initial compliance strategy. Consult with an expert and the relevant regulatory agencies. Also consider good manufacturing practice (GMP) and relevant ISO standards and evaluate whether there is a need for specialized equipment certifications, procedures, personnel qualifications and legal appointments, validations, etc.

Draw up a (material) safety data sheet for the product(s).

Stage-gate meeting

Hold a stage-gate meeting with all stakeholders. Also include project-external subject experts to provide a multi-perspective view. Do at least the following:

•Review the project documents, policies and boundaries established in the project definition phase as a reminder of the project guidelines and goal. Ensure that they are still valid and applicable. Update if necessary.

•Review KPIs for the industrially relevant laboratory trials phase. All KPIs must be met before the scale-up phase may be commenced. This is extremely important because it prevents unnecessary expensive and time-consuming equipment acquisition, plant assembly and test run repetitions.

•Prepare for the scale-up phase. Ensure that all information and resources required will be available.

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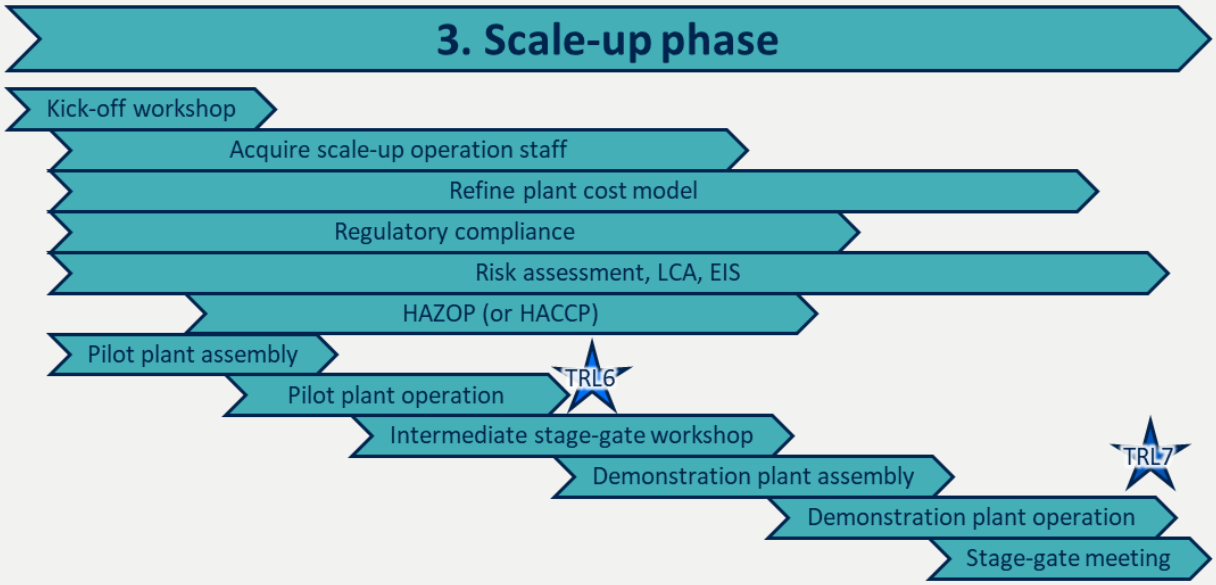
The roadmap – Scale-up phase

This is the second and most costly phase of the valley of death. It is also the most important value creating step and the only way to ensure that the full commercial scale will be viable. Like a child's teenage years, these are the most difficult but also the most crucial steps in developing a healthy adult. Skipping or neglecting any step in piloting and demonstration will likely result in commercial scale failures that are even more costly and time consuming. It can sink the business. DO NOT skip piloting and demonstration. Apply FEL 2 and 3. TRL 6 and TRL 7 must be achieved in this project phase.



Kick-off workshop

Hold a kick-off workshop with all stakeholders. Do at least the following:

• Align targets and priorities with all stakeholders. Ensure that all stakeholders understand the complexity of the process.

• Determine what resources would be needed in the Scale-up phase and plan how to acquire it. Consider that some things may have a long lead time (such as custom manufactured equipment) or limited availability (such as competent staff).

•Expand the RASCI chart with detailed phase-specific action items for the Scale-up phase to ensure that the required TRLs will be achieved with sufficient statistical confidence. Define deliverables and resources dedicated to the tasks. Do not over-dedicate personnel resources to a variety of tasks, because this will result in diluted efforts. Rather dedicate specific persons and resources to as few tasks as possible per person, to ensure adequate dedication and focus.

•Expand the Gantt chart for Scale-up phase with more detail. Set realistic time-frames.

•Set relevant KPIs and clarify existing KPIs to be achieved in the Scale-up phase.

Acquire scale-up operation staff

Most tolling facilities have sufficient staff to operate the equipment. Making use of the tolling facility staff, however, will not cost less than having your own staff. It is advised to have your own staff operate the pilot and demonstration plants or at least collaborate in the operation because this builds a deeper understanding of the process and its behaviors. This provides an

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opportunity to build up a knowledgeable and qualified pool of personnel for operating the commercial plant later on.

Ensure that operating and piloting knowledge remains with the project staff, not with the external partner's staff. Your own staff are also more likely to have priorities that align with yours, rather than the tolling facility staff.

HAZOP (or HACCP)

Conduct a hazard- and operability (HAZOP) study (or HACCP (Hazard analysis critical control points) for food products) and correct at least the critical- and high-risk issues. Consider local health and safety regulations and environmental regulations as well as explosion risk and ATEX controls. Involve ALL affected parties. This includes operational staff, maintenance staff, safety representatives, management, process controllers and external SUBJECT EXPERTS. A HAZOP study is not only a paper exercise to show in the event of a health and safety inspection. It is a practical interdisciplinary brainstorming exercise to identify all potential process behaviors and misbehaviors, their potential and most likely effects on the business, and the required measures to control behaviors that would (if uncontrolled) result in significantly detrimental effects.

Refine the plant cost model

Refine the cost model using cost engineering principles and up-to date published cost databases. Acquire quotations for large and long-lead-time equipment. Consider inflation. Equipment cost represents a large fraction of the processing plant investment cost. Therefore, updating one's cost model helps to make reasonable decisions on which equipment, materials of construction and processes to select. Quotations with indications of lead times also give guidelines in terms of construction planning and when to place orders for equipment.

Regulatory compliance

REACH regulations are likely to apply by now. Consider when and how it applies and when it does not. Act accordingly. Consider ISO 14001 environmental management standards and ISO 15001 energy management standards. Develop a regulatory compliance roadmap and supporting documentation. It is advisable to keep up to date with changes and developments in applicable regulations.

If the product is novel and not yet market approved, apply for market approval. Market approval may take years.

Risk assessment, LCA, EIS

Draw up a new risk assessment for piloting and demonstration. Refer to the list at the end of this document and select the applicable types. Conduct an updated LCA and an environmental impact study (EIS) and update these to a full LCA and EIS after piloting and demonstration. The environmental impact study includes the product end-of-life, therefore it is important to interact closely with the customer. Consider the waste management hierarchy as prescribed in the (*KrWG - Gesetz zur Förderung der Kreislaufwirtschaft und Sicherung der umweltverträglichen Bewirtschaftung von Abfällen*, 2012)).

Pilot plant design and assembly

Design and assemble pilot plant. Make use of equipment dimensions and process variables based on established correlations (Cleaver, 2023). It is advised to operate a pilot plant before demonstration. A pilot plant is a small-scale version of the real plant. It is too small to be economically viable, but large enough to represent real process conditions and

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operation. Therefore, real operational problems can be identified and solved at lower risk than demonstration scale.

Due to the high capital cost of equipment, it is common practice to conduct these scale-up steps at tolling facilities and/or to rent the required equipment. Consider pre-engineered, standardized and modular equipment (if possible and available) as described in the whitepaper, “Modular plants” (ProcessNet, 2016), to reduce investment risk. This may be suitable for pharma- and specialty chemicals processes.

Consider that it is often not possible to pilot the entire process at one facility, thereby introducing the risk of not being able to observe the behavior of the process as a whole with all steps acting on one-another. If this is the case, best practice would be to rent or purchase additional equipment to be able to pilot the entire process in one location. Also consider the expected transport time and distance between process units in the commercial scale plant. This may have non-negligible effects on the intermediates being transported.

Pilot plant operation

Operate the process and test its viability and robustness. Pay attention and investigate unexpected behaviors. Apply lean tools to optimize and streamline operations. Monitor changes in flow, pressure, conversion, etc. over time to indirectly monitor the rates of fouling, catalyst degradation, etc. Update the in-silico process models to reflect reality. Record process behaviours and operating procedures, because this is valuable material with which to prepare for commissioning the commercial scale plant.

TransBIB resources
One-stop-shop
Bioeconomy database
Competence pool
Certification systems database
AI assistant chatbot
Scale-up infrastructure database
Matchmaking platform
LCA guidelines

Intermediate stage-gate workshop: Pilot to demonstration

Hold a stage-gate workshop with all stakeholders. Do at least the following:

•Review KPIs for the pilot plant. Only continue with the demonstration plant if all KPIs have been met.

•Critically discuss issues that came up in the pilot plant operation and generate realistic solutions to all problems before continuing with the demonstration plant. What process changes occurred over time? Is there a need for any additional sensors? Is there suitable data for the development of a soft-sensor? Integrate problem solutions into the demonstration plant design.

•Confirm or update relevant KPIs to be achieved in the demonstration plant.

• Confirm that the list of resources needed for the Demonstration plant is still valid and complete and confirm the plan to acquire it. Consider that some things may have a long lead time or limited availability.

•Review the RASCI chart with detailed phase-specific action items for the Scale-up. Are the action items, deliverables and resource allocations still relevant?

•Review the Gantt chart for Scale-up phase. Are the time-frames still realistic?

The pilot plant is meant to show commercial production scale problems without the commercial scale cost thereof. If these problems are not solved before continuing to a larger scale, they will occur again, cost more, and/or

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pose a greater risk to the environment and human health.

Demonstration plant design and assembly

Design and assemble the demonstration plant. A demonstration plant is a small-scale version of the commercial plant. It is only just large enough to be economically viable, close to break-even point. In some rare cases, it may be sufficient to simply extend the pilot plant for this purpose. When designing the plant, consider the market, technical feasibility, Capital expenditure (CAPEX), operating expenditure) OPEX, schedule and risk involved when choosing a construction concept (stick-built, modular construction, modular flexible plant, or combinations thereof) (Eckrich et al., 2024). Consider sizing-up and/or numbering-up with the aim of demonstrating what is to be expected in commercial scale. The combination of both sizing-up and numbering-up may be advantageous in a market with volatile demand.

If possible, conduct demonstration at tolling facilities, contract manufacturing companies (CMOs), and/or rent the required equipment. One may need to demonstrate different sections of the process at different facilities. If renting is not possible, (which is very likely) purchase the equipment. Do not compromise and do not contract risky CMOs. The demonstration plant should ideally be an exact scale model of the envisioned commercial scale plant, including the complete piping, instrumentation and control system. Again, consider the expected transport time and distance between process units in the commercial scale plant which may have non-negligible effects on the intermediates being transported. Whenever reasonable (such as for pharma- or specialty chemicals production plants) consider standardized, modular equipment which carries reduced investment risk and certain construction advantages (ProcessNet, 2016). Consider including fouling sensors to understand how and when fouling occurs during operation.

Demonstration plant operation

Operate the process and prove its viability and robustness. Apply lean tools to optimize, debottleneck, and streamline operations. At least 1000 hours of stable operation without failure is required to prove process operability, robustness and consistent product quality. Optimize the process, including plant maintenance, as much as possible with the full commercial scale plant in mind, to ensure the smoothest possible operation. Simplify and fool-proof operation as much as possible to prevent mistakes caused by operator fatigue, negligence or novice. Record process behaviours and operating procedures, because this is valuable material with which to prepare for commissioning the commercial scale plant.

Update the in-silico process models to reflect reality.

Stage-gate meeting

Hold a stage-gate meeting with all stakeholders. Also include project-external subject experts to provide a multi-perspective view. Do at least the following:

•Review the project documents, policies and boundaries established in the project definition phase as a reminder of the project guide-lines and goal. Ensure that they are still valid and applicable. Update if necessary.

•Review KPIs for Scale-up phase. All KPIs must be met before the commercial phase may be commenced. This is extremely important because it prevents unnecessary expensive and time-consuming failures in equipment acquisition, plant assembly and commissioning.

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•Prepare for the commercial phase. Ensure that all information and resources required will be available.

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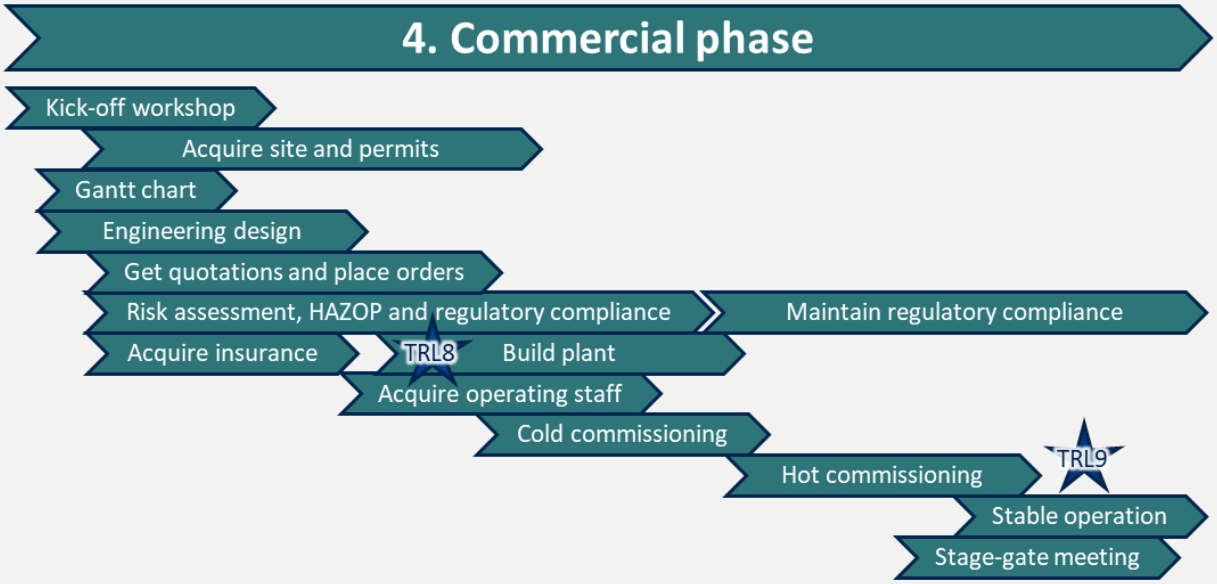
The roadmap – Commercial phase

In this phase, full scale commercial production generates income and rewards the investment. It is important to keep a good overview during construction and commissioning. Ensure that each component, each step and each activity is exactly up to standard before continuing to the next steps. Do not become complacent once commissioning is over and stable full capacity operation is achieved. Continuously improve to remain competitive. Apply FEL 3. TRL 8 and TRL 9 must be achieved in this project phase.



Kick-off workshop

Hold a kick-off workshop with all stakeholders. Do at least the following:

• Align targets and priorities with all stakeholders. Ensure that all stakeholders understand the complexity of the process.

• Determine what resources would be needed in the commercial phase and plan how to acquire it. Consider that some things may have a long lead time or limited availability.

•Expand the RASCI chart with detailed phase-specific action items for the commercial phase to ensure that the required TRLs will be achieved. Define deliverables and resources dedicated to the tasks. Do not over-dedicate personnel resources to a variety of tasks, because this will result in diluted efforts. Rather dedicate specific persons and resources to as few tasks as possible per person, to ensure adequate dedication and focus.

•Expand the Gantt chart for the commercial phase with more detail. Set realistic timeframes.

•Set relevant KPIs and clarify existing KPIs to be achieved in the commercial phase.

Acquire site and permits

Acquiring the site usually means purchasing it, but renting or some other kind of agreement with the site owner are also possible options.

Acquire the necessary building-, commercial operating-, water use- and environmental protection permits. Apply early enough to ensure that work can commence and continue as

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planned. This step often takes a long time due to bureaucracy, which is entirely out of the control of the applicant. Therefore, apply with time to spare.

Gantt chart

Create realistic project Gantt chart and communicate to all relevant parties. Unfortunately, project timelines often do not keep to the planned Gantt chart. This leads to frustration, financial penalties and delayed income generation. To avoid this, it is important to remain realistic in one's expectations when drawing up a Gantt chart. Experience in the field helps to identify areas where delays are likely to occur so that provisions can be made. Consider the effects of stick-built vs. modular construction in the construction timeline and task interconnectivities.

Engineering design

The conceptual engineering conducted and the models that were created in the conceptual phase and updated throughout the industrially relevant laboratory trials and scale-up phases provide the basis for the basic- and detailed engineering needed in the commercial phase. When engineering design commences, process design must be frozen. No more changes are allowed. Engineering design is the first step of creating high-cost fixed assets, which are extremely difficult and expensive to change, and therefore should not require any change.

Detail engineering includes for all process unit equipment: the dimensions, materials of construction (MOC), connections, weight, static- and dynamic forces acting on- and within the unit. Also for the entire plant structure: the dimensions, MOC, connections, weight, static- and dynamic forces acting on the supports, the layout, piping dimensions, MOC and routing, cable sizing, cable racks and routing, roads, walkways, escape routes, three-dimensional computer aided design (3D-CAD) models of the entire plant and its components. Selection and specifications of isolations and insulation for noise, vibration and heat, and considerations and applications of explosive environment (ATEX) design must be conducted. A control philosophy and wiring diagrams must be designed. Utilities and amenities such as control rooms, substations, lavatories, kitchens and offices, with the associated plumbing, fire safety systems, storage for deliveries and dispatch are to be included.

The time available for detail engineering as a fraction of the commercial phase Gantt chart is heavily influenced by the choice of stick-built vs. modular construction. In the case of modular construction, the scope of work for construction is fixed relatively early in the timeline to ensure that all components align with one-another. This is clearly the more challenging option from an engineering and assembly perspective. In case of stick-built construction, changes in the engineering details are still actionable for some time after construction has commenced.

Get quotations and place orders

Once detail engineering is done and specifications for equipment and plant components are clear, acquire quotations for all construction, equipment, piping and instrumentation. Also, equipment for utility supply. Place orders early enough to ensure on-time or early delivery. Wherever possible, acquire at least three competing quotations in order to secure the best price. Consider second hand equipment only if the price benefit outweighs the operating uncertainty. For more complicated work, such as supply of an entire process system (e.g. water treatment facility) or construction project management, one may also consider a formal

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tender procedure to get offers from qualified, capable and interested providers.

Risk assessment, HAZOP and regulatory compliance

Conduct a formal risk assessment for the commercial plant. (See list of risk assessments below) Apply ISO 14001 environmental management standards and ISO 15001 energy management standards as well as relevant technical standards. Re-do the HAZOP study that was initially done in the scale-up phase. Document regulatory compliance for full-scale operation. Keep a well-organized and backed up database of all documents relating to Health, safety and environmental activities in the plant and keep the database up to date.

Maintain regulatory compliance

Continuously monitor applicable laws and regulations for changes. Maintain regulatory compliance. Laws and regulations change over time (usually becoming stricter). Being compliant this year does not mean that the same will apply next year. One must proactively implement improvements and changes to the process and internal policies to remain compliant.

Once the process is operating under stable conditions, measure real input and output flows and compositions and draw up LCA for the operational system. Maintain the LCA.

Acquire insurance

Many things can go wrong. Equipment can get damaged, customers can suffer damages, employees can get injured, etc. It is important to be legally and financially covered for these events.

Build the plant

Check and test components as soon as they are in a state that can be tested. For most projects, it is common practice to include inspection hold points at which the customer and provider conduct inspections or tests together, then sign a document either agreeing that everything is up to standard or agreeing on how to remedy the situation. Handover certificates are signed at the end of a project on the same principle. These inspection documents often also correspond to payment milestones. These inspections and tests are to be done diligently because the supplier will not accept responsibility for defects after the customer has agreed in writing that all is in order. It is also much more time consuming and expensive to correct defects later on in the project. Generate as-built drawings.

Continually update/maintain the Gantt chart and manage progress. If any changes occur in the Gantt chart, assess its effects and act appropriately.

TransBIB resources
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Learning modules and webinars
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Acquire operating staff

Operating staff include not only operators and plant supervisors, but also cleaners, human resources (HR), legal- and environmental consultants, maintenance staff, a legally appointed responsible engineer, electricians and instrumentation technicians. Depending on the chosen shift-work system, one would require 3 or 4

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sets of plant operators and supervisors. Train the staff to achieve required competencies. It is recommended to have a core- and a back-up team trained.

Cold commissioning

Operate the equipment with water only. Check for leaks, correct pressures and flow rates, heating and cooling rates. Test safety devices. Commissioning a plant always starts with just water. It is safer and cheaper to test and fail with water than it is with process streams or raw materials. The likelihood of discovering issues such as leaks during cold commissioning is also very high, therefore, water is the best choice. Test safety devices by purposefully operating the plant outside of design range. If the safety devices fail, the likely risk is much lower with just water in the system than with chemicals. Conduct inspections and tests diligently before signing cold commissioning handover certificates. In the case of modular construction, it is better to conduct cold commissioning at the manufacturer's facilities.

Hot commissioning

"Hot commissioning" refers to operating the plant as designed for the first time. This phase of the project requires very close monitoring to ensure best process performance and to measure the baseline performance of clean, new equipment. Close monitoring also allows for the early identification of deviations from what was expected and for quick response to unwanted occurrences. Learnings from starting and operating the pilot and demonstration plants are to be applied during hot commissioning. Due to the safety risk, financial risk and reputational risk involved, starting up and ramping up is done step by step in a controlled manner. Conduct inspections and tests diligently before signing handover documents.

- ✓ Start first step operations at minimum capacity. Stabilize operating parameters.
- ✓ Identify and solve problems and operational risks.
- ✓ Start consecutive steps and stabilize operating parameters. Identify and solve issues.
- ✓ Ramp up operations to full design scale. Monitor for problems and operational difficulties. Solve issues.

Stable operation

Once commissioning is successfully completed, production should be maintained at full capacity. This does not mean that development has stopped. One must remain vigilant, monitor the process and continually look for opportunities to improve in order to remain competitive in an ever-changing market. Apply lean tools to optimize, debottleneck and streamline operations. Document lessons learned for future reference.

Create a digital twin of the process plant and keep it updated with real operation data. Data from the demonstration plant may be used as first estimation to train the model, but data from the commercial scale plant will always be superior. A digital twin is often an invaluable tool for both troubleshooting as well as continuous process monitoring and improvement.

Stage-gate meeting

Hold a stage-gate meeting with all stakeholders. Also include project-external subject experts to provide a multi-perspective view. Do at least the following:

•Review the project documents, policies and boundaries established in the project definition phase as a reminder of the project guide-lines and goal. Ensure that they are still valid and applicable. Update if necessary.

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•Document achievements, deviations, lessons learned for future reference.

•Review KPIs for the commercial phase. All KPIs must be met before the project may be deemed completed and fully handed over to operations.

•Prepare for project closure and continual commercial operation. Ensure that all resources remain available for sustainable operation until the planned plant lifetime is over and for site rehabilitation thereafter.

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Laws and risk assessments

This section lists some laws that may be applicable to production plants in the EU as well as some forms of risk assessments. The book “Engineering verfahrenstechnischer Anlagen” (Weber, 2016) also contains a useful list in chapter 2.3. These lists are non-exhaustive and do not negate the need for a thorough research campaign into the laws applicable to your individual processing plant in the country and legal climate where the process is intended to operate and trade.

Non-exhaustive list of potentially applicable EU regulations

Environmental Regulations

- Industrial Emissions Directive (2010/75/EU)
- Environmental Impact Assessment Directive (2011/92/EU, amended by 2014/52/EU)
- Waste Framework Directive (2008/98/EC)
- Water Framework Directive (2000/60/EC)
- REACH Regulation (EC 1907/2006)
- BImSchV/G (BGBl. Nr. 33 vom 08.06.2017 S. 1440)

Safety regulations

- Seveso III Directive (2012/18/EU)
- Machinery Directive (2006/42/EC)
- ATEX Directive (2014/34/EU)
- Pressure Equipment Directive (2014/68/EU)

Worker safety

- Workplace Safety Directive (89/391/EEC)
- Chemical Agents Directive (98/24/EC)
- Carcinogens and Mutagens Directive (2004/37/EC)

Important ISO standards

- ISO 9001 - Quality Management Systems
- ISO 14001 - Environmental Management Systems
- ISO 45001 - Occupational Health and Safety Management
- ISO 50001 - Energy Management Systems
- ISO 14040/14044 - Life Cycle Assessment
- ISO 31000 - Risk Management
- ISO 14067 - Carbon Footprint

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Risk assessment types
process hazard analysis (PHA) for chemical processes
HAZOP (Hazard and Operability) studies
FMEA (Failure Mode and Effects Analysis)
quantitative risk assessment for major hazard installations
Environmental risk assessment
Occupational health risk assessment

Suggested reading

Engineering verfahrenstechnischer Anlagen – Praxishandbuch mit Checklisten und Beispielen (Weber, 2016)

Thank you

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