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

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aufgrund eines Beschlusses
des Deutschen Bundestages

Professorship of Bioprocess Engineering
Campus Straubing for Biotechnology and Sustainability
Technical University of Munich

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 analysis before making decisions or taking actions based on the information presented in this document.

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1. Introduction

A recent study by the EU (“Choose Europe for Your Startup and Scaleup - European Commission”), revealed a substantial shortage of skilled professionals capable of scaling bioprocesses from conceptual to commercial scale. Th is gap threatens to hinder the growth of the bioeconomy, not only in Germany but globally. In response, this white paper provides a comprehensive roadmap for scaling bioprocess concepts to industrial scale. The guide outlines essential steps, considerations, and best practices for each stage, 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 scaling challenges and unlock the full potential of the bioeconomy.

Successfully developing and commercializing a bioprocess requires a diverse team of experts and extensive planning. In this document, the reader is provided with a roadmap that includes all the important steps for successful commercialization. The process is divided into four phases:

1. Conceptual phase
2. Industrially relevant lab trials phase
3. Scale-up phase
4. Commercial scale phase

Additional information, best practices and applicable TransBIB resources are given in the elaboration section.

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Colour codes are also assigned to the different disciplines involved in each step to help provide some clarity.

Dark blue	Project management
Dark green	Process technical
Orange	Health, safety and environmental protection
Dark teal	Legal
Green	Finance
Brown	Market and economics
Grey	Construction technical
Light teal	Logistics and purchasing
Black	Human resources

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2. The roadmap - overview

The process of developing and commercializing a bio-process is divided into four phases. These phases also roughly correspond to TRLs (Technology Readiness Levels). The four phases are:

2.1 The conceptual phase

This phase corresponds with TRL 1 to 3. 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. -page 4-

2.2 Industrially relevant lab trials

This phase corresponds to TRL 4 and 5 and is considered part of the “valley of death”. Process steps and systems are developed and optimized in the laboratory considering conditions that are to be expected in full commercial scale. 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. -page 9-

2.3 The scale-up phase

This phase corresponds to TRL 6 and 7. This is the second half of the “valley of death”. 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. To survive the valley of death, do not skip or neglect any step in piloting and demonstration. -p. 14-

2.4 Commercial phase

This phase corresponds to TRL 8 and 9. In this phase, the process is brought into full commercial production scale and operated continuously. 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. -page 18-

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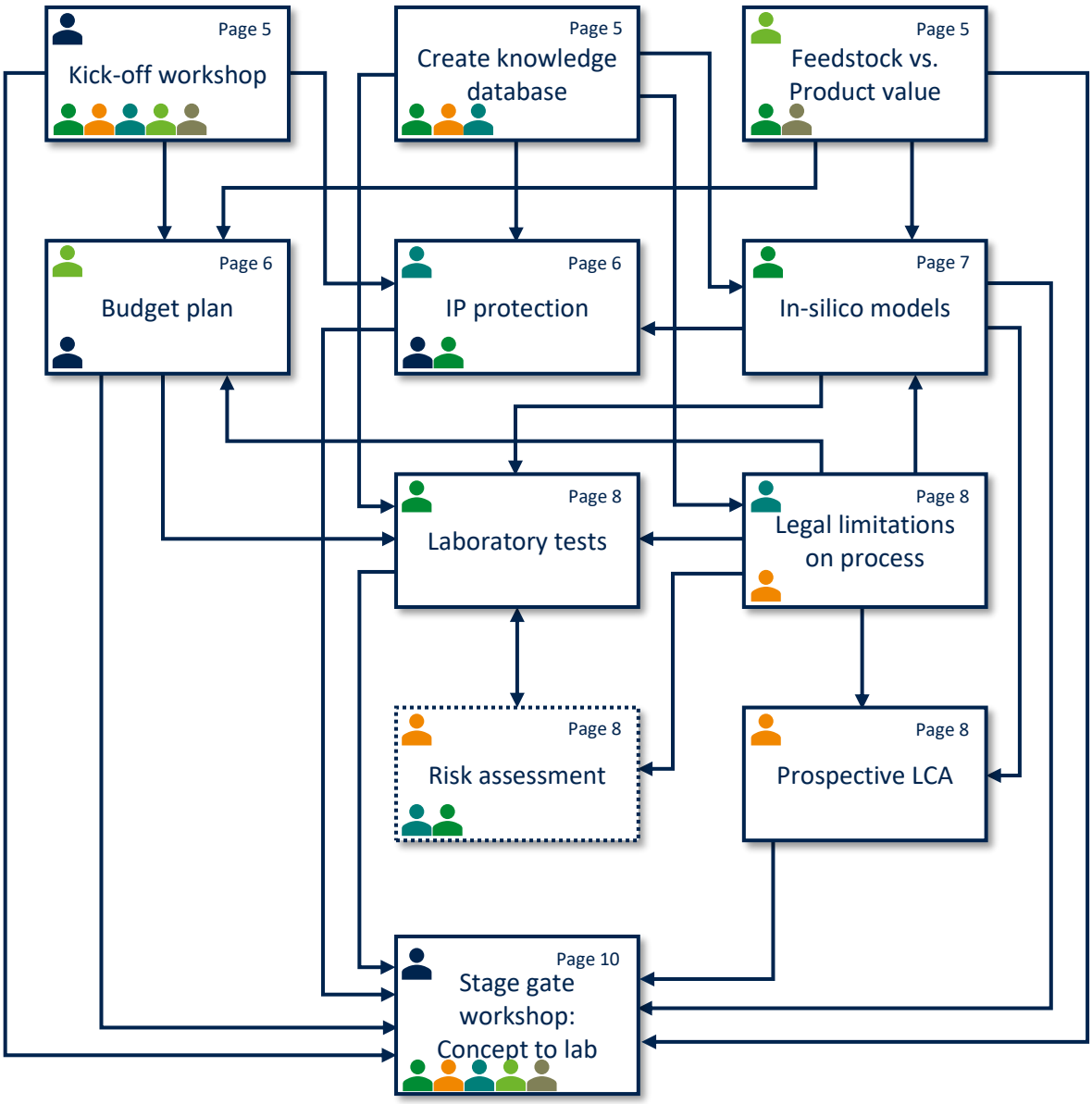
3. The roadmap – Conceptual phase

The diagram below shows the steps that are required in the conceptual phase. The colour coded icons indicate the disciplines that would be involved in the step as a minimum, with the top icon indicating the lead discipline. Each step is discussed including some best practices. You will also find a list of useful TransBIB resources for each step.



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3.1 The kick-off workshop

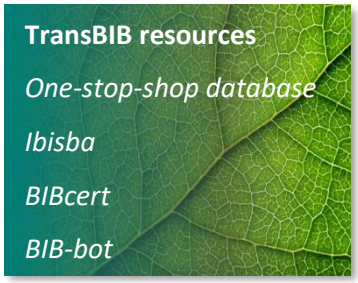
Hold a project kick-off workshop with all stakeholders. Do at least the following:

- Define the scope of the project. What is in scope, what is out of scope, what is "potentially in scope if necessary"
- Draw up a RACI chart to clarify and define who must be involved, how, and in which steps/actions
- Conduct a SWOT analysis on the envisioned project
- Generate a realistic Gantt chart for the project
- Set relevant KPIs to be achieved in the conceptual phase.

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

3.2 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, interactions and environmental impact studies. Also, relevant laws, regulations and standards. Make use on an interdisciplinary team. Collaborations with universities, networks, 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 at the end of this document.



3.3 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. The aim is to create value.

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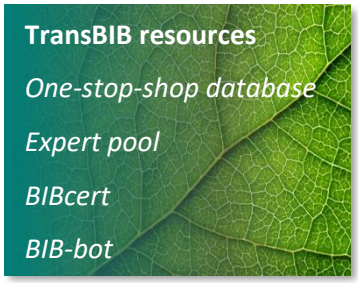
The price of some publicly traded chemicals and materials are publicly available, including the price trends over time. It is advised to request quotations from industrial suppliers to obtain reasonable estimates for privately traded compounds. For new market entries, several interviews are to be conducted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

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.

3.4 The budget plan

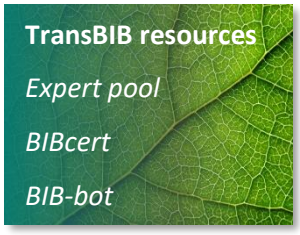
Draw up a budget plan for the project. Understanding the costs of process development activities, why they are required, and when to expect certain cash flows is important for financial management, investor communication and defending one's expenses. Understand that the "valley of death" has earned this 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.

3.5 IP protection

One may already consider protection strategies for intellectual property. 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.



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3.6 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 scales.

Modelling provides several advantages:

- 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 impact factors and stream summaries are also generated. These are important 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 likelyhood 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. 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 is not critical. 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, as well as continuously updating and improving the simulation design and inputs with accurate information.

While creating a process simulation model, some 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.

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3.7 Laboratory tests (and Risk assessment)

Conduct laboratory tests to collect or confirm information required to improve the validity of the simulated model. 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 most degrees of freedom in your process development. Therefore, conduct these steps diligently. Do not skip steps. Do not ignore minor issues. Acquire statistically relevant information. Ensure minimal uncertainty. Collaborate with universities or research institutions.

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Scale-up facility database

Ibisba

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

3.8 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 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.

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3.9 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).

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Expert pool

LCA tool

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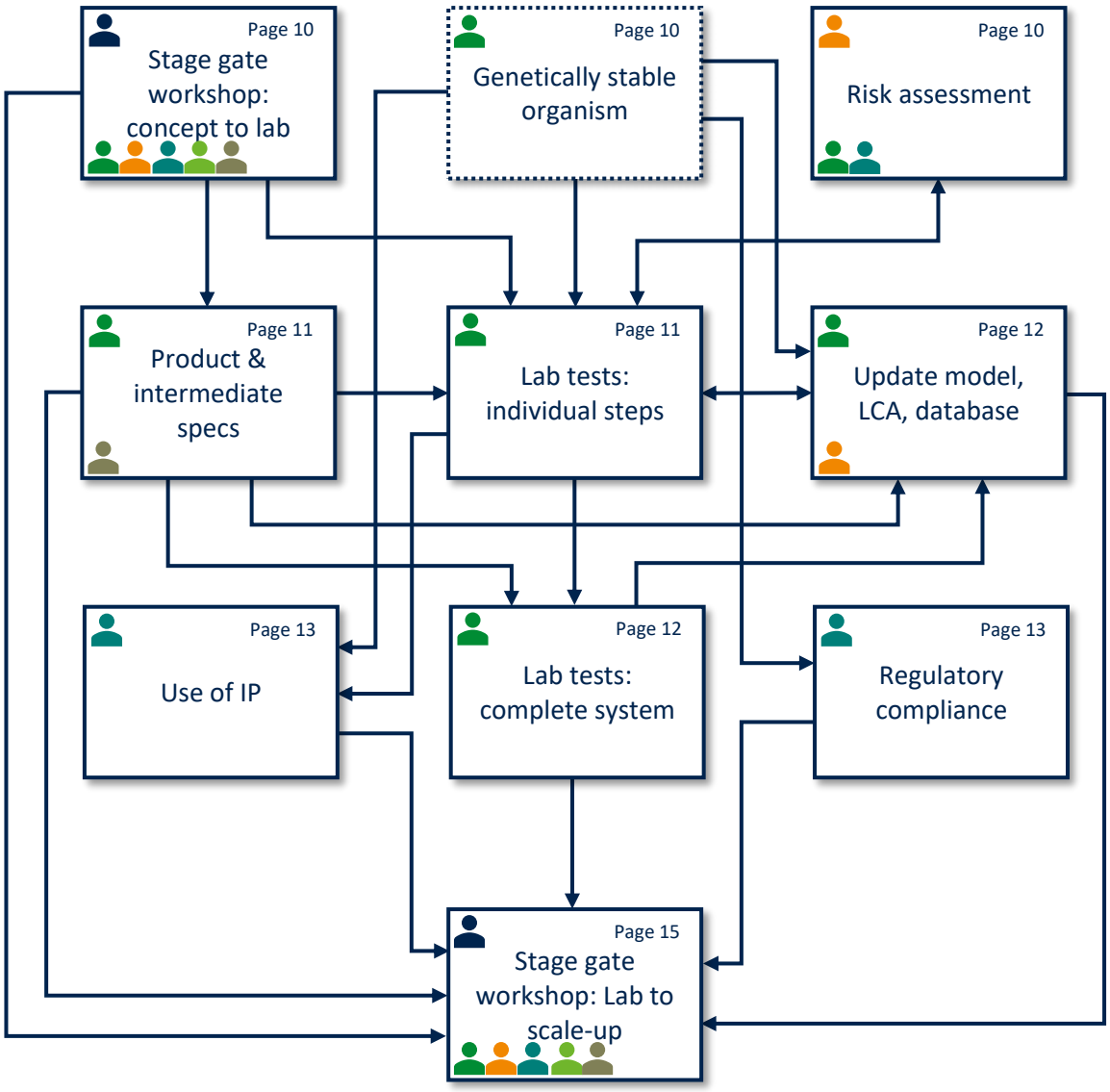
4. The roadmap – Industrially relevant lab trials

The diagram below shows the steps that are required in the industrially relevant lab trials phase. 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.



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4.1 Stage gate workshop: Concept to Lab

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

- Review project scope, RACI chart, SWOT analysis and Gantt chart drawn up in the kick-off workshop. Also, the budget plan. Update if necessary.
- Review KPIs for the conceptual phase. Only continue with industrially relevant lab trials if all KPIs have been met.
- Set relevant KPIs to be achieved in the industrially relevant lab trials phase.

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Reviewing the original documents allows re-alignment with the original idea and refreshing one's awareness of important factors. It also allows updating the documents in case this becomes necessary. Continuing to industrially relevant lab trials without completing the KPIs set in the conceptual phase may result in wasting time and money.

4.2 Genetically stable organism

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.

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In production scale, antibiotics are prohibitively expensive. Antibiotic resistant DNA is also not allowed outside of a controlled lab 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.

4.3 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.

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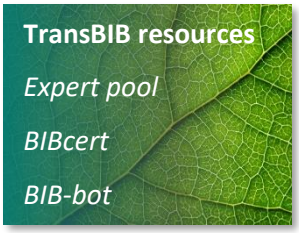
4.4 Product and intermediate specs

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 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?



4.5 Lab tests: individual steps

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

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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?
- 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.

4.6 Lab 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. Results should be statistically relevant.

Also consider the potential effects of recycling process streams. Recycling process streams tend to increase yield and recovery, but may also accumulate contaminants and increase equipment cost. 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.

4.7 Update model, LCA, database

Continually update your simulation model(s), LCA and research inventory with new proven information. 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 major cost drivers in a process. This provides guidance as to which areas deserve development focus.

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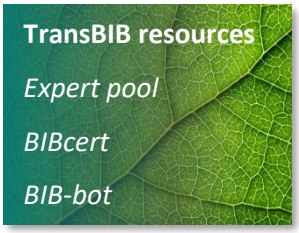
4.8 Use of IP

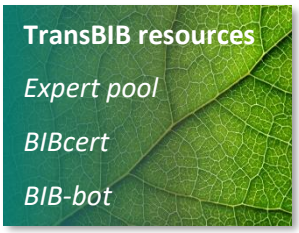
Research legal requirements related to IP and use of patents. Conduct a thorough patent search to ensure that you do not accidentally infringe on a registered patent. Find legal solutions as soon as possible. Either develop something that has not been patented and protect the IP yourself, or pay for the use of a registered patent. 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.



4.9 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 relevant ISO standards and evaluate whether there is a need for specialized equipment certifications.

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



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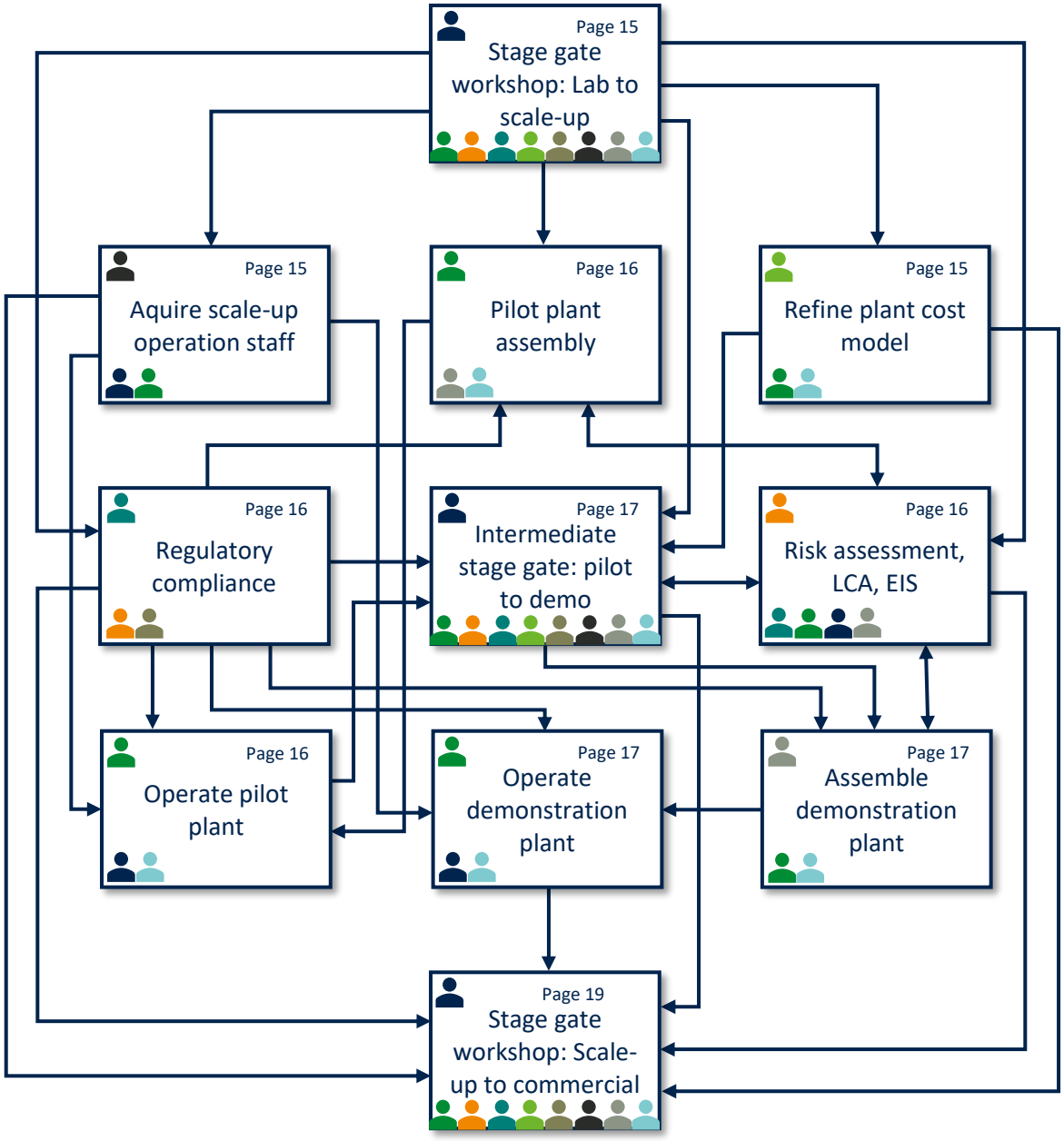
5. The roadmap – Scale-up phase

The diagram below shows the steps that are required in the Scale-up phase. This phase is costly and time consuming, but it is also the only way to ensure that the full commercial scale will be viable. Skipping or neglecting any step in piloting and demonstration will likely result in commercial scale problems that are even more costly and time consuming. It can sink the business. DO NOT skip piloting and demonstration.



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5.1 Stage gate workshop: Lab to scale-up

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

- Review project scope, RACI chart, SWOT analysis, Gantt chart and budget plan from the industrially relevant lab trials workshop. Update if necessary.
- Review KPIs for the industrially relevant lab trials phase. Only continue with scale up if all KPIs have been met.
- Set relevant KPIs to be achieved in the scale up phase.

Continuing to scale up without completing the KPIs set in the industrially relevant lab trials phase may result in wasted time and money.

5.2 Acquire scale-up operation staff

Most tolling facilities have sufficient staff to operate the equipment. Making use of the tolling facility staff only, 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 opportunity to build up a knowledgeable and qualified pool of personnel for operating the commercial plant later on.

Your own staff are also more likely to have priorities that align with yours, rather than the tolling facility staff.

5.3 Refine plant cost model

Refine cost model using cost engineering principles and up-to date published cost databases. Acquire quotations for large and long-lead-time equipment. 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.

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5.4 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.

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

5.5 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 full LCA and environmental impact study. The environmental impact study includes the product end-of-life. Consider the waste management hierarchy as prescribed in the Kreislaufwirtschaftsgesetz (KrWG).

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5.6 Pilot plant assembly

Design and assemble pilot plant. 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 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.

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Scale-up facility database

5.7 Operate pilot plant

Operate the process and test its viability and robustness. Pay attention and investigate unexpected behaviors. Apply lean tools to optimize and streamline operations.

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5.8 Intermediate stage gate: Pilot to demo

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. Integrate problem solutions into the demonstration plant design.
- Set relevant KPIs to be achieved in the demonstration plant.

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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 and cost more.

5.9 Assemble demonstration plant

Design and assemble the demonstration plant. A demonstration plant is a small-scale version of the real plant. It is only just large enough to be economically viable, close to break-even point.

If possible, conduct demonstration at tolling facilities and/or rent the required equipment. If not, purchase it. Do not compromise. The demonstration plant should be an exact scale model of the envisioned commercial scale plant.

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5.10 Operate demonstration plant

Operate the process and prove its viability and robustness. Apply lean tools to optimize 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 as much as possible with the full commercial scale plant in mind, to ensure the smoothest possible operation.

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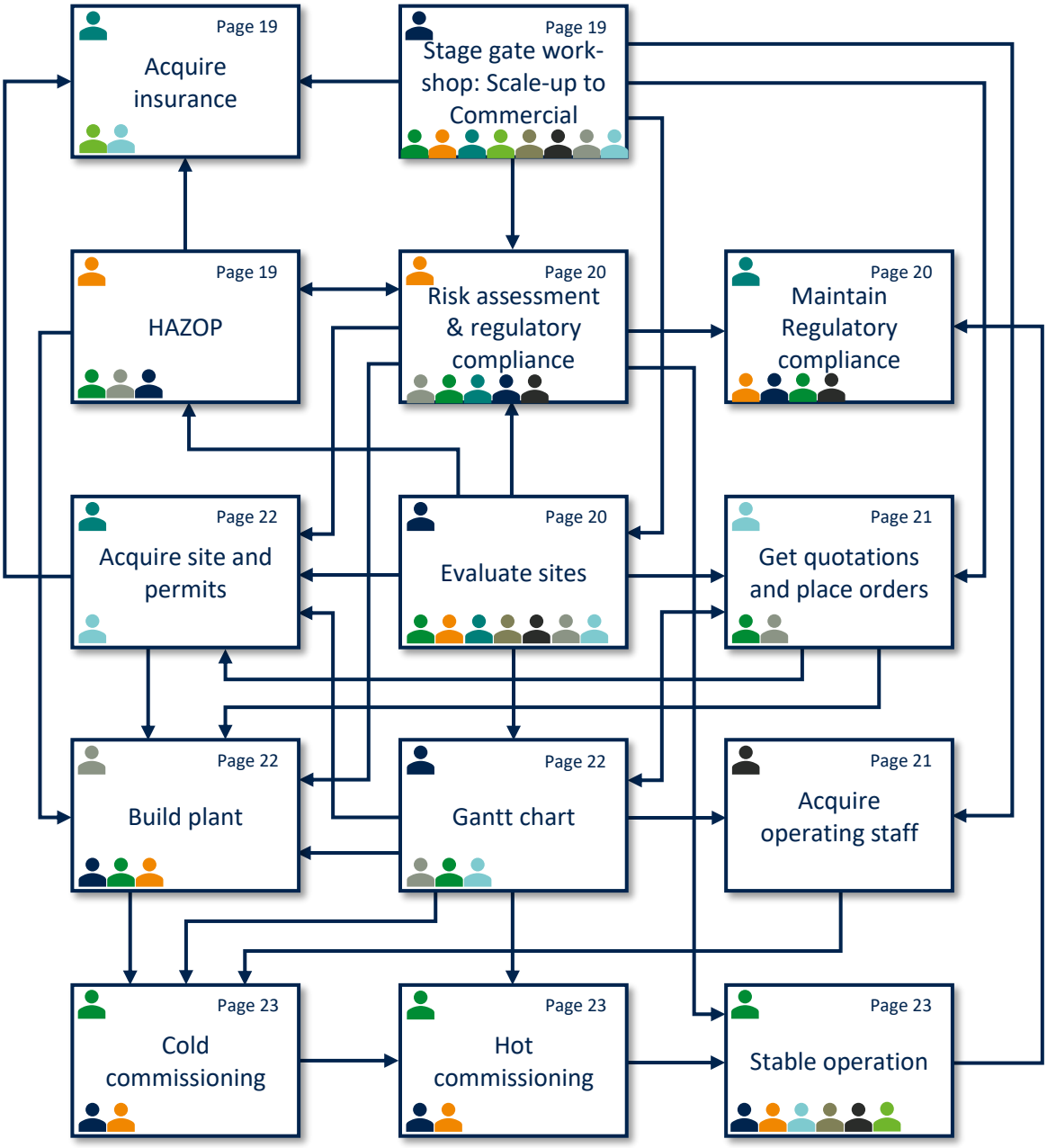
6. The roadmap – Commercial phase

The diagram below shows the steps that are required in the Commercial phase. 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.



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6.1 Stage gate workshop: Scale-up to Commercial

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

- Review project scope, RACI chart, SWOT analysis, Gantt chart and budget plan from the scale up workshop. Update if necessary.
- Review KPIs for the scale up phase. Only continue with the commercial scale phase if all KPIs have been met.
- Set relevant KPIs to be achieved in the commercial scale phase.

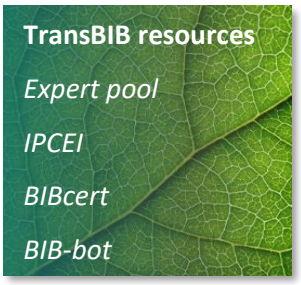
Continuing to commercial scale without completing the KPIs set in the scale up phase is likely to result in costly mistakes.

6.2 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.

6.3 HAZOP

Conduct a HAZOP study (or HACCP 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.



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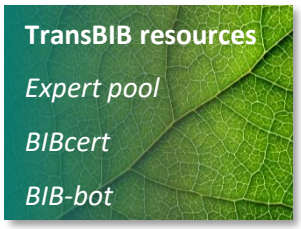
6.4 Risk assessment and regulatory compliance

Conduct a formal risk assessment for the commercial plant. (See list of risk assessments below)

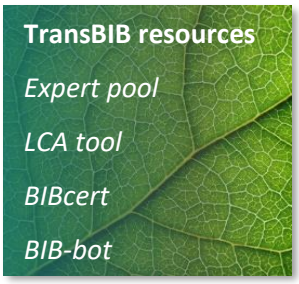
Apply ISO 14001 environmental management standards and ISO 15001 energy management standards as well as relevant technical standards. Document regulatory compliance for full-scale operation. Keep a well-organized and backed up database of all documents relating to Health, safety and environmental activities in the plant and keep the database up to date.



6.5 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 pro-actively 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.

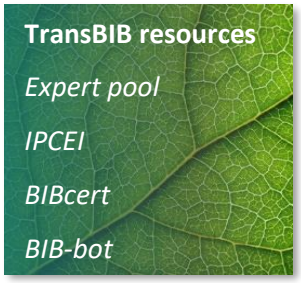


6.6 Evaluate sites

Shortlist potential sites for the full-scale processing plant. 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



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industrial scale process plant. (See non-exhaustive list below) 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.

6.7 Get quotations and place orders

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

TransBIB resources

Expert pool

One stop shop database

Workshops, Webinars, meet-and-match

6.8 Acquire operating staff

Operating staff include not only operators and plant supervisors, but also cleaners, 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 sets of plant operators and supervisors.

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6.9 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.

6.10 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 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.

6.11 Build plant

Check and test components as soon as they are in a state that can be tested. For large 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.

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

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6.12 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 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.

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6.13 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. 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.

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6.14 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 and streamline operations. Document lessons learned for future reference.

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7. Laws and risk assessments

This chapter lists some laws that may be applicable to production plants in the EU as well as some forms of risk assessments. 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.

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)

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

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