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**Pitfalls in piloting**

Extensive insight is already available on the good practice and importance of piloting bioprocesses. It is highly recommended to study selected articles before starting related works[1] [2] [3] [4]. The article in hand however adds the perspective of an external service provider on this topic.

Piloting serves different purposes: To down-scale as well as up-scale a manufacturing process. To test a process using industrial type equipment. For proof-of-concept. To mitigate manufacturing as well as scale-up risk. To collect engineering and feasibility data. To develop product specifications. To provide samples for application testing at customers. To convince investors by the readiness of your technology. Many further good reasons exist.

Depending on the process novelty, process complexity, the expectable economics of a product (=in sum the risk) piloting might be repeated in different scales and facilities, in dedicated facilities or multi-purpose facilities, typically in a 1:10 - 1:100 volume-scale ratio. Piloting and demonstration are somewhat similar terms, mainly differing by the fact that the demo scale is actually closest to manufacturing scale and typically should run the process as close and integrated to the manufacturing design.

Piloting is a critical part in process development and commercialization. It involves significant cost and will consolidate parts of your technology. As such special care is needed in defining campaign targets, choosing a facility, in planning and preparing works from all relevant perspectives.

Most companies that are approaching a CRO/CDMO are looking for conclusions regarding proof-of-concept, process robustness, scalability and industry (equipment) fit. Step yields, consolidated mass balances and representative product samples are of core interest. Reconsidering these anticipated and critical results, it sometimes was striking which distractions could be observed:

- Surprisingly many customers did not perform a technical due diligence on the suitability of the facility for certain works, later realizing that things were different as expected

- Quite often piloting targets kept moving. Projects were signed starting on the assumption that it is all about doing proof-of-concept work or getting first smaller samples but ending up in searching engineering-type data, minimizing overall losses or running process integrations and the like. Needless to say, that all of the latter would actually have required a different project preparation, schedule, cost structure or even technical modifications beforehand

[1] https://academic.oup.com/femsle/article/365/13/fny138/5026621
[2] https://www.genomatica.com/wp-content/uploads/2017/01/20160421-Industry-Lessons-Lievense.pdf
[3] https://link.springer.com/book/10.1007/978-3-319-41966-4
[4] https://warneradvisorsllc.com//wp-content/uploads/2015/05/Lessons-Learned-Final-Part-1.pdf

- Frequently it was difficult to achieve consensus on what the customer (minimally) needs to achieve in the available campaign window, i.e. which goals should be prioritized if a compromise would become necessary based on the performance of the trials (e.g. quality over yield etc). Some companies even seemed internally disconnected as answers on project targets from BD/commercial and technical teams could be contrary.

Those items should actively be addressed from both sides, the customer and the service provider. It needs a precise understanding on the targets and execution how to achieve them. Therefore certain (maybe even painful) discussions and conceptual works are needed before signing a service contract. Wrong expectations are the basis for project turbulence later on.

Many of the technologies have still shown surprisingly large gaps even when clients were approaching or performing scale-up into the 10-100m³ scale. This holds especially true when questioned from an overall process design and/or technology commercialization point of view, and not primarily from a fermentation scale-up readiness. The readiness to transfer a process into the piloting facility was vastly differing between customers:

- Some customers have gone through other projects before and could provide detailed documentation. They typically know best what they want and understand what they can expect from the work at the facility. Other customers however approached with a 1-pager of general remarks but were already looking for a certain product spec. No process description and only very limited data available. Of course, piloting can be used to develop such description/data, but the project preconditions and expected outcomes need to be realistically downsized

- Nearly most technologies were significantly better defined on the upstream part, whereas there was frequently only a weak guess on how the DSP could look like

- Some customers haven't been aware that their current process might not yet be ready / suitable for an industrial setting (use of antibiotics, expensive or scarce inducers in production scale, stability issues, ATEX environments, problematic waste streams)

Quite often clients were surprised not only by the significant cost associated with piloting. Also schedules and lead times consistently draw discussions:

- Customers frequently started with very optimistic assumptions that not necessarily match the ones from the individual CMO. If a project is squeezed together turbulences (in addition to the normal process surprises) become more likely.

- The lead time to start a project, depends on the availability of plants and resources as well as the complexity of the contractual, preparational and tech transfer works. Some companies tend to compromise on the planning/preparation needed to achieve certain goals prior an upcoming board or investor meeting etc. This can make things more risky and more likely to deliver a suboptimal result.

Realistic schedules should always be the basis for quality works. To build confidence and trust they should be thoroughly discussed with the service provider before works are started. If a project progresses over several distinct work packages (e.g. different scales) it might also be wise to work with a general contractual frame and order each work package independently. This provides flexibility and allows for a faster start of initial low-risk phases as those might not need certain long lead preparations. Later work packages could be detailed over time depending on the progress of the initial phases. This approach can lead to higher planning cost, but it can avoid a complex change management process if things work out differently as initially projected.

If you develop a product with a stunning feasibility and low requirements on its purification you might be rather relaxed before starting pilot work. However, if you are developing a process for a biobased commodity, each unnecessary compromise on process or equipment design resulting from suboptimal facility fit or short-cut could risk the overall feasibility or product quality. Piloting success is intrinsically linked to diligence, preparation, evaluation and iteration and it depends on core pillars[5]:

1. The (documented) technology with reasonable TRL in regards to the activity ahead
2. The fit of the facility and mindsets for the works of interest
3. Mutual expectation management on project targets and execution
4. Level of planning, preparation, communication and coordination before and during the project (=project management)
5. Quality and quantity of data and its evaluation
6. Experience
7. Continuous learning

[5] See further https://www.genomatica.com/wp-content/uploads/2017/01/20160614-Alex-Patist-AIChE-PD-June-2016.pdf

**About the author**

Dr.-Ing. Markus Fritsch is a bioprocess engineer and has been working in the Industrial Biotechnology sector on R&D, engineering, scale-up & biomanufacturing assignments. In particular he enjoyed the last ten years, in which he was managing projects in various positions at the interface of an industrial scale multi-purpose plant that acted as a gateway for commercialization projects.

Markus repeatedly experienced the challenges and dynamics arising out of different perspectives and requirements from customers, technology-, engineering- and service providers, end-users and financial institutes. Now he is providing independent engineering and consulting services for technology ventures, service providers and other stakeholders of the bioeconomy.

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