Fritsch Bioprocess
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Routes towards biomanufacturing

There's more than one way to skin a cat[1]. This also holds true for commercialization of bioprocesses. As pointed out before[2] the classic approach from bench via pilot and (integrated + dedicated) demo to commercial scale follows good industry standards, but it is also the most cost and time consuming. However for 1st-of-its-kind technologies and low-cost bulk chemicals/fuels, there is still no better choice available from a risk perspective, as world-scale production plants require huge investments. Financing such project sizes is only possible by tremendous governmental support and bank loans which typical require de-risked strategies. Venture capital isn't available for those investments.
The higher the price of your product and the lower its volume, other routes will come into perspective. Those routes might have larger parts of the development and commercialization cycle performed externally, at existing multi-purpose facilities of CDMO or CMO. That way market acceptance could be tested at lower risk especially for products with unique characteristics but without available offtake.

A good reason to go external could also be if your team primarily consists of subject matter experts. The CRO/CDMO option looks attractive as they can enable you quite fast and efficient to work on the complete value chain without intensive recruiting and team building. *If managed properly,* working with them naturally offers huge benefits for less experienced companies as the technical infrastructure and team is typically available and functional. Despite the need to do tech transfer and scale-up, the time and cost to get to full operation can be much shorter as within a new dedicated plant. Typically, such facilities have trained people of different background available to support the step from bench R&D into commercial scale operation.

However, working with external partners can have undesired side-effects as well. For developmental activities it is often wise to search for the leverage you need. The strength of the partner ideally fits to your weakness. For manufacturing purposes, you should look for cost efficiency and track records. In any case you should consider strategic holds/fork points in your planning as market conditions or trial results could require fast re-planning. No matter which route you are choosing, you should mimic as much of the good engineering standard from the classic approach in any case. This can provide more flexibility for the future as you could switch CMOs more easily if needed or even have the data to design your own plant once the time is right.

Figure 1 provides an example how both sides might work together and how this fits into the overall commercialization of the product[3] [4] [5]. A client has developed a biotechnology and is now about to

[1] I actually like cats very much (and the German meaning "Viele Wege führen nach Rom")
[2] Paper on "About the importance of conceptual thinking in technology commercialization"

[3] General description is from left to right and from top to bottom. The sequence of the steps from left to right can also overlap in case of long-lead paper-based activities, technical modifications or raw material supply.
[4] „n.1" means stage-gate 1 of partner n. As there could be subsequent projects phases with other service providers, the same stage-gate might have to be taken again but with other partners in a different phase of the overall technology commercialization
[5] Stages in bold letters stand for phases in which providers could be changed more efficiently

commercialize it. The company is young, primarily active in strain and fermentation development. A standard DSP concept has been proven bench scale, but isn't necessarily optimized or completely quantified. The product is of moderate value. Annual volumes largely depend on individual acceptance in various customer segments. For the moment future BOO (build-own-operate) or external biomanufacturing at CMOs could both be reasonable options. Decision was made to go external to look for an external source to help scaling and producing initial material for customer sampling.

A screening for service providers led to a short-list of possible facilities to work with (2-4). NDAs have been signed, project targets defined and complete process documents exchanged with all of them to evaluate the fit to the facilities. All this work is typically done by a dedicated project manager at the client site and experienced sales-personal at the CRO/CDMO. If obvious showstoppers (typically technology, equipment, regulatory) are absent the first stage-gate is taken.

To get into a commercial agreement key technical personal of the CDMO is now working closely with the sales team (technical and commercial contract initiations (CI)). In exchange with the client a technical concept is developed that provides the basis for the scope of work, choice of equipment, schedule, cost etc. Both sides need to understand the basic technical fit and necessary larger mechanical modifications before any work can start. However, both sides should be aware that the concept might need revision once further results or planning progress is available. This compromise is necessary to avoid greater delays to start the project. Typically, a contract is drafted that consists of multiple work packages and clauses to deal with necessary changes. As the project typically undergoes certain phases (e.g. tech transfer, scale-up, manufacturing) it is wise to consider the possibility of adaptations over time (contract and concept documents). As the knowledge basis develops changes become likely.
In general documents developed in this phase should be transferrable (technology) and flexible (contracts) to efficiently deal with progress or changes in the later project.

If the fee for service and other terms are acceptable the contract will be signed. Stage-gate 2 is taken and the project handed over to a dedicated project manager at the CDMO for start of tech transfer (TT).

The practical contents, steps and scale of this phase depend on the complexity and criticality of the process and analytics and their degree of novelty. Typically TT is a mix of paperwork and test runs, ideally performed on both sides. During TT it is important to not only discuss the latest or most successful run, but a typical range of observations. It is necessary to identify unknowns, hurdles or question marks for upcoming scale-up trials. With this (kind of holistic) input the technical execution concept developed earlier shall be refined. A troubleshooting concept shall be drafted as well.

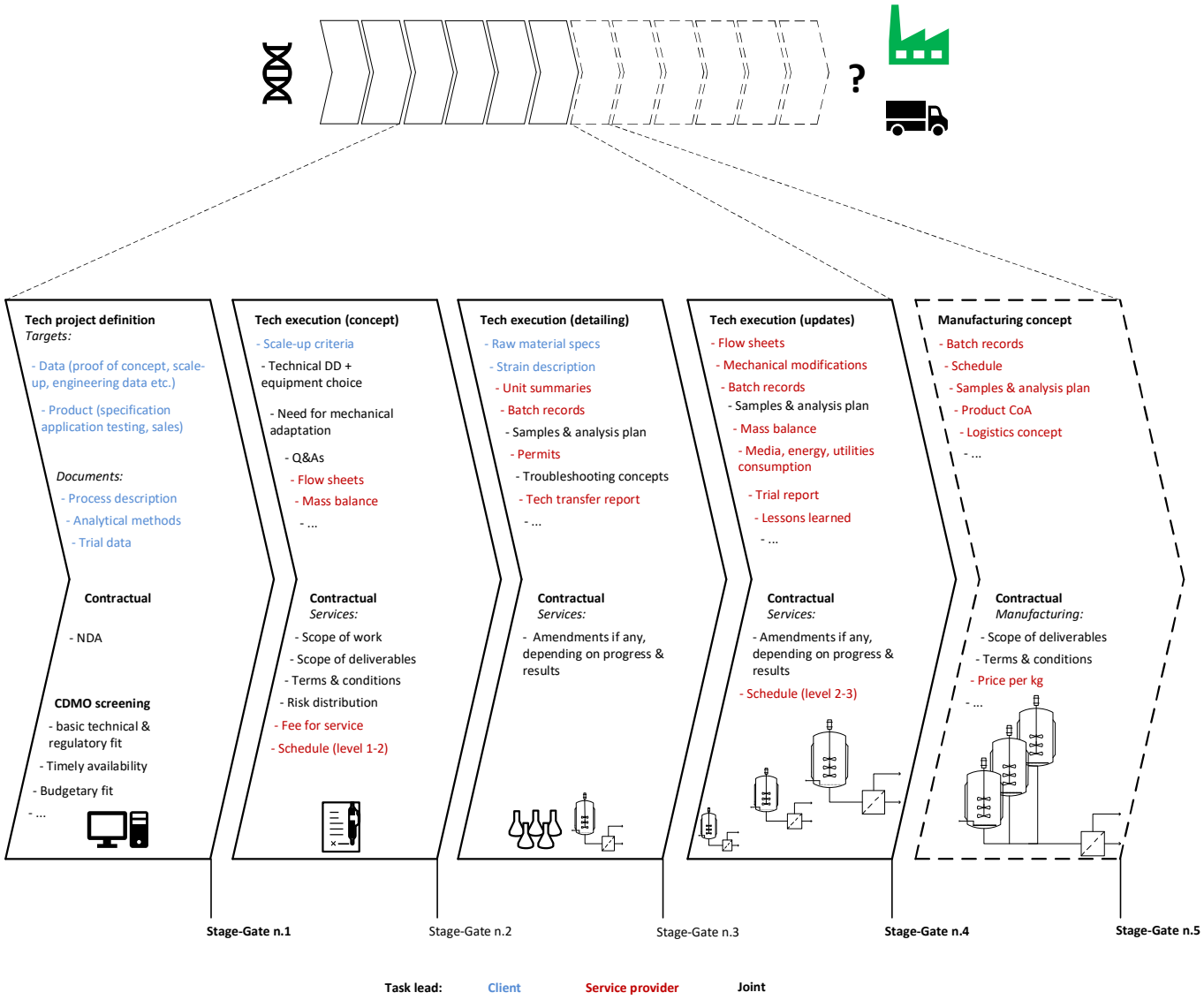

Figure 1: Typical phases of external work packages at external facilities as part of overall commercialization

Timewise it is also important to start potentially long lead items already at start of this phase which are needed in later stages of the project (e.g. permits).

Once the agreed tech transfer runs have been performed and critical process metrics have been validated in the facility of the service provider, stage-gate 3 is taken as well. A more thorough description of the CI and TT phase can be found here[6].

The actual heart of the project starts next. The trials in this phase can either be test runs to proof concepts, scale-up test for unit operations, longer piloting trials of partially integrated processes or even a sample manufacturing at larger scale. This all depends on the TRL and the point in commercialization. This project phase typically consists of several work packages, e.g. linked to different scales or process phases (in case of separating USP and DSP). The more general paperwork from TT and CI now needs to be translated into actual operative documents such as batch records, sampling plans etc. It is important that the service provider has reached a level of technical depth in the foregoing phases to combine this knowledge with its operational and logistical knowhow on an equipment basis. It is worth noting here that this phase produces lots of very detailed papers typically in the native language of the operators. That means international clients might not be able to fully understand those documents or need significant time to approve them if they want to.

Once the trials are running the service provider needs to extract and document the relevant data on the trials and execution. This is by far not only online data. This is about a critical assessment of the work of the operating team, about keeping track of non-conformities or unexpected surprises and discussing it with the client. Even if the client is onsite the full picture will only be available to the CDMO personal.

From my past experience I can say that the best projects have been those which had a sufficiently long and in-depth CI + TT phase before anything practical started. It was also helpful to agree on sampling and analytical needs before the tests. Quite frequent clients tend to overwhelm the operations team with adhoc requirements for analysis, samples, tests etc. It is important to understand that this unnecessarily raises pressure in the most precious and failure-prone project phase.

When it comes to the point that first samples shall be manufactured in large scale it is important to discuss if a further tolling phase is planned in that facility. If yes, it is highly recommended to perform the sample manufacturing at scale under operating conditions that can yield improved cost of product (or at least yield a calculation basis therefore). This can mean to test under increased timely pressure and to run unit-operations close to their maximum (CDMO business is time driven). It can also mean to run tests such a way that DSP losses as well as energy/utility consumptions are sufficiently quantified or to run fermenters at maximum level if this hasn't been done before. Both sides need to be convinced by the available data to come from a fee for service to a €/kg price. This is an important and difficult task

[6] Paper on "Fundaments of project success"

especially if the number of sample manufacturing batches is very limited, as both process (= client responsibility) and equipment/operations (=CDMO responsibility) need to be brought under one roof.
It happened several times in my past that this topic was simply skipped as it of course increases the initial cost of the project. However, once it was known later on that an optimized tolling scenario was needed it could be a struggle for both sides to agree on a price per kg or yield per batch. Finally, the cost (and risk) impact on the actual manufacturing batches (next phase) has been way larger as the initial cost increase in this phase would have been.

Once stage-gate 4 is taken the actual biomanufacturing can take place, typically under a new type of contract, at least if the number of batches is significantly high.
Within this phase the manufacturer is in the sole lead of the project execution. In the phases before the client at least had supportive functions. Once a process is proven at scale the service provider typically has an interest to manufacture independently. This means less (or no) insight into documentation, data or samples for the client. The risk is placed at the manufacturer, same with the profit (even if some optimization potential was hidden during initial service phases). In case the toll manufacturing concept deviates from the sample manufacturing batches (as highlighted before), this precise cut is hard to achieve. However, in theory it is all about the final product and its quality. Then stage-gate 5 is taken.

Depending on the overall stage in commercialization the project can now be

- Transferred to a different provider (further scale-up, more integration, different DSP, more cost-efficient etc.)
- Repeated at second CMO to increase security of supply
- Put ON HOLD in case time for customer feedback or product applications are needed
- Ended or re-visited in case market feedback was poor or new breakthrough ideas are available
- Used to generate a process design package and engineering concept + financing plan for a production facility

This is all possible after stage-gate 4 & 5.

Working together is complex, multi-dimensional and challenging, for clients and service providers. To make things effective projects it requires a deep understanding on the expectations from the other side.

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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