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Custom Development & Manufacturing Organization (CDMO)

From cell bank to market: how Arxada helps pave the way in white biotechnology

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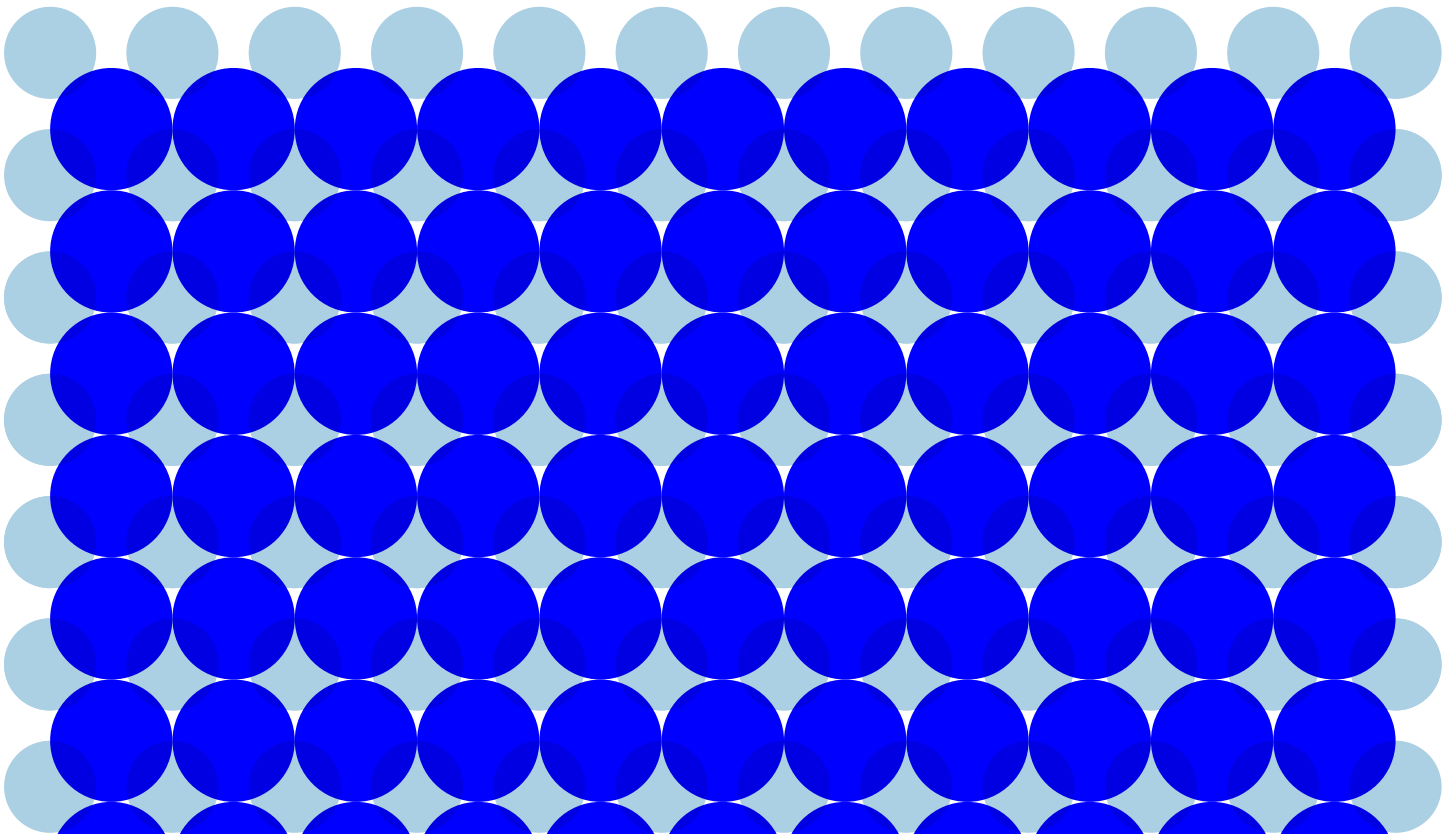
Industrial biotechnology harnesses the power of fermentation for sustainable production of various ingredients. Microorganisms convert natural carbon sources, such as sugar, yielding molecules that can find applications across numerous industries. Arxada proudly hosts an adept and experienced biotechnology CDMO (contract development and manufacturing organization) team, operating within a state-of-the-art facility in Europe. We feel it is time to shed light on its core capabilities. This paper is intended to introduce our customers' experience and share it with a broader audience.



From cell bank to market: how Arxada helps pave the way in white biotechnology

Truly little solid innovative ideas in biotechnology find their intended market applications. Crossing the notoriously known valley of death may represent a long and costly route accompanied by numerous technical and managerial hurdles. Time to market is a crucial parameter for many companies to successfully position the product on the market and attract further investor funding to grow and broaden the product portfolio. Efficient synergy of (early stage) entrepreneurial ideas and industry operating at commercially relevant volumes represents a way forward with the aim to enable the rapid development of innovative solutions.

Although known from pharmaceutical industry for commercial scale production of therapeutic proteins, the field of microbial fermentation has expanded over a few decades to deliver products for applications in various other industries such as food & beverage, feed & agriculture, or personal care. Industrial scale fermentation is a capital-intensive business. Proper understanding of the manufacturing process from small inoculum of microbial cells to final formulated product, its key economical parameters and process management tasks are essential to achieve a cost-efficient and commercially attractive process. Many companies therefore outsource their scale up efforts to CDMOs possessing facilities and expertise in the above-mentioned parameters critical for commercial success. Here you can find out how Arxada can support de-risking your way to market to avoid targeting the right product with wrong tools.

The biotechnology product portfolio nowadays spans from commodity chemicals with market prices below 10 USD/kg over specialty chemicals to very valuable active pharmaceutical ingredients. Despite the difference of product application and intended use,[1] some common drivers moving biomanufacturing forward can be recognized. These are economical (manufacturing costs), regulatory and legislative (*i.e.* subsidy policies), customer perception (bio-solutions, bio-alternatives and sustainability objectives) and innovation (advances in the field of synthetic biology, metabolic engineering, and computational analysis of complex biological systems).[2]

The biotechnology product development cycle starts with a market need followed by an idea and a solution definition. It continues with often iterative engineering cycles of a selected production organism in the laboratory.[3] The host organism then yields a product of interest in a fermentation process. Nowadays, the most common bioprocess is carried out in liquid suspension in sterile bioreactors, where key process conditions can be monitored and controlled.[4] Large fermentation volumes are usually required for production to be economically viable. Bioprocess scale-up, a transition from laboratory settings to larger industrial vessels, and a labyrinth of pipes and valves, ideally in a fully automated environment, stands as a critical phase of the product development cycle. (Figure 1). The scale-up carries a lot of risks. To name a few: a) Cells undergo several multiplication steps to generate enough biomass for production fermenter inoculation. This may result in genetic changes influencing the host performance and stability. b) Process performance at large scale is different. Cells experience chemical-, temperature- and pressure gradients potentially resulting in poor process productivity. c) Raw materials and additives used for fermentation impact the purification steps (downstream processing) of the targeted product(s). d) Some downstream processing operations might not be feasible or too costly at large scale.

Some of the challenges mentioned above might be solved early in the process design stage. However, the success of any process scale-up depends on the experience of people managing and operating the production process and their synergies. This skillset is unique and different from the chemical industry personnel experience. Here the product development cycle reaches the stage where uncertainties need to be reduced fast to avoid high development costs. Addtionally, let us emphasize that the ultimate goal of any scale-up effort is to address and reduce product unit costs.

[1] Nielsen J, Tillegreen CB, Petranovic D., *Trends in Biotechnology* **2022**; 40:1160–72, https://doi.org/10.1016/j.tibtech.2022.03.007

[2] Hoff B, Plassmeier J, Blankschien M, Letzel A-C, Kourtz L, Schröder H, et al., *Angewandte Chemie International Edition* **2021**; 60:2258–78, https://doi.org/10.1002/anie.202004248.

[3] Meyer H-P, Minas W, Schmidhalter D. *Industrial Biotechnology*, **2017**, p. 1–53, https://doi.org/10.1002/9783527807833.ch1.

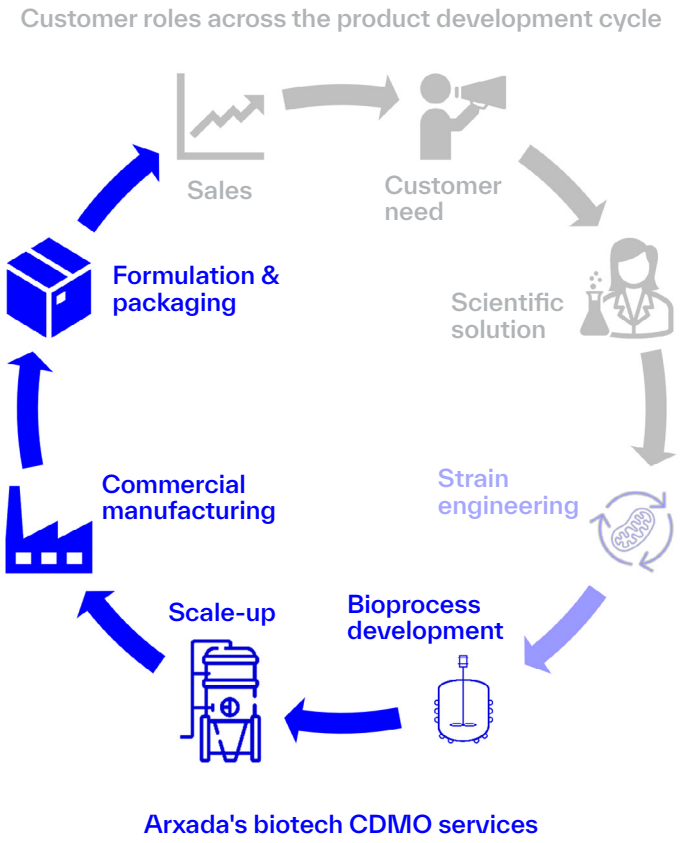
[4] Balakrishnan R, Mohan N, Sivaprakasam S. Chapter 11 - Application of design of experiments in bioprocessing: process analysis, optimization, and reliability. In: Sirohi R, Pandey A, Taherzadeh MJ, Larroche C, editors. Current Developments in Biotechnology and Bioengineering, Elsevier, **2022**, p. 289–319. https://doi.org/10.1016/B978-0-323-91167-2.00013-7.

Arxada's CDMO has a decades-long legacy of fermentation, product purification and formulation, and industrial-scale manufacturing. Due to the extensive experience with various microbial strains and processes, efficient tools for performing engineering studies and fast techno-economical evaluation process Arxada's team:

1. Saves customers' time and thus shortens the time to market.
2. Reduces costs by identification and solving technology gaps early enough.
3. Avoids costly re-iteration at production scale.
4. Adjusts the processes to avoid high capital investments.
5. Supports customers' regulatory dossiers with pilot-scale registration batches and required documentation.
6. Delivers high product quality using reliable state-of-the-art equipment operated by skilled personnel.
7. Meets even challenging product specifications.

During the past decade, Arxada has transferred over 80 technologies to commercial scale with a proven record of satisfied customers.

Figure 1. Where Arxada CDMO fits in a biotech product development cycle.



Where science, technology and industry meet

Arxada operates a multipurpose biotechnology facility with 450 m³ total nominal fermentation volume divided into six production lines operated independently. Various reactor volumes and a wide range of downstream process equipment offer significant flexibility in product volume output (Figure 2). As the fermentation and purification process often varies based on customer needs and quality requirements, a lot of operational flexibility and adequate planning is required. This model, typical for CDMO operations favors specialty ingredients with higher added value. Low value products are often produced in large quantities in facilities with larger fermentation capacity using dedicated processes. However, such processes are often not fully optimized at the initial stages of development. In this context, time-to-market may take priority over optimizing for economic efficiency. Arxada supports production processes of such ingredients before the market is penetrated or developed. Later the process can be transferred to a dedicated facility with fully optimized (yet rigid) process set-ups.

Arxada focuses on solving technological challenges and continuous process optimization rather than simple toll manufacturing. Major goal of Arxada's team is: a) To identify critical process parameters and their impact on the product quality and yield. b) Foresee potential scale-up issues. c) Adjust the fermentation and purification process conditions to reflect conditions and unit operations used in manufacturing scale. d) Find the most economical set-up for a customer's process.

Figure 2. From laboratory to manufacturing – Overview of Arxada's biotechnology capabilities.

Microbiology and analytical laboratories

- Cell banking
- Bioburden monitoring
- In-process analysis
- Release analysis
- Analytical method development

Process design and optimisation

- Bioreactors: glass bench top (2L) and
- Steel (20 or 75L)
- Scale down studies
- Lab scale DSP

Manufacturing lines

- 1.5m³
- 2 x 15m³
- 3 x 15m³
- 2 x 50m³
- 3 x 50m³
- 2 x 75m³

Versatile downstream processing equipment

- Centrifuges
- Homogenizers
- Ion exchange chromatography
- MF/UF/NF filtration
- Crystallization
- Lyophilization
- Tray/spray drying

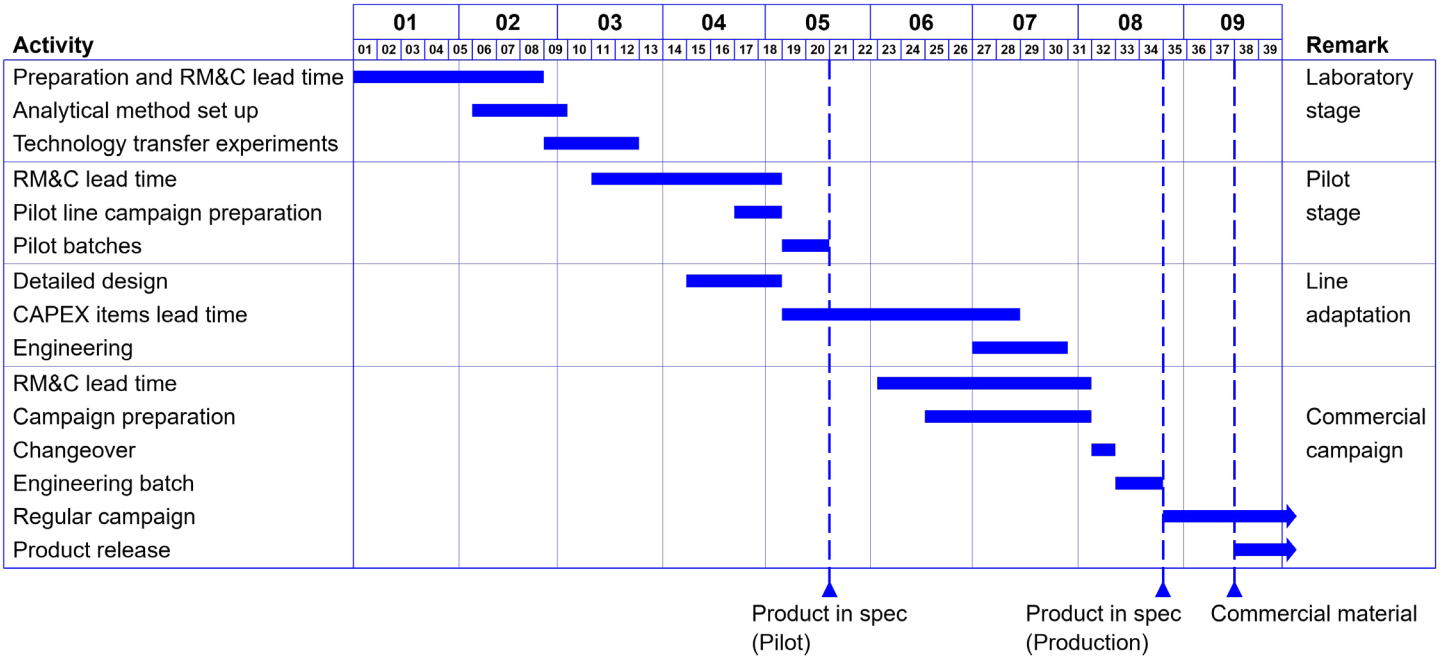
Arxada supports processes at any stage of technology readiness level or product development chain. Arxada´s bioprocess laboratories are equipped for initial process design (e.g. thorough feedstock and medium component screening, design and adjustment of feed rates or setting up optimum of basic parameters such as temperature and pH using design of experiment methodology) as well as process optimization or troubleshooting (Figure 2). While the basic principles of upstream processing and its instrumentation are more or less similar over all applications, downstream processing is always specific for a particular product. Purification steps and unit operations vary significantly based on product size, chemical characteristics and are driven by the product final formulation and specification. Suitable downstream processing is often omitted in the initial process design. It is even more difficult in the laboratory to mimic and test conditions that would be performed by unit operations and equipment at larger scale. Arxada's flexible downstream equipment can deliver products from small to large molecules, or active biomass in either liquid or solid form (Figure 2).

Finally, process development and manufacturing at Arxada is supported by QC laboratories (both microbiology and chemistry) with cell banking capabilities, inoculum preparation, bioburden monitoring, product release analyses, raw materials testing as well as off-line in process measurements (Figure 2). Should it be required, laboratories offer stability study design, analytical method development, and validation of analytical methods based on relevant quality standards.

Time to scale up a process depends on numerous factors, such as the complexity and novelty of the process, availability of equipment and raw materials as well as related regulatory requirements. At Arxada we always transfer the process to scale as quickly as possible, helping our customers with timely product launches.

Timelines for technology transfer of a recombinant protein production process, from laboratory over 1.5 m³ pilot up to 15+ m³ scale are illustrated below (Figure 3). However, robust and well-developed processes with small production line adjustments may be transferred faster, piloting step skipped if not bringing any value, and a commercial campaign can eventually start in less than 6 months.

Figure 3. Indicative timelines for manufacturing of a recombinant protein. All stages from laboratory to production and associated essential tasks are shown. Time scale is displayed in months (upper row) and weeks. RM & C – raw materials and consumables.



Why Arxada CDMO?

As we outlined above, Arxada has extensive biomanufacturing experience. We serve customers either small or large across various industries and applications. We help the customers place the product of interest on the market in the most economical way, with tremendous speed and quality. This approach always results in a win-win situation for both parties.

If you want to know more about
- how a technology transfer documentation for smooth and fast process transition and operational planning should look like,
- why is well structured project management important for successful manufacturing campaigns,
- how we actually do technology transfer,
- how we solved some common scale-up pitfalls in fermentation and downstream processing,
- and much more

Stay tuned for next issues of our monthly white papers

Our offer

- **CDMO services from a single source in the field of industrial biotechnology**
- **Engagement at any stage of product/process development stage**
- **Dedicated team for the entire process - from laboratory over scale-up to commercial manufacturing**
- **Facility registered as food manufacturing site at FDA. Certified for ISO 9001:2015, FSSC 22000/HACCP, EFfCI GMP FAMI QS, Halal, Kosher**
- **Management of entire supply chain**
- **Cultivated operation excellence with high quality, speed, and strong focus on continuous process improvement**
- ***Focus on what matters to you***

Acknowledgments

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